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Professionally Applied Topical Fluoride for Caries Prevention in Children and Adolescents: A Systematic Review and Network Meta-analysis

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Abstract

Objectives

To evaluate, through a systematic review and network meta-analysis, the effectiveness of professionally applied topical fluoride agents in preventing dental caries in children and adolescents aged ≤18 years with a minimum follow-up of 1 year.

Methods

A network meta-analysis was conducted using data from randomised controlled trials evaluating professionally applied topical fluoride agents for caries prevention in children and adolescents, using a frequentist random-effects model. Interventions included fluoride varnish, gel, foam, SDF, and fissure sealant, with the latter retained as an active non-fluoride comparator. Separate networks were constructed by outcome and dentition type. Risk of bias was assessed using the RoB 2. Sensitivity analysis was performed. Confidence in network estimates was assessed using CINeMA.

Results

Forty randomized trials involving 26,382 participants were included, of which 11 studies contributed to at least one network or supplementary quantitative analysis. High risk of bias was assessed in 12 trials. In the permanent dentition, fluoride varnish demonstrated the largest reduction in caries increment versus inactive control among topical fluoride agents, followed by APF gel. Fissure sealant ranked highest overall but was interpreted separately as a non-fluoride comparator. CINeMA confidence ranged from low- to-moderate.

Conclusions

Among topical fluoride agents, FV showed the most favourable estimate compared with inactive control in the permanent dentition/first permanent molar continuous outcome network

Overall, the findings favoured active preventive interventions, but interpretation should remain cautious because several estimates were based on sparse, single-study, or indirect evidence.

Clinical significance

Professionally applied topical fluoride agents generally favoured caries prevention compared with inactive control.

1 INTRODUCTION

Dental caries remains one of the most common preventable diseases affecting children and adolescents worldwide. According to the Global Burden of Disease (GBD) 2021 estimates, untreated caries in permanent teeth continues to be the most common health condition. The World Health Organization reports that oral diseases affect over 3.5 billion people worldwide [1]. Furthermore, current GBD data show that between 1990 and 2019, the incidence of caries in permanent teeth increased by 15.25% among children aged 5 to 14 years [2]. The necessity of effective caries prevention throughout childhood and adolescence, encompassing primary, mixed, and permanent dentitions, is further supported by this ongoing burden.

The effect of early childhood caries goes beyond the tooth level. Caries affecting primary teeth is a key risk predictor of future caries experience in permanent teeth, and may result in toothache, oral infection, sleep disturbance, compromised chewing, impaired growth, poorer oral health-related quality of life [3]. Preventive interventions delivered early in life through community or school-based programmes are therefore essential to paediatric oral health care.

Professionally applied topical fluoride is still considered the primary non-invasive treatment method for the prevention of dental caries in individuals under 18 years. It acts by suppressing the demineralization and stimulating remineralization at the tooth-surface level [4, 5]. Professionally applied topical fluoride agents include fluoride varnish, fluoride gels, fluoride foams, fluoride solutions and silver diamine fluoride. These agents differ in fluoride concentration, cost, acceptability, technique of application, application time, mechanism of action, safety considerations, and suitability for preschool, school-based, or community programmes [5–8].

Evidence from a Cochrane review support the preventive effectiveness and safety of fluoride-based topical agents. Fluoride varnish application when compared with placebo or no treatment, showed caries reductions of 43% in permanent teeth and 37% in primary teeth [6].

Although there is consistent evidence that topical fluoride agents prevent caries, a clinically relevant question remains less clearly answered: which agent is most appropriate in different patient-care contexts? Previous evidence syntheses have largely focused on whether individual agents are effective compared with placebo, no intervention, or routine care. However, such conventional pairwise comparisons support the overall role of topical fluoride but offer limited information and insufficient guidance to oral health professionals and policymakers when choosing between fluoride varnish, fluoride gel, fluoride foam, fluoride mouth rinse and other available options [6–8].

Network meta-analysis is therefore methodologically appropriate to address this evidence gap because it pools direct and indirect evidence within a connected network of randomised trials and facilitates concurrent comparison of several fluoride agents to determine their relative effectiveness. However, for reliable evidence we need careful clinical and methodological assessment across studies, and the assumptions of transitivity and consistency [9, 10]

This systematic review and network meta-analysis aimed to compare the effectiveness of topical fluoride agents for preventing dental caries in children and adolescents aged up to 18 years, based on evidence from randomised controlled trials. It sought to move beyond the established question of whether topical

fluoride is effective and to examine the relative effectiveness of currently used topical fluoride agents across primary, mixed, and permanent dentitions.

2. Materials and methods

2.1 Protocol Registration

This systematic review and meta-analysis was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and reported in accordance with the PRISMA 2020 statement and the PRISMA extension for network meta-analysis [11–13]. The protocol was prospectively registered in the PROSPERO database to ensure transparency and reproducibility in the methodology.

2.2 Eligibility criteria

Eligibility criteria were defined according to the PICOS framework [11, 12].

2.2.1 Inclusion criteria

Randomized, cluster-randomized controlled, split- randomized controlled trials evaluating topical fluoride agents for caries prevention in children and adolescents aged ≤ 18 years were eligible. Only English-language, peer-reviewed RCTs available as full-text publications were considered. Geographical location was not regarded as a constraint.

Eligible interventions comprised fluoride varnish, sodium fluoride gel, acidulated phosphate fluoride gel, acidulated phosphate fluoride foam, amine fluoride preparations, and silver diamine fluoride. Silver diamine fluoride was considered eligible only when it was used to prevent new caries lesions or when outcomes were reported as caries incidence or caries increment. Self-applied fluoride interventions were included only where they contributed to a clinically comparable preventive network; otherwise, they were summarised narratively.

Eligible comparators were placebo, no treatment, usual care, oral health education alone, another topical fluoride agent, or resin fissure sealant. The primary outcome was caries increment assessed using dentine-level or cavitated caries indices after a minimum follow-up of 12 months. Continuous outcomes were eligible when reported as dmfs/dmft, DMFS/DMFT, DFS, or equivalent cavitated caries increment measures. Secondary outcomes included caries incidence, fissure or occlusal caries incidence, caries-free status, and enamel-level outcomes assessed using ICDAS

2.2.2 Exclusion criteria

We excluded non-randomized studies, observational studies, case reports, case series, reviews, editorials, review articles, commentaries, animal studies, in vitro studies, conference abstracts without extractable data. Studies with follow-up shorter than 12 months were also excluded. Studies evaluating unrelated non-fluoride preventive agents were excluded.

Studies reporting only enamel-level D_1/D_2 lesions, ICDAS 1–2, QLF outcomes, microbiological outcomes, plaque outcomes, or caries-arrest-only outcomes were excluded from the primary network and analysed separately or narratively. Studies that only reported adjusted estimates (without raw data), categorical outcome measures, or those that did not report mean differences or provide adequate data (mean and standard deviation or data convertible to these measures) were also excluded from the meta-analysis [11].

2.3 Information sources and search strategy

Human RCTs were identified were identified by searching MEDLINE via PubMed, Embase, Scopus, Cochrane CENTRAL, and Google Scholar from inception to April 2026. Additional studies were identified through manual review of reference lists of relevant studies and systematic reviews. Trial registries and grey literature sources were also searched to identify unpublished or ongoing trials.

The search strategy combined indexed Medical Subject Headings (MeSH) and free-text terms together with Boolean operators (AND and OR) consisting of relevant text words related to population (children and adolescents up to 18 years with primary/permanent dentition), intervention (topical fluoride agent), comparison (placebo, other topical fluoride alternatives, or no intervention), outcome (dental caries), and study design (randomized controlled trials). Full search strategy is provided in Supplementary Table 4.

2.4 Study selection and data extraction

All retrieved records were imported into reference-management software, duplicates were removed, and screening was performed using Rayyan [14]. Two reviewers (K.P.R. and S.K.C.) independently screened titles and abstracts, followed by full-text assessment of potentially eligible studies. Disagreements were resolved through discussion or consultation with a third reviewer (A.S.). Reasons for full-text exclusion were recorded and summarised in the PRISMA flow diagram [12].

Studies meeting the broader eligibility criteria were included in the systematic review. Inclusion in the network meta-analysis required treatment-node connectivity, compatible preventive outcomes, and sufficient clinical comparability [9–11, 13]. Studies with important differences in diagnostic threshold, outcome format, intervention intent, dentition type, or co-intervention context were retained for supplementary, sensitivity, or narrative synthesis.

Data were extracted independently using a standardised extraction form. The extracted information included study author, year, country, design, setting, participant age, dentition type, sample size, intervention and comparator details, follow-up duration and quantitative outcome data.

For continuous outcomes, sample size, mean caries increment, and standard deviation were recorded. For dichotomous outcomes, the number of events and total analysed were extracted according to the unit reported in the original study. Where adjusted estimates were reported, effect estimates with standard errors or 95% confidence intervals were extracted [11].

When duplicate or secondary reports described the same trial population, the report with the longest follow-up or most complete outcome data was used. Multi-arm trials were handled under a single study identifier to avoid duplication of shared comparator groups [11, 13].

2.5 Dealing with missing data

When data were unclear or incomplete, corresponding authors were contacted where feasible. Missing numerical data were managed according to the Cochrane Handbook for Systematic Reviews of Interventions. Where appropriate, numerical values were estimated from graphical data [11].

2.6 Risk-of-bias (ROB)/quality assessment

Two investigators (K.P.R. and S.K.C.) independently assessed the risk of bias of all included randomized, cluster-randomized, and split-mouth randomized trials using the Cochrane RoB 2 tool [15]. For cluster-randomized trials, relevant cluster-specific considerations were applied. Risk of bias was assessed across five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Disagreements were resolved by discussion, with arbitration by a third reviewer (A.S.) when required.

2.7 Treatment node classification

Treatment nodes were defined a priori according to fluoride compound, formulation, delivery vehicle, application frequency, preventive intent, and clinical comparability. This approach was used to preserve clinical interpretability and support the transitivity assumption required for network meta-analysis [9–11, 13].

Fluoride varnish and sodium fluoride gel were retained as separate nodes because they differ in delivery vehicle, retention time, application protocol, and clinical use. Similarly, APF gel and APF foam were analysed as separate nodes.Fissure sealant was interpreted as an active non-fluoride comparator and was not included in the ranking of topical fluoride agents. Placebo, no treatment, usual care, oral health education, and counselling-only arms were grouped as inactive control when no active topical fluoride or sealant was delivered.

Combination or multicomponent interventions were assigned to a treatment node only when the active preventive component was clearly identifiable and clinically comparable across studies [11, 13].

Node	Definition
FV	Fluoride varnish, including sodium fluoride varnish
APF gel	Acidulated phosphate fluoride gel
APF foam	Acidulated phosphate fluoride foam
NaF gel	Sodium fluoride gel
AmF	Amine fluoride
SDF	Silver diamine fluoride, prevention-oriented studies only
FS	Resin fissure sealant, active non-fluoride preventive comparator
Inactive Control	Placebo, no treatment, usual care, reference care, or oral health education alone

2.8 Data synthesis and statistical analysis

2.8.1 Pairwise meta-analysis

Pairwise meta-analysis was performed when at least two clinically comparable studies evaluated the same intervention and comparator using a similar outcome structure. Pairwise meta-analyses were conducted using Review Manager 5.3. Heterogeneity was assessed using the I^2 statistic, and a random-effects model was used where clinical or methodological heterogeneity was expected [11].

For continuous outcomes, standardised mean differences (SMDs) with 95% confidence intervals were used when different but conceptually related caries increment indices were combined. Mean differences (MDs) were used in sensitivity analyses where studies reported sufficiently comparable dmfs/dmft increment data. For dichotomous outcomes, risk ratios (RRs) with 95% confidence intervals were used. Negative SMD or MD values indicated lower caries increment favouring the intervention.

2.8.2 Network meta-analysis

Network meta-analysis was performed to compare topical fluoride agents and active preventive comparators within connected networks. Analyses were conducted only when studies were clinically comparable and sufficiently connected to support transitivity [9–11, 13].

Continuous and dichotomous outcomes were analysed separately. Continuous caries increment outcomes were analysed using SMD when different but related indices were combined. Dichotomous outcomes, including caries incidence or caries-free status, were analysed using RR or OR, as appropriate.

Analyses were performed in R version 4.6.0 using the netmeta package [16]. A frequentist random-effects model was used where clinical or methodological heterogeneity was expected [11, 16]. Because a frequentist network meta-analysis framework was used, Bayesian prior distributions were not applicable. Network plots showed treatment nodes and direct comparisons, while league tables presented relative treatment effects [16]. Multi-arm trials were handled to account for within-study correlations and avoid double counting [11, 13]. P-score rankings were interpreted alongside effect estimates, confidence intervals, heterogeneity, inconsistency, transitivity, and certainty of evidence [17, 18].

2.8.3 Assessment of transitivity and inconsistency

Transitivity was assessed by comparing key clinical and methodological factors across treatment comparisons, including age, dentition type, baseline caries risk, fluoride agent, application frequency, follow-up duration, diagnostic criteria, co-interventions, and risk of bias [9–11, 13].

Inconsistency was assessed only where closed loops were available. Because the networks were sparse and several comparisons were based on single studies or indirect evidence, formal inconsistency testing was limited. Where statistical testing was not possible, inconsistency was assessed descriptively using network geometry and clinical comparability [10, 11, 13].

2.9 Sensitivity and subgroup analyses

Sensitivity analyses were conducted to examine whether the main findings were robust to important clinical or methodological differences [11]. For the primary dentition pairwise meta-analysis, the high-frequency quarterly fluoride varnish study by Latifi-Xhemajli et al. was excluded because its application schedule differed from the remaining studies and contributed to heterogeneity. The analysis was repeated using both random-effects and fixed-effect models.

For permanent dentition/first permanent molar continuous outcomes, a sensitivity analysis restricted to topical fluoride agents was performed after excluding resin fissure sealant, as it is a non-fluoride physical barrier comparator. Because each comparison was informed by a single study, results were summarised descriptively.

Formal subgroup meta-analysis was not performed because most categories included too few studies or single-study comparisons. Instead, analyses were stratified a priori by dentition type and outcome format.

2.10 Certainty of evidence

Confidence in the network meta-analysis estimates was evaluated using the CINeMA framework, across six domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence. Ratings were summarised as high, moderate, low, or very low. Incoherence was interpreted cautiously when networks were sparse or closed loops were unavailable. Treatment rankings were not graded as independent evidence and were interpreted alongside effect estimates, confidence intervals, and CINeMA ratings [17, 18].

3 RESULTS

3.1 Study selection and study characteristics

The comprehensive electronic search identified 2017 records across the selected databases, registers and other sources. Of these, 1202 duplicate records were removed. Subsequently,121 studies were considered potentially relevant and underwent full-text evaluation. A total of 81 studies were excluded for various reasons. Finally,40 randomized, cluster-randomized, or split-mouth randomized trials [19–58] met the inclusion criteria and were selected for qualitative analysis. Of these, 11 studies [20, 25, 26, 31, 36, 39, 43–45, 52, 53] were included in at least one quantitative network or supplementary comparative analysis. (Fig. 1). The included studies recruited a total of 26,382 participants. The study population included children and adolescents across primary, mixed, and permanent dentitions. Interventions included fluoride varnish, sodium fluoride gel, APF gel, APF foam, amine fluoride solution, silver diamine fluoride, and fissure sealants as active non-fluoride comparators. Comparator groups included placebo, no treatment, usual care, oral health education or counselling alone, and active preventive comparators. Detailed characteristics of all the included studies are presented in Table 1

Table 1

Characteristics of included randomized and cluster-randomized trials evaluating professionally applied topical fluoride agents for caries prevention in childre

Study (Year)	Country	Design	Population / dentition	Age at baseline	Sample size analysed, n (IG/CG)	Intervention	Comparator	Follow-up (months)	O
Agarwal et al., 2022 [19]	India	Cluster RCT	Preschool children	3–4 y	392 (196/196)	FV	Placebo	36	C (I
Agouropoulos et al., 2014 [20]	Greece	RCT	Preschool children	2–5 y	328 (174/154)	FV + OHE + FTP	Placebo	24	C (c
Agrawal et al., 2011 [21]	India	Cluster RCT	Mixed dentition; high-caries-risk children	9–16 y	257 (130/127)	APF gel + OHE	OHE	12	C (D
Anderson et al., 2016 [22]	Sweden	Cluster RCT	High-risk toddlers	1 y	2536 (1231/1305)	FV + OHE	Control	24	C (I
Arruda et al., 2012 [23]	Brazil	RCT	Children/adolescents; permanent dentition	6–14 y	210 (113/97)	FV	Placebo	12	C (I
Brambilla et al., 1997 [24]	Italy	RCT	Children; first permanent molars	6 y	248 (128/120)	AmF	Placebo	60	C (D
Bravo et al., 1997/2005 [25]	Spain	Cluster RCT	Children; first permanent molars	6–8 y	314 (FS/FV/control: 100/98/116)	FS; FV	Control	24; 108	C (D
Chestnutt et al., 2017 [26]	UK	RCT	Children; first permanent molars	6–7 y	835 (417/418)	FS	Active comparator	36	C (I
Gugwad et al., 2011 [27]	India	RCT	Mixed dentition children	6–7 y	211 (106/105)	FV	Control	12	C (c
Hardman et al., 2007 [28]	UK	Cluster RCT	Mixed dentition children	6–8 y	664 (334/330)	FV	Control	26	C (c
Holm et al., 1984 [29]	Sweden	RCT	Children; first permanent molars	5 y 9 mo	109 children (50/59); 381 molars (166/215)	FV	Control	24	C (F
Honkala et al., 2015 [30]	Kuwait	Split-mouth RCT	Children; primary molars	4–5 y	106 children; 267 matched pairs	FS	Active comparator	12	C (I
Jiang et al., 2005 [31]	China	Cluster RCT	Children; first permanent molars	6–7 y	612 (APF foam/APF gel/control:191/200/221)	APF foam; APF gel	Control	24	C (D
Jiang et al., 2014 [32]	Hong Kong	RCT	Preschool children	8–23 mo	415 (Control/OHE/FV + OHE: 134/144/137)	FV + OHE	OHE	24	C ai
Johnston et al., 1995 [33]	Canada	RCT	Mixed dentition children	6–7;10–11 y	329 (frequency: 168/161; prophylaxis: 182/147)	APF gel	Active comparator	36	C (c
Khairnar et al., 2026 [34]	India	RCT	Children; first permanent molars	6–8 y	84 children; 330 teeth (163/167)	FV	Active comparator	24	C (I
Lam et al., 2024 [35]	Hong Kong	RCT	Preschool children; primary second molars	3–4 y	479 (NaFV/GIS: 254/225)	FV	Active comparator	18–24	C (I
Latifi-Xhemajli et al., 2019[36]	Kosovo	RCT	Preschool children	Mean 21 mo	427 (218/209)	FV	Control	24	C ai
Lawrence et al., 2008 [37]	Canada	Cluster RCT	Preschool children	6 mo-5 y	1275 (915/360)	FV + OHE	OHE	24	C ai
Linčir et al., 1993 [38]	Croatia	RCT	Preschool children	3–4 y	199 (55/53/61/30)	AmF	Placebo	24	C (c
Liu et al., 2012 [39]	Hong Kong	RCT	Children; first permanent molars	Mean 9.1 y	485 (FS/FV/SDF/control: 121/116/121/124)	FS; FV; SDF	Placebo	24	C (I
Manchanda et al., 2024 [40]	Hong Kong	RCT	Preschool children	3–4 y	135 (45/45/45)	FV	Active comparator	24	C ai
Mellberg et al., 1978 [41]	USA	RCT	Permanent dentition children	9–12 y	1235 (255/227; 193/184; 190/186)*	APF gel	Control	12	C (D
Milsom et al., 2011 [42]	UK	Cluster RCT	Children; first permanent molars	7–8 y	2967 (1473/1494)	FV	Control	36	C (D
Muñoz-Millán et al., 2018 [43]	Chile	RCT	Preschool children	2–3 y	275 randomized (131/144); 189 completed (89/100)	FV	Placebo	24	C ai

Study (Year)	Country	Design	Population / dentition	Age at baseline	Sample size analysed, n (IG/CG)	Intervention	Comparator	Follow-up (months)	O
Oliveira et al., 2014 [44]	Brazil	RCT	Preschool children	1–4 y	181 (89/92)	FV	Placebo	24	C a
Seppä et al., 1995 [45]	Finland	RCT	Permanent dentition children	12–13 y	254 (125/129)	FV	Active comparator	36	C (D
Sirivichayakul et al., 2023 [46]	Thailand	RCT	Primary dentition;	4–6 y	155 (placebo/FV/SDF: 52/53/50)	FV; SDF	Placebo	18	R ca
Sköld et al., 2005 [47]	Sweden	RCT	Permanent dentition adolescents	13–16 y	758 (190/186/201/181)	FV	Control	36	R ca
Slade et al., 2011 [48]	Australia	Cluster RCT	Preschool children	18–47 mo	543 (281/262)	FV + OHE	Control	24	C a
Souza et al., 2021 [49]	Brazil	RCT	Children; permanent smooth surfaces	6–8 y	60 (TiF4/NaF/placebo: 20/20/20)	FV	Placebo	18	Q pl
Tickle et al., 2017 [50]	UK	RCT	Preschool children	2–3 y	1096 (549/547)	FV + OHE + FTP	OHE	36	C a
Uhlen-Strand et al., 2024 [51]	Norway	Split-mouth RCT	Children; first permanent molars	6–10 y	369 children; split-mouth tooth-pair design	FS	Active comparator	36	B o
van Rijkom et al., 2004 [52]	Netherlands	RCT	Mixed dentition children	4.5–6.5 y	732 (372/360)	NaF gel	Placebo	48	C (D
Wang et al., 2022 [53]	China	Cluster RCT	Children; first permanent molars	6–7 y	5005 (2385/2620)	FV + OHE	OHE	24	C a
Weinstein et al., 2009 [54]	USA	RCT	Preschool children	36–71 mo	600 (294/306)	FV	Active comparator	36	C (p su
Weintraub et al., 2006 [55]	USA	RCT	Preschool children	6–44 mo	376 (annualV/biannual FV/control:24/126/126)	FV + OHE	OHE	24	C a
Zheng et al., 2023 [56]	Hong Kong	RCT	Primary dentition; upper anterior teeth	3–4 y	434 (209/225)	SDF	Active comparator	12	C (c
Zheng et al., 2026 [57]	Hong Kong	RCT	Primary dentition; upper anterior teeth	3–4 y	621 (307/314)	SDF	Active comparator	30	C (c
Zimmer et al., 1999 [58]	Germany	RCT	Permanent dentition schoolchildren	Age NR	253 (110/143)	FV	Control	24	C (D D

3.2 Risk-of-bias assessment in studies

Cochrane RoB 2 tool was used for Risk of bias assessment for 40 randomised studies (Fig. 2). Overall, 10 studies were judged to be at low risk of bias, 18 raised some concerns, and 12 were assessed as having a high risk of bias. The observation of high risk of bias was mainly attributed to concerns in the randomization process, missing outcome data, and measurement of outcome domains. Some concerns were observed across several studies, mainly due to unclear reporting of randomization procedures, missing outcome data, outcome measurement, or selection of the reported result. Figure 2 illustrates the domain-wise and overall risk-of-bias judgments across all included studies.

3.3 Network geometry

Separate evidence networks were constructed according to dentition type and outcome format to avoid clinically inappropriate pooling of heterogeneous outcomes [11, 13].

For permanent dentition/first permanent molar continuous outcomes, the network included six nodes: fluoride varnish, APF gel, APF foam, NaF gel, fissure sealant, and inactive control. The network was connected but sparse, with most interventions linked through control and several direct comparisons informed by single studies.

For primary dentition continuous outcomes, the network included three nodes: fluoride varnish, NaF gel, and inactive control. Both fluoride varnish and NaF gel were directly compared with inactive control, while the comparison between fluoride varnish and NaF gel was informed indirectly.

For permanent dentition binary outcomes, the network included fissure sealant, fluoride varnish, silver diamine fluoride, and inactive control. The network was connected, but direct comparative evidence was limited. For primary dentition binary outcomes, only a two-node comparison of fluoride varnish versus inactive control was available; therefore, this outcome was interpreted as direct pairwise evidence rather than network meta-analysis.

3.4 Network meta-analysis of continuous outcomes

Continuous caries increment outcomes were analysed separately for primary dentition and permanent dentition outcomes because of differences in dentition type and clinical comparability.

The primary dentition continuous network included five studies [20, 36, 43, 44, 52] and three nodes: fluoride varnish, NaF gel, and inactive control. Fluoride varnish was directly compared with inactive control in four studies [20, 36, 43, 44], whereas NaF gel was informed by a single direct comparison [52]. The primary dentition network plot is presented in Supplementary Fig. 3. Because this network was sparse, the findings were interpreted as supportive rather than definitive comparative evidence.

The permanent dentition/first permanent molar continuous network included four studies [25, 31, 45, 52] and six nodes: fluoride varnish, APF gel, APF foam, NaF gel, fissure sealant, and inactive control. The network was connected but sparse, with several direct comparisons informed by single studies. The network plot is shown in Fig. 3.

In the NMA estimates versus inactive control, all topical fluoride agents favoured lower caries increment (Fig. 4). Among the topical fluoride agents, fluoride varnish showed the largest reduction in caries increment (SMD − 0.35, 95% CI − 0.55 to − 0.15), followed by APF gel (SMD − 0.17, 95% CI − 0.32 to − 0.03). APF foam (SMD − 0.15, 95% CI − 0.31 to 0.00) and NaF gel (SMD − 0.14, 95% CI − 0.28 to 0.00) also favoured caries reduction, although the estimates were borderline.

According to the P-score ranking, fluoride varnish ranked highest among the topical fluoride agents, followed by APF gel, APF foam, and NaF gel (Supplementary Fig. 1). Fissure sealant ranked highly in the full network but was interpreted separately because it is a non-fluoride physical barrier intervention. The league table for the permanent dentition/first permanent molar continuous NMA is presented in Supplementary Table 1. The arm-level continuous outcome data used for the primary dentition and permanent dentition/first permanent molar continuous network meta-analyses are provided in Supplementary Table 5.

3.5 Network meta-analysis of binary outcomes

Binary caries outcomes were analysed separately for permanent and primary dentitions.

The permanent dentition binary network included three studies [26, 39, 53] across four intervention nodes: fissure sealant, fluoride varnish, silver diamine fluoride, and inactive control. The network was connected but sparse, with several comparisons informed by single studies or indirect evidence; therefore, the binary NMA was interpreted as supportive rather than definitive comparative evidence.

The primary dentition binary outcome included two studies [43, 44]. As the evidence was limited to a two-node comparison between fluoride varnish and inactive control, this outcome did not form a full treatment network. It was therefore analysed as direct pairwise evidence rather than through network meta-analysis. The arm-level binary outcome data used for the primary dentition binary analysis and permanent dentition/first permanent molar binary network meta-analysis are provided in Supplementary Table 6.

3.6 Sensitivity analyses

Two sensitivity analyses were performed to assess the robustness of the evidence. First, the high-frequency quarterly fluoride varnish study by Latifi-Xhemajli et al. [36] was excluded from the primary dentition continuous meta-analysis. After exclusion, heterogeneity was eliminated ($I^2 = 0\%$), while the direction of effect remained in favour of fluoride varnish. The pooled estimate showed a small, borderline reduction in caries increment compared with control/placebo (MD − 0.47, 95% CI − 0.93 to 0.00; p = 0.05). The estimate was unchanged under random-effects and fixed-effect models, suggesting that the result was not dependent on model choice (Supplementary Fig. 2).

Second, a sensitivity analysis restricted to topical fluoride agents was conducted after excluding resin fissure sealant, which was considered a non-fluoride physical barrier comparator. In the direct pairwise analysis, fluoride varnish significantly reduced caries increment compared with inactive control in the Bravo trial [25] (SMD − 0.41, 95% CI − 0.68 to − 0.14). APF foam, APF gel, and NaF gel showed favourable but non-significant or borderline trends compared with inactive control. In the direct active-agent comparisons, statistically insignificant difference was observed between the agents as each comparison was based on a single study, these findings were presented descriptively rather than included in a quantitative synthesis (Supplementary Table 2)

3.7 Transitivity and inconsistency

Transitivity was considered clinically reasonable within the defined networks after comparing age, dentition type, outcome type, intervention category, follow-up duration, co-interventions, and risk of bias. However, formal inconsistency testing was limited because the networks were sparse and had few closed loops. Therefore, inconsistency was interpreted descriptively using network geometry and clinical comparability [11, 13].

Publication bias was not formally assessed because the number of studies per comparison was too small and the networks were sparse. Funnel-plot asymmetry would therefore be unreliable to interpret [11].

3.8 Certainty of evidence

CINeMA confidence ratings for the NMA estimates are presented in Supplementary Table 3. CINeMA confidence ratings ranged from low-to-moderate [18]. Downgrading was mainly due to reporting bias, imprecision, heterogeneity, sparse network structure, single-study comparisons, and indirect-only evidence. For primary dentition binary caries incidence/conversion, FV versus inactive control was rated as low confidence because only two direct studies contributed and the comparison did not form a full connected network. For permanent dentition binary caries incidence, confidence was moderate for FS versus FV and FV versus SDF.

4. Discussion

4.1 Principal findings

This systematic review and network meta-analysis compared professionally applied topical fluoride agents for caries prevention in children and adolescents. Although topical fluoride is already known to prevent caries, the relative performance of different agents remains less clear. Network meta-analysis was therefore appropriate because it allows multiple interventions to be compared within a connected evidence network, using both direct and indirect evidence, when transitivity and coherence are clinically reasonable [9–11, 13].

Overall, active topical fluoride agents favoured caries prevention compared with inactive control. In the permanent dentition/first permanent molar continuous network, fluoride varnish showed the most favourable estimate among topical fluoride agents, followed by APF gel, while APF foam and NaF gel showed favourable but less precise effects. However, these results should be seen as a comparative evidence map rather than conclusive evidence that any single topical fluoride agent is superior because the network was small and some comparisons relied on individual studies [13, 17, 18].

4.2 Biological and clinical differences between topical fluoride agents

The existing evidence supports that fluoride varnish has important clinical advantages in paediatric patients. It is applied directly onto the tooth surface and forms a retentive film, which aids in sustained fluoride contact for a prolonged duration compared with many tray-delivered formulations [5, 6].

The variation in professional topical fluoride agents is because these agents vary in composition, delivery vehicle, retention time, and ease of application. Their therapeutic effect is determined not only by fluoride concentration, but also by how long fluoride remains available at the tooth–biofilm interface during recurrent acid exposure, where it facilitates remineralisation and reduces demineralisation [4, 5].

APF gel and APF foam vary from varnish because they are usually applied using trays or supervised clinical application and have limited contact time. Their acidulated formulation may promote fluoride uptake by enamel, but their preventive effect depends on adequate contact time, tray placement, proper isolation, and patient compliance. Evidence supports the preventive effect of fluoride gels, particularly in permanent dentition, while evidence in primary dentition remains less robust [7].

APF foam requires less material as compared to gel, which lowers the risk of swallowing and toxicity in children, and it may be easier to apply as it spreads evenly; however, its benefit still depends on adequate tooth contact and exposure time [59]. Its main limitation is that the evidence base for foam is less robust compared with gel or varnish [6, 7].

NaF gel was classified as a distinct intervention node from fluoride varnish because differences in formulation vehicle, application protocol, and fluoride substantivity may influence clinical effectiveness. Fluoride varnish forms a retained coating on enamel that prolongs fluoride availability, whereas NaF gel provides brief fluoride exposure and relies more heavily on tray-mediated administration, salivary control, and patient compliance [5–7].

4.3 Differences between primary and permanent dentition

Primary and permanent dentitions vary in their morphology, stage of eruption, and caries progression pattern. Primary dentition have reduced enamel and dentine thickness which may lead to more rapid caries progression. Similarly, newly erupted permanent teeth, especially first permanent molars, are more susceptible because of incomplete enamel maturation after eruption, deep pits and fissures, and more plaque accumulation during eruption [3–5].

This distinction is relevant when evaluating the clinical effect of fissure sealants. Sealants are different from other preventive agents as they act as a physical barrier over pits and fissures [60]. Their mode of action differs from topical fluoride agents, which mainly promote remineralisation and reduce demineralisation [4]. Therefore, fissure sealant was retained as an active non-fluoride comparator where it improved network connectivity.

The evidence network was stronger for permanent dentition/first permanent molar outcomes than for primary dentition outcomes. Primary dentition studies were fewer, more heterogeneous, and less consistently connected through common comparators. Therefore, findings from permanent dentition should not be directly generalised to preschool children. More direct comparative trials of topical fluoride agents are needed in primary dentition.

4.4 Comparison with previous evidence

The results of the present study are supported by the existing Cochrane review by Marinho et al., which reported a caries-inhibiting effect of fluoride varnish in both primary and permanent teeth, but pairwise reviews have limited ability to compare multiple fluoride agents directly [6]. The present review extends this evidence by using a network meta-analysis approach to compare multiple topical fluoride agents within connected evidence networks [9, 10, 13].

The results also align with the network meta-analysis by Manchanda et al., on prevention of early childhood caries (ECC) by professionally or self-applied topical fluorides. The study reported very low-to-moderate certainty evidence for professionally applied topical fluoride interventions and advised cautious interpretation of rankings in sparse networks [61]. Similar limitations were observed in the present analysis, where several comparisons relied on limited direct evidence and relevant clinical modifiers, such as formulation and concentration of fluoride, application schedule, caries susceptibility, and community fluoride exposure, were not consistently reported across studies.

Unlike other ECC-specific reviews [61], the present review includes children and adolescents up to 18 years of age and assessed primary and permanent dentition. This wider inclusion not only strengthens the clinical applicability but also highlights the importance of dentition-based interpretation instead of assuming that findings from one dentition are generalisable to another dentition.

Recent evidence in high-risk infants also suggests that developmental defects of enamel and dental caries are common in early childhood, supporting the need for early risk-based preventive strategies [62].

Related evidence on early enamel lesions has also shown that remineralisation-focused interventions are commonly compared with fluoride agents, but such reviews address lesion management rather than comparative prevention of new caries across dentitions [63].

4.5 Interpretation of ranking, risk of bias, and certainty of evidence

Treatment rankings should be interpreted cautiously as supportive information and not as direct clinical recommendations. They may be unstable when networks are sparse, lack precision, have limited-to-moderate certainty, or when some nodes are informed by single studies [17, 18].

Although fluoride varnish has shown a favourable caries-preventive direction among topical fluoride agents, the evidence is insufficient to support a definitive conclusion that any individual agent is superior in all contexts across dentition groups, age categories, caries risk categories or healthcare settings [17, 18].

4.6 Strengths, novelty, and limitations

This review has several methodological and clinical strengths. The main novelty of this review is its comparative approach. It not only assessed whether topical fluoride works, but compared different topical fluoride agents within connected evidence networks [9, 10, 13]. Treatment nodes were defined in advance based on fluoride type, delivery method, application frequency, preventive purpose, and clinical similarity. This kept the comparisons clinically meaningful and avoided grouping interventions that were too different. Fissure sealants were kept as non-fluoride active comparators, so they could improve network connectivity without being treated as topical fluoride agents.

Other strengths included separate analysis of continuous and dichotomous outcomes, dentition-specific interpretation, consideration of clinical effect modifiers, and interpretation of findings with RoB 2, CINeMA, sensitivity analyses, network estimates, and cautious interpretation of rankings using P-score rankings in a sparse network [15, 17, 18].

The main limitation was the sparse evidence structure at the comparison level. Although 11 studies contributed to at least one network or supplementary quantitative analysis, several treatment contrasts were based on single studies and only a few closed loops were available, limiting formal assessment of inconsistency. This reduced confidence in indirect comparisons and treatment rankings. Transitivity was also difficult to judge fully because important effect modifiers were inconsistently reported across trials. Since several nodes were supported by a limited number of studies, small-study effects and publication bias could not be robustly evaluated. The small number of studies also restricted reliable subgroup analysis or network meta-regression for effect modifiers. Inclusion of cluster-randomized and multi-arm trials may have introduced additional methodological complexity despite adjustment procedures.

Another limitation was the use of standardised mean differences (SMDs) for continuous outcomes. Although this approach allowed pooling of studies reporting related caries increment indices, it reduced direct clinical interpretability compared with raw dmfs/dmft or DMFS/DMFT mean differences and may have introduced additional heterogeneity related to differences in outcome variability across studies. Finally, adverse effects, fluorosis, acceptability, and cost-effectiveness were inconsistently reported, limiting assessment of benefit–harm balance and real-world implementation in paediatric populations [11, 12].

4.7 Implications for practice and research

Evidence supports a risk-oriented and setting-specific strategy for professionally applied topical fluoride rather than a single-agent strategy. Fluoride varnish is clinically feasible for preschool children, community programmes, and children with special needs because of ease of application, less technique sensitivity and longer adherence to the enamel surface [5, 6]. Other topical fluoride agents like APF gel, APF foam, and NaF gel may still be useful in older cooperative children or clinic-based settings where controlled application is feasible [7]. Fluoride agent selection should depend on type of dentition, caries susceptibility, fluoride intake from other sources, patient compliance, risk factors, economic implications, and local feasibility [5].

Future trials should focus on direct comparisons of commonly applied topical fluoride agents, especially fluoride varnish, APF gel, APF foam, and NaF gel, rather than relying primarily on fluoride-versus-control comparisons [6, 7, 45]. Future studies should use standardised dentine-level caries outcomes and clearly report fluoride concentration, application frequency, baseline caries risk, community fluoride exposure, adjunctive interventions, adverse effects, clustering adjustments, and economic efficiency [11, 13]. Economic evaluation and longer-term monitoring are also needed to inform public and school-based oral health programmes.

5. Conclusion

Professionally applied topical fluoride agents showed an overall preventive effect against dental caries in children and adolescents. Among the topical fluoride agents, fluoride varnish had the most favourable comparative effect although the comparative results remained inconclusive. The findings require cautious interpretation because the evidence networks were limited, risk-of-bias judgements were mixed, and CINeMA certainty ranged from low to moderate The treatment choice should remain risk- and setting-specific, clinical feasibility, and certainty of evidence rather than being guided by ranking alone.

Abbreviations

FV
fluoride varnish
FS
fissure sealant

APF
acidulated phosphate fluoride
NaF
sodium fluoride.

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Figures

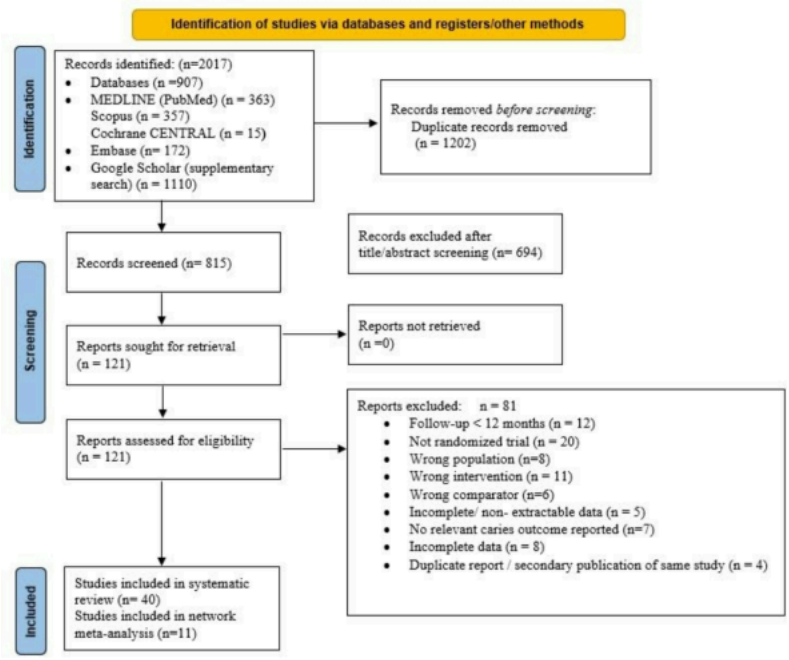


Figure 1

PRISMA flow diagram

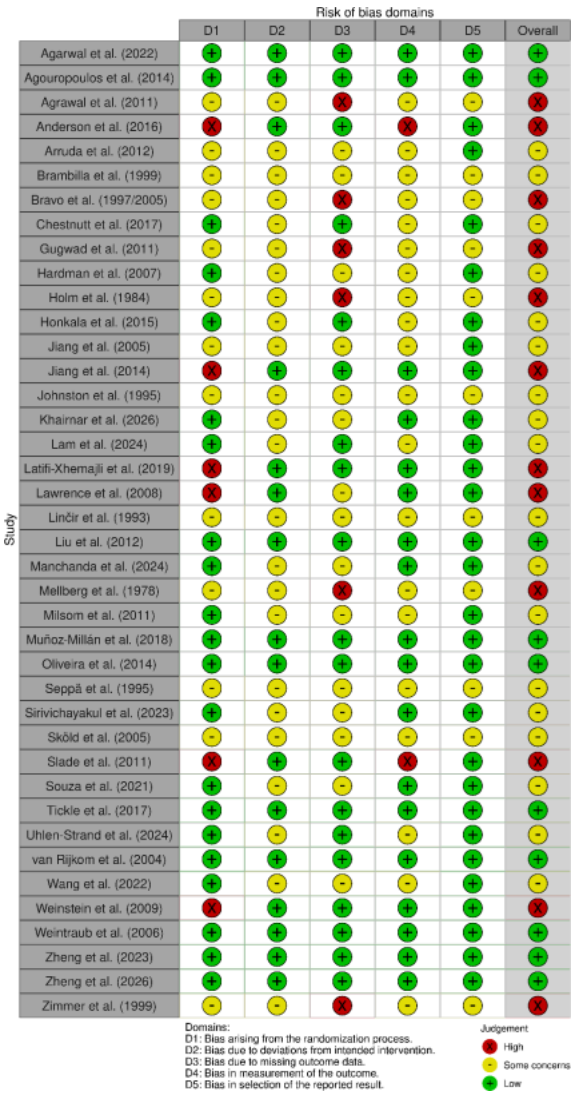


Figure 2

Risk-of-bias summary of included randomized trials using the Cochrane RoB 2 tool.

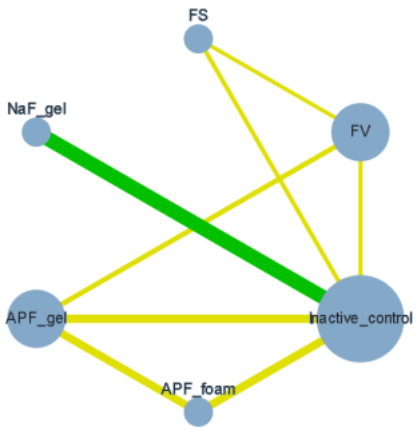


Figure 3

Network plot for permanent dentition/first permanent molar continuous caries increment outcome.

Caption: Node size reflects the number of studies contributing to each intervention, and edge thickness reflects the number of direct comparisons. Edge colour represents the majority risk-of-bias judgement for each comparison (green = low risk; yellow = some concerns). FS was interpreted separately as a non-fluoride physical barrier comparator.

Abbreviations: FV, fluoride varnish; FS, fissure sealant; APF, acidulated phosphate fluoride; NaF, sodium fluoride.

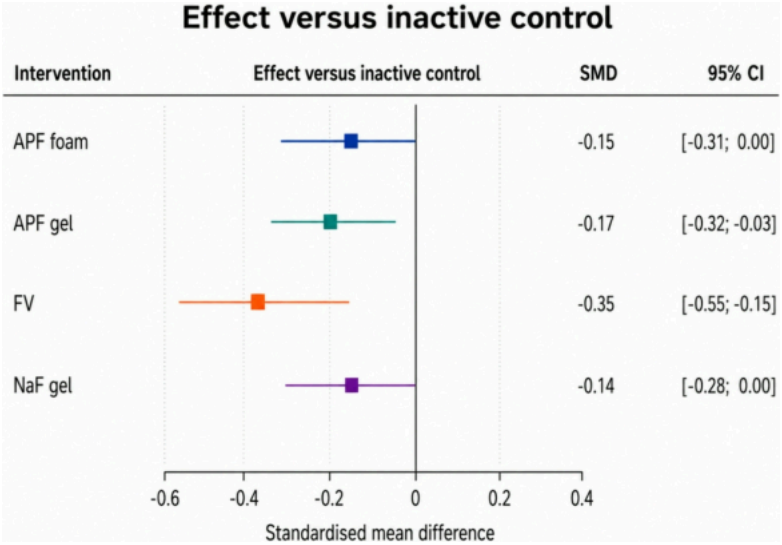


Figure 4

Network meta-analysis relative effects of topical fluoride agents versus inactive control.

Caption: The plot presents standardised mean differences with 95% confidence intervals for each topical fluoride agent compared with control. Negative SMD values favour the active intervention, indicating lower caries increment. Findings should be interpreted cautiously because some estimates were based on sparse evidence or single-study comparisons.

Abbreviations:APF, acidulated phosphate fluoride; CI, confidence interval; FV, fluoride varnish; NaF, sodium fluoride; SMD, standardised mean difference.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Abbreviations.docx
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