

RESEARCH ARTICLE

# Effect of non-fluoride agents on the prevention of dental caries in primary dentition: A systematic review

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## Abstract

### Objective

To assess the effect of non-fluoride agents on the prevention of dental caries in primary dentition.

### Materials and methods

Medline, Web of Science, Embase, Cochrane Library, CBM and CNKI databases were searched to identify all the relevant articles published prior to 16 December 2016. Grey literature was also searched. Randomized controlled human clinical trials in which non-fluoride agents were delivered by any method were considered.

### Results

Of the 1,236 studies screened, 39 full articles were scrutinized and 14 selected for inclusion in the final sample. Five chemical agents, namely arginine, casein phosphopeptide-amorphous calcium phosphate (CPP-ACP), chlorhexidine, triclosan and xylitol were investigated in these included studies. The cariostatic effects of non-fluoride agents *in vivo* were evaluated in comparison with fluoride or placebos in randomized controlled trials. There is evidence that the use of certain doses of xylitol may be effective in arresting dental caries in primary dentition. However, quantitative synthesis could not be carried out because of the clinical and methodological heterogeneity of the included studies.

### Conclusions

A study at low risk of bias indicated that daily use of xylitol wipes is a useful adjunct for caries control in young children, however, this conclusion should be interpreted with caution as this study had a very limited sample size. Chlorhexidine and CPP-ACP may be more effective than a placebo in managing caries in primary dentition, but their effectiveness is borderline

when compared with fluoride. Arginine-containing mint confection and 0.3% triclosan varnish were found to reduce caries development in primary teeth but the evidence was at high risk of bias. High quality randomized controlled trials are needed in order to make a conclusive recommendation.

## Introduction

Dental caries, a worldwide public health problem, affects a large number of people. In recent decades, although the prevalence of dental caries has dramatically decreased with the development of diagnostic methods, prevention and treatment of caries, the situation is still of concern for high-risk individuals, especially children [1]. It has been reported that approximately 30% of total caries experience occurs in the primary teeth [2], and nearly half of the children in the US suffer from dental caries before entering kindergarten [3].

Caries lesions usually develop more rapidly in primary teeth than in permanent teeth due to the differences in enamel structure and dietary habits. The enamel in primary teeth is thinner, and the surface micro-hardness is relatively lower, compared with permanent teeth [4,5]. Also, primary teeth have a less well-structured crystal arrangement and comparatively less mineralization. These differences in enamel structure may lead to the caries susceptibility and faster caries progression in primary teeth. Moreover, children's dietary habits, such as greater consumption of sugar and acidic drinks, may also contribute to the higher caries prevalence in primary teeth [5].

The development of carious lesions has been considered as a repeated dynamic process of de-/re-mineralization, which can be arrested or reversed by preventive factors in the environment or oral hygiene practice [6]. For example, chemical agents including fluoride, xylitol, chlorhexidine, and casein phosphopeptide-amorphous calcium phosphate (CPP-ACP), have demonstrated anti-caries effects in primary dentition in a large number of *in vivo* and *in vitro* studies [7–11]. The cariostatic potential of fluoride delivered in various vehicles has been demonstrated for decades, and the beneficial effects of topical fluoride agents have been examined in a series of Cochrane systematic reviews [12–14]. However, fluoride has a dose-response relationship, and improper delivery of fluoride agents may lead to adverse effects such as fluorosis [15]. Thus, numerous clinical trials have been conducted to test the ability of non-fluoride agents to enhance or supplement the remineralizing effect of fluorides, but until now their effect and safety are not clear. There are two previous systematic reviews that each assessed the efficacy of a single product for preventing dental caries in children and adults [16,17]. The authors of these reviews only found low quality evidence to suggest that xylitol may be effective for preventing caries in the permanent teeth of children. The authors of a report from the American Dental Association (ADA) on non-fluoride caries preventive agents could not make recommendations on the prevention of early childhood caries partly because insufficient studies could be found at the time this review was conducted (April 2010) [18].

The aim of this systematic review was to assess the anti-caries effect of a variety of non-fluoride agents in primary teeth, with an updated and expanded literature database search (December 2016).

## Materials and methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines ([www.prisma-statement.org](http://www.prisma-statement.org)). The review was not registered before data collection.

## Search strategy and databases

A systematic search to identify all the relevant studies was conducted on the following six databases: MEDLINE (via PubMed. No restrictions were employed on language or year of publication), Web of Science, EMBASE, CENTRAL (The Cochrane Library), CBM (Chinese Biological Medical) database and CNKI (Chinese National Knowledge Infrastructure) database. A supplemental manual search was conducted by reviewing the reference lists of the related papers and review articles. The search strategy included controlled vocabulary and free terms. It was developed for MEDLINE and adapted for the other databases (S2 Table).

Grey literature was searched on Clinicaltrial.gov, OpenGrey and the World Health Organization's International Clinical Trial Registry Platform. All searches were firstly conducted on 25 December 2015 and updated on 16 December 2016.

## Selection criteria

Human randomized controlled clinical trials were included. Studies in which participants had carious lesions in the primary dentition or mixed dentition (outcome reported on primary teeth) at the start of the study were considered for inclusion in this review, irrespective of the baseline caries experience. The inclusion age range of participants was 0–12 years old. All carious lesions (including ICDAS 1 and 2) were included. Studies in which participants had systemic disease were excluded.

## Type of intervention reviewed

Studies using non-fluoride agents, such as arginine, chlorhexidine (CHX), xylitol, casein phosphopeptide–amorphous calcium phosphate (CPP-ACP) and bioactive glass in any modality that were compared with placebos and/or fluoride were included. No restrictions were implemented regarding the dose, frequency, duration or method of non-fluoride agent administration.

The primary outcome of studies was caries increment in primary teeth or change in the proportion of participants developing new caries on primary teeth. The secondary outcome was the side effects from using the non-fluoride agents, such as gastrointestinal complaints, pain and discomfort, tooth staining, oral hygiene deterioration, quality of life and patient satisfaction.

## Data extraction

Two calibrated reviewers (Y.W. and J.L.) screened the titles and abstracts of the identified studies independently and in duplicate. Consensus was obtained by discussion and consultation with the third reviewer (L.M.) to resolve any disagreements during study selection and data extraction. Studies not meeting the inclusion criteria were excluded, and the reasons for exclusion are noted in S3 Table. The two reviewers (Y.W. and J.L.) independently extracted data from the studies using a data extraction form. The following data were collected: author and year of publication, number and age of participants, details of interventions and controls, assessment methods and time points, primary and secondary outcomes, and follow-up period.

## Methodological quality appraisal

Each study was assessed using the evaluation method recommended by the Cochrane Handbook for Systematic Reviews for Interventions 5.1.0 (<http://handbook.cochrane.org>). Two reviewers (Y.W. and J.L.) appraised the studies independently according to the following aspects: random sequence generation, allocation concealment, blinding, completeness of

outcome data, selective outcome reporting, and other biases. Each aspect was classified as having either a low, high, or unclear risk of bias. Thus, the overall level of risk for each study was subsequently classified as low (all quality items were met), unclear (unclear risk of bias for one or more domain), or high (high risk of bias for one or more domain).

Continuous outcomes were analysed using mean differences (MD) and standard deviations (SD), and dichotomous outcomes were analysed by calculating Peto odds ratios (OR) and 95% confidence intervals (95% CI). If there were sufficient homogeneities among the included studies, meta-analyses were performed. Review Manager Version 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) was used to conduct this analysis.

## Results

### Study selection

A total of 1,236 articles were screened for relevance (Fig 1). After applying inclusion and exclusion criteria, 1,197 studies did not meet the inclusion criteria and were excluded. A total of 39 full papers were retrieved and reviewed, among which 25 articles were excluded for the reasons given in S2 Table. Finally, 14 studies [19–32] were included in the systematic review.

### Study characteristics

In the 14 articles included in the review (Table 1), a total of 4,269 participants were evaluated, all of them were classified as healthy by the authors. All studies reported the age of participants (age range, 0 to 11 years), the sample size (ranged from 37 to 1,306), and the duration of the study (varied from 3 to 36 months). The delivery modalities of the agents included in the systematic review were sugarless mint confection, paste, gel, varnish, snacks, tablets and wipes (Table 1).

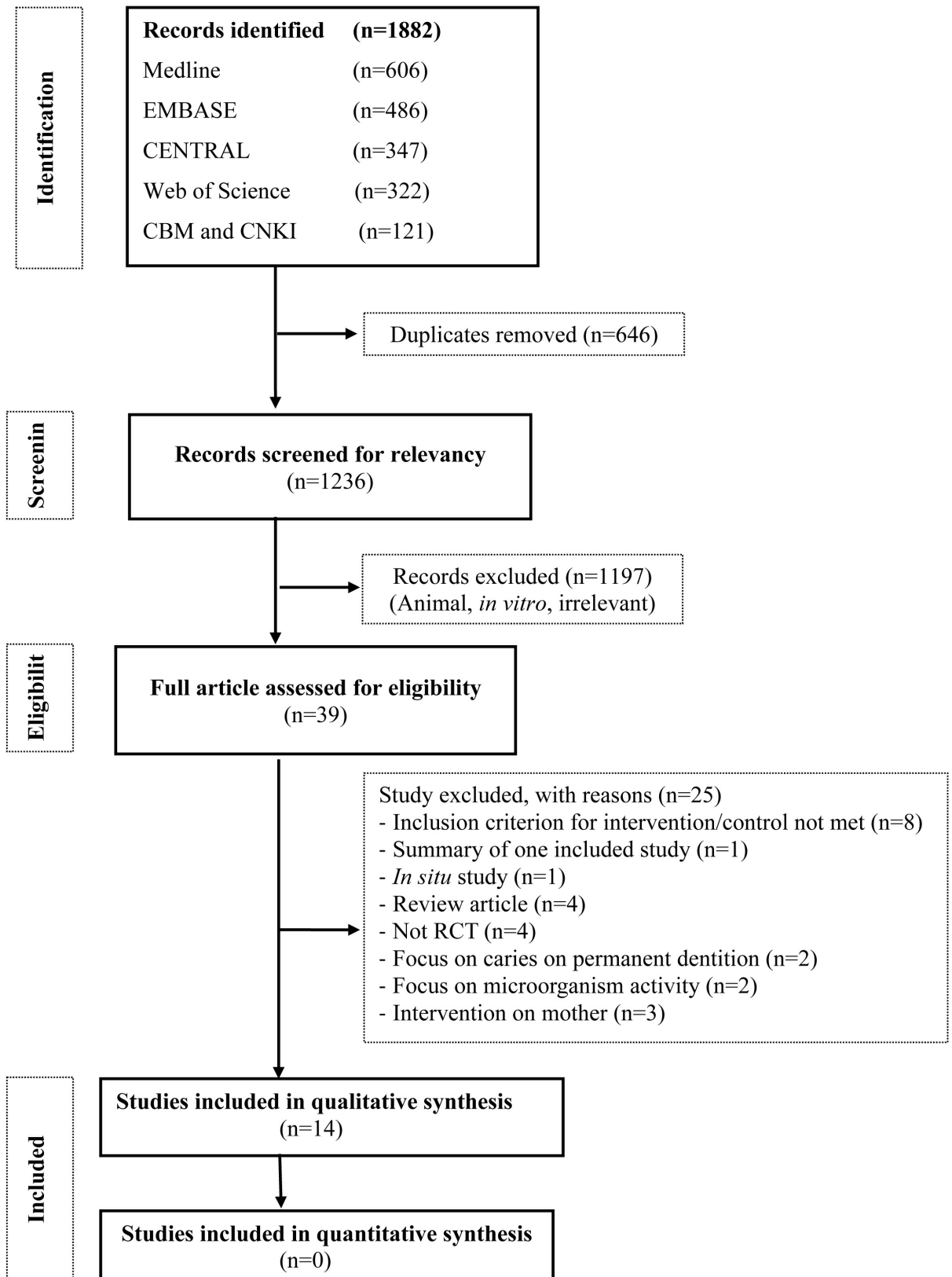
One study reported the topical application of arginine for the prevention of dental caries on primary molars [19]. Seven studies investigated the efficacy of chlorhexidine on the prevention of caries in primary dentition compared with other interventions [20–23,25,30,31]. Two studies compared the effect of daily application of CPP-ACP on dental caries in preschool children with fluoride varnish or placebo [24,26]. Three studies reported the anti-caries effect of xylitol in the form of wipes, tablets and snacks on caries progression in primary teeth [27–29]. One study assessed the clinical effect of the 0.3% triclosan varnish on caries prevention [32].

### Primary outcome of the studies

The primary outcome measures used in the 14 studies included clinical assessment using the International Caries Detection and Assessment System (ICDAS) criteria or dmfs/dmft index, clinical assessment for the white spot lesions and VPI (Visible Plaque Index), and bitewing radiography for approximal caries increment. No study used fluorescence-based assessments.

One study found arginine-containing mint confection significantly reduced caries development in primary molars compared with placebo after 6 months and 12 months [19].

Seven studies showed that chlorhexidine had caries-reducing potential in primary teeth [19–23,25,30,31]. However, there was conflicting evidence regarding the efficacy of chlorhexidine when used in conjunction with fluoride. One study found the combined application of chlorhexidine and low-dose fluoride did not significantly increase the caries-preventive effect compared with low-dose fluoride alone [20]. Another two studies reported the synergistic effect of chlorhexidine with fluoride in controlling the demineralization of primary dentition [21,23].



**Fig 1. Systematic review flow diagram.** (RCT = Randomized controlled trials).

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One study reported that the application of CPP-ACP mousse during the 12-month intervention period reduced the size of white spot lesions in the anterior primary teeth and was associated with smaller increase in dmft index values compared with placebo or fluoride varnish [24]. However, another study did not find the daily use of CPP-ACP paste was any better at controlling early childhood caries than low-fluoride toothpaste [20]. In addition, the daily application of 10% w/v CPP-ACP and fluoride toothpaste did not show synergism in preventing caries in the primary dentition of pre-school children [26].

Xylitol wipes (4.2g/d) were found to be effective in controlling dental caries in primary teeth [29]. However, a study that evaluated products containing low-doses of xylitol (0.5–1.0 g/tablet [27]) did not find any cariostatic activity. The daily application of xylitol gummy bears (7.8 g/d) did not provide additional benefit beyond regular oral hygiene [28].

One study indicated that 0.3% triclosan varnish was more effective than blank control in reducing caries incidence for children aged 2–5 years old during its one-year follow-up period [32].

## Secondary outcomes of the studies

Some studies included in the systematic review failed to report on the side effects of these non-fluoride agents [19,21,22,23,27,32]. Four studies presented information on the side effects of chlorhexidine varnish and gel. No serious side effects were reported during the 24-month observation period [20, 25, 30,31]. The use of 10% CPP-ACP paste was also found to have no adverse effects [24]. Another study of CPP-ACP paste failed to provide information on side effects [26]; the author was contacted by email and confirmed that no extra calculus formation had occurred on the primary teeth in their experimental group. In a 12-month trial of xylitol wipes, no side effects (including allergy, flatulence and diarrhoea) were reported by the parents [29]. No major side effects from the xylitol-containing gummy bears intervention was reported [28].

## Risk of bias

The risk of bias assessment revealed that only one study had a low risk of bias [29], three studies had an unclear risk of bias [23,30,31], and the remaining 10 were scored as high risk of bias [19–22,24–28,32] (Figs 2 and 3).

## Discussion

The current review systematically assessed the effect of non-fluoride agents compared with placebos and/or fluoride in the prevention of caries in primary dentition. Five non-fluoride agents were used in the included studies: arginine, chlorhexidine, CPP-ACP, triclosan and xylitol. The current research evidence is not sufficient to confirm that the use of these non-fluoride agents is more effective than placebo or fluoride for preventing dental caries in primary dentition.

One limitation of this systematic review is that the general quality of the currently available RCTs was not high. Of the 14 studies included in this review, only one study was assessed as having low risk of bias [29], and the others were graded either unclear or at high risk of bias. The most common risks of bias were selection bias and detection bias. Future trials should adopt a parallel group design that incorporates the use of randomization, blinding, as well as the allocation concealment method.

Meta-analyses are usually performed for studies with similar interventions and outcome measures. In this review, two studies on the effect of chlorhexidine varnish on dental caries in preschool children [30,31] were found to be homogeneous, however, they were conducted by

**Table 1. Summary of the included studies.**

Type of intervention	First Author (year)	Participants intervention/control (age)	Follow-up protocol	Intervention modality	Comparative/control	Assessment method	Primary outcome
Arginine	Acevedo, AM. (2008)	96/99 subjects (10.5-11y)	Baseline, 6, 12m	Confection containing CaviStat® + F toothpaste, 4 times a day	Control confection without CaviStat® + F toothpaste	defs scores	Test / control (Mean±SD) defs: 0m: 0.67±1.66 / 0.51±1.21 6m: 0.95±1.46 / 1.29±1.85 12m: 0.81±1.43 / 1.09±1.57
Chlorhexidine	Gisselsson, H. (1994)	59/58/116 subjects (4-7y)	Baseline, 3y	(1) 1% chlorhexidine gel, 4 times a year	(1) Placebo gel, 4 times a year (2) Control group (no treatment)	defs scores	Test/placebo/control (Mean ±SD) Baseline: 0.19/0.03/0.4 3 years: 2.78±3.27/4.57±4.04/4.6±4.86
	Tai, B.J. (2003)	440/451/415 subjects (3-7y)	Baseline, 2y	40% chlorhexidine varnish, once every 6 months	(1) Placebo varnish, once every 6 month (2) No treatment	defs scores/dmfs molar scores	Test/placebo/control (Mean ±SD) 3yrs group: Baseline: 2.98±4.72/4.20±5.86/4.6±4.86 2 years: 4.20±5.86/4.64±5.45/4.11±5.68 5yrs group: Baseline: 2.81±4.22/2.63±4.14/3.07±4.23 2 years: 3.81±4.58/4.24±4.93/4.9±5.2 6-7yrs group: Baseline: 0.25±0.75/0.41±0.85/0.3±0.93 2 years: 0.52±1.41/0.9±1.28/1.77±1.44
	Baca, P. (2004)	86/95 subjects (6-7y)	Baseline, 2y	(1) 1% chlorhexidine-thymol varnish, once every 3 months	Control group (no treatment)	dmft and dmfs scores	Test/ control (Mean±SD) dmfs: Baseline: 3.75±6.75/3.07±6.03 2y:(dft = 0 at baseline) 0.94 ±2.10/1.73±2.68 (dft>0 at baseline) 3.04±3.15/3.4±3.88
	Du, M.Q. (2006)	155/135 subjects (4-5y)	Baseline, 2y	40% chlorhexidine varnish, once every 6 months	Placebo varnish, once every 6 month	dmfs molar scores	Test/control (Mean±SD) dmfs-molar: Baseline: 2.8±0.3/2.6±0.4 2y:3.8±0.4/4.2±0.4
	Amorim, R.G. (2008)	18/19/20/19 subjects (3-5y)	Baseline, 3m	(1) Chlorhexidine varnish (2) Fluoride varnish (3) Chlorhexidine and fluoride varnish once every week, 4 times.	Control group (no treatment)	Clinical assessment was performed at 1 m and 3 m follow-up with VPI and WS scores	Test1/test 2/test 3/control (Mean ±SD) WS score (T1-T3): -0.89±1.45/-1.05±1.54/-1.4 ±2.21 / 0.37±1.01
	Plonka, K.A (2013)	183/171/188 subjects (6-24m)	6 m (baseline)/12 /18 /24 m	(1) Twice daily tooth-brushing + 0.12% chlorhexidine gel, once daily (2) Twice daily tooth-brushing + 10% CPP-ACP paste, once daily	No product+ twice daily tooth-brushing	Percentage of children with ECC/ MS/LB	Test 1/test 2/control Number with caries/Total (%) Test 1: 4/180 (2%) Test 2: 2/163 (1%) Control: 3/188 (2%)
	Pukallus, M.L. (2013)	61/58subjects(0-2y)	Newborn, 6/12/18/24 m	Twice daily low-dose fluoride toothpaste+ 0.12% chlorhexidine gel, once daily	Low-dose fluoride toothpaste tooth-brushing, twice daily	Percentage of children with ECC/ MS/LB	Test/control: Number with caries/Total (%) Test: 3/61 (5%) Control: 4/58 (7%) Children with MS: 28(46%)/27 (47%) Children with LB: 116(63%)/38 (66%)

(Continued)

Table 1. (Continued)

Type of intervention	First Author (year)	Participants invention/control (age)	Follow-up protocol	Intervention modality	Comparative/control	Assessment method	Primary outcome
CPP-ACP	Sitthisettapong, T. (2012)	117/112 subjects (2.5–3.5y)	Baseline, 6m, 1y	10% CPP-ACP mousse + fluoride toothpaste	Placebo toothpaste + fluoride toothpaste	Clinical assessment with ICDAS criteria	Test 1/ test 2/ control (Mean ±SD) Baseline to 12 month (No progression/ progression): OR: 1.002, 95%CI (0.86, 1.17)
	Memarpor, M. (2015)	30/29/31/32 subjects (1-3y)	Baseline, 4,8,12m	(1) Oral hygiene and CPP-ACP mousse, twice a day (2) Oral hygiene and 5% NaF vanish (3) Oral hygiene + diet counselling	Control (no treatment)	Change in mean WSL size and change in dmft index	Test 1/teat 2/control 1/control 2 Baseline to 12 m: -0.63±0.62/-0.51±10.56/-0.1±1.12/1.15±1.26 Dmft index: 12 m: 0.17±0.53/0.3±0.9/0.42±0.99/2±2
Triclosan	Cao, H.Z. (2007)	296/265 subjects (2–5 y)	Baseline, 1 y	0.3% triclosan vanish, twice a year	Control (no treatment)	Dmft and dmfs scores	Test/control (Mean ±SD) Dmft Baseline: 0.98±2.11/0.93±2.06 12m: 1.34±2.60/1.72±2.82 dmfs Baseline: 1.24±2.60/1.18±2.28 12m: 1.47±2.54/2.11±2.93
Xylitol	Oscarson, P. (2006)	55/63 subjects (2-4y)	Baseline, 24m	Xylitol tablet, once per day. Two tablet per day after 6 m. This intervention was terminated when children was 3.5 yrs old	No tablet	defs score and salivary MS level	Test/control Baseline: Number with caries/ total (%) Test: 4/66 (6%) Control: 4/55 (7%) 24m dmfs: 0.8±2.8 / 1.2±3.5
	Zhan, L. (2012)	20/17 subjects (6-35m)	Baseline, 3,6,12m	Xylitol wipe, 6 wipes daily+ tooth brushing	Placebo wipe	defs score and salivary MS and LB level	Number with caries/Total (%) Test: 1/20 (5%) Control: 6/17 (35%) MS level (Test/control): Baseline: 1.25±2.28/1.1±2.0 1yr: 1.25±2.63/3.38±2.75 LB level (Test/control): Baseline: 0.14±0.65/0.07±0.34 1yr: 0.11±0.48/0.53±1.21
	Lee, W. (2015)	122/138 subjects (5-6y)	Baseline, 30m	Xylitol gummy bear, 3 times per day	Placebo gummy bear	dmfs score	Test/control New d3-6mfs: 5.0±7.6/4.0±6.5 New d1-6mfs: 5.7±7.6/4.7±6.7

CaviStat®: an arginine bicarbonate calcium carbonate complex; WS: white spot; WSL: white spot lesion; F: fluoride; defs: decayed, extracted, filled surfaces; dmfs: decayed, missing, filled surfaces; dmft: decayed, missing, filled tooth; VPI: Visible Plaque Index; ECC: Early Childhood Caries; MS: mutans streptococci; LB: lactobacilli; ICDAS: The International Caries Detection and Assessment System; m: month; y: year.

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the same group of authors and on the same patient population. Thus meta-analyses could not be carried out due to publication bias.

Another important concern is that some of the studies included in the review did not present information concerning adverse effects [19,21,22,23,27,32]. For example, xylitol has been found to cause side effects such as bloating, flatulence and diarrhoea [17]; chlorhexidine sometimes causes staining of the teeth and tongue, mucosal soreness and desquamation, temporary taste disturbances, parotid gland swelling and hypersensitivity [33,34]. Thus safety assessments should be considered as an essential part of a well-designed RCT.

Arginine-containing products have been found to provide significant benefits in managing dental caries in previous studies [35,36]. In this review, an RCT investigating CaviStat [19], which contains arginine, and which was incorporated into a sugarless mint confection,



	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Acevedo, A.M 2008	?	?	?	+	?	-	?
Amorim, R. G 2008	?	?	-	?	?	?	+
Baca, P 2004	?	?	-	-	?	+	-
Cao, H.Z 2007	?	?	-	+	?	?	?
Du, M. Q 2006	+	?	+	+	?	+	+
Gisselsson, H 1994	?	+	+	?	?	?	+
Lee, W 2015	+	?	+	+	+	+	-
Memarpour, M 2015	+	?	-	+	+	+	?
Oscarson, P 2006	?	?	-	+	-	?	?
Plonka, K.A 2013	+	?	-	+	+	+	+
Pukallus, M. L 2013	+	?	-	+	-	+	-
Sitthisetapong, T 2012	-	+	+	+	+	+	-
Tai, B.J 2003	?	?	?	+	+	+	?
Zhan, L 2012	+	+	+	+	+	+	+

Low risk of bias  
 Unclear risk of bias  
 High risk of bias

**Fig 2. Risk of bias summary.**

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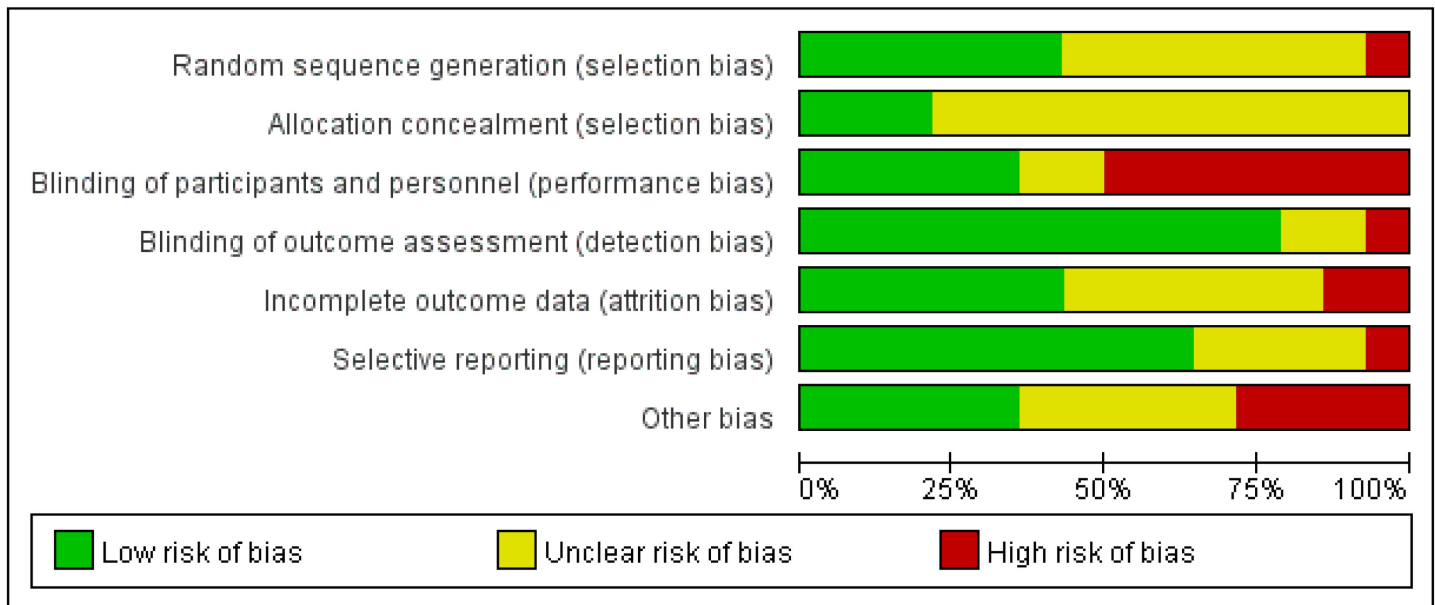


Fig 3. Levels of bias types.

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appeared to be effective in reducing caries development and progression in primary teeth. However, this was the only study in this review to meet the inclusion and exclusion criteria and this study was scored as having high risk of bias. Thus, well-designed clinical studies are still required to provide adequate evidence on the effect of arginine on primary dentition.

Fluoride is generally known to promote remineralization, but the use of fluoride alone has been reported to be insufficient to prevent progressive mineral loss [1]. Chlorhexidine, a cationic bis-biguanide with a broad spectrum of antibacterial activity, has been well recognized as a chemotherapeutic agent active against *Streptococcus mutans*, which plays a major role in tooth decay [16]. Several clinical trials and *in vitro* studies have demonstrated that combination treatment with chlorhexidine and fluoride is effective in caries reduction [37–41]. However, the synergistic effect of chlorhexidine and fluoride is still unclear [25]. This synergistic effect between chlorhexidine and fluoride were not supported by all clinical trials[20], although in Plonka’s study[20] the caries rate in the intervention and control groups were both very low (For details, see Table 1).

Numerous studies have demonstrated the anti-caries effect of CPP-ACP by promoting remineralization and inhibiting demineralization [42,43]. They also reported that CPP-ACP was effective in repairing the microstructure of enamel through significantly increased hydroxyapatite crystal size and calcium/ phosphorus mol ratios. The result is in agreement with a recent review, which indicated a long-term remineralization efficacy of CPP-ACP on carious lesions [44]. The advantage of using CPP-ACP as the agent rather than fluoride, however, is still unclear. Since fluoride-containing toothpastes are now widely used for daily oral hygiene, it is recommended that future RCTs consider using fluoride as a control.

As a non-cariogenic sweetener, the cariostatic effect of xylitol on primary dentition has been investigated in several clinical studies [45,46]. Its anti-caries effect remains controversial according to this review. One reason for this may be the dose-effect relationship. It has been found that exposure to at least 4g xylitol/day is necessary to be clinically effective [47,48] The low xylitol dose (0.5-1g/tablet), which was used in one study [27] included in the review, did not prevent caries in primary teeth. Other reasons for the inconclusive results are the limited

sample sizes. The study that evaluated the effects of xylitol-containing wipes found that the daily application of xylitol (4.2g/day) was useful in controlling caries in preschool children [29], however, the sample size was 20 or fewer for each group, hence, the conclusion should be interpreted with caution.

The effectiveness of administering these non-fluoride agents, *e.g.* daily topical toothpaste, may be influenced by patient compliance, especially in children who usually show relatively poor cooperation compared to adults [49]. Delivery vehicles that are less patient-dependent, such as varnishes that are applied by professionals, have been shown to be effective in children [13,22,24,30]. In addition to the therapeutic agents included in the review, other non-fluoride agents, such as bioactive glass, pit and fissure sealants and resin infiltration, have also been extensively studied [50–52]. However, those studies did not meet the inclusion criteria for this review, because most of them either focused on the caries-preventive effect on permanent teeth or were not RCTs. High quality RCTs on the preventive effect of non-fluoride agents in primary dentition are still required.

The follow-up period of the studies included in the review varied from 3 to 36 months. Although the duration of the clinical trials involving cariostatic products should, according to the consensus statement by the International Consensus Workshop on Caries Clinical Trials [53], be sufficient to observe the progression of carious lesion development (2 to 3 years), the participants in the studies on the preventive measures for dental caries in primary dentition were all children; and mostly they were caries-active. Considering that primary teeth are more prone to carious lesion progression, the observation period could be relatively shorter for primary dentition than for permanent dentition. Previous studies have demonstrated a follow-up period should be for at least three months [42,44]. However, studies show that the anti-caries effects of non-fluoride agents were not stable over time. It has been found that using chlorhexidine-containing varnishes resulted in early reductions in mutans streptococci (MS) levels at 3 and 6 months in the permanent dentition, but this effect was not sustained after longer periods of follow-up at 12, 24 and 36 months [54]. Similarly, another study also showed no reduction in the MS level in mothers after xylitol-gum use for 2 years [55]. These results could be due to the development of MS resistance to chlorhexidine/xylitol over time. Although the MS level is a proxy outcome, it is unclear how reductions would translate into any effect on caries prevention. Considering the influence of time, an adequate follow-up period should be employed to reveal all the potential effects, both beneficial and detrimental, of the intervention method.

A number of non-invasive methods have been developed as potential diagnostic aids for clinicians, for example, quantitative light-induced fluorescence (QLF), a system based on the measurement of fluorescence loss following enamel demineralization [56]. This method has shown high sensitivity and specificity in detecting caries lesions [57,58,59]. Optical Coherence Tomography (OCT) is another non-invasive imaging technique that constructs high-resolution cross-sectional images of internal biological structures [60]. Previous studies have shown that OCT has the potential to detect, and quantify, demineralization in *in vitro* caries-like models [61,62]. Photothermal radiometry and modulated luminescence (PTR/LUM), commercially marketed as the Canary System<sup>®</sup> (Quantum Dental Technologies, Toronto, Ont., Canada) is based on the combination of two slightly different responses of the tooth tissues from a periodic irradiation with a pulsating laser beam [63]. The Canary System has demonstrated a greater accuracy in detecting proximal lesions than International Caries Detection and Assessment System (ICDAS) II and bitewing radiography (BW) [64]. Moreover, the Canary System also serves as a clinical tool to detect and monitor the status of caries lesions and tooth structure underneath sealant [65]. These new methods serve as supplemental aids to traditional visual examination (*e.g.* the World Health Organization method) and have been generally considered to have high accuracy but low repeatability between different examiners [66].

However, all the studies included in this review used only traditional methods for detecting and monitoring dental caries. It would be beneficial in future studies to use a combination of the traditional and electronic diagnosis methods to investigate the initiation, progression and reversal of dental caries [66].

## Conclusion

A study at low risk of bias indicated that daily use of xylitol wipes is a useful adjunct for caries control in young children; however, this conclusion should be interpreted with caution as this study had a very limited sample size (20/17). Chlorhexidine and CPP-ACP may be more effective than placebo in managing caries in primary dentition, but their efficacy relative to fluoride is still unclear. Arginine-containing mint confection and 0.3% triclosan varnish were found to reduce caries development in primary teeth but the evidence was at high risk of bias. High quality randomized controlled trials are needed to make a definitive recommendation.

## Supporting information

**S1 File. Search strategies.** Table A in S1 File. Search strategy for Medline via PubMed. Table B in S1 File. Search strategy for EMBASE. Table C in S1 File. Search strategy for Cochrane library. Table D in S1 File. Search strategy for Web of Science. Table E in S1 File. Search strategy for CBM. Table F in S1 File. Search strategy for CNKI.

(DOCX)

**S1 Table. PRISMA 2009 checklist.**

(DOCX)

**S2 Table. Articles excluded from this review.**

(DOCX)

**S3 Table. Risk of bias in included studies.**

(DOCX)

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