Universidade do Estado do Rio de Janeiro
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Instituto de Medicina Social

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Efeito do dentifrício fluoretado na incidência de cárie na dentição decídua e fluorose na dentição permanente: revisões sistemáticas e metanálises

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CATALOGAÇÃO NA FONTE
UERJ / REDE SIRIUS / BIBLIOTECA CB/C

S237 Santos, Ana Paula Pires dos.
Efeito do dentifrício fluoretado na incidência de cárie na dentição decídua e fluorose na dentição permanente: revisões sistemáticas e metanálises / Ana Paula Pires dos Santos. – 2011.
156 f.

Orientador: Paulo Nadanovsky.
Coorientador: Branca Heloisa de Oliveira Martins Vieira.
Tese (Doutorado) – Universidade do Estado do Rio de Janeiro, Instituto de Medicina Social.

1.Cáries dentárias – Teses. 2. Fluorose dentária – Teses. 3. Dentição primária. 4. Dentição permanente – Teses. 5. Dentifrícios - TesesI. Nadanovsky, Paulo. II. Vieira, Branca Heloisa de Oliveira Martins. III. Universidade do Estado do Rio de Janeiro, Instituto de Medicina Social. IV. Título.

CDU 616.314-002

_____ _____

Assinatura Data

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Aprovada em 29 de setembro de 2011.

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Rio de Janeiro
2011

AGRADECIMENTOS

A minha querida mãe Alice, minha irmã Carmelina e meu padrasto Sidnei, pelo amor, cumplicidade e apoio incondicionais.

Ao meu orientador Paulo Nadanovsky, por ter sido um verdadeiro e generoso mestre. Muito obrigada pela excelente orientação e pelo incentivo e paciência inesgotáveis. Ser sua aluna foi uma experiência muito rica e essencial para o meu amadurecimento profissional.

A minha co-orientadora Branca Heloisa de Oliveira Martins Vieira, um exemplo de profissional, por me apresentar à epidemiologia e pela confiança ao me indicar ao Prof. Paulo Nadanovsky. Muito obrigada pela atenção, paciência, disponibilidade, amizade e carinho demonstrados ao longo desses anos.

Ao professor Evandro da Silva Freire Coutinho, pela ajuda oferecida durante a realização deste trabalho e pela leitura prévia tão cuidadosa e generosa.

Ao professor Ronir Raggio Luiz, pela disponibilidade para esclarecer dúvidas durante a realização deste trabalho.

Aos professores componentes da banca examinadora, titulares e suplentes, por aceitarem participar deste momento tão importante na minha vida.

Aos professores do departamento de epidemiologia do Instituto de Medicina Social da UERJ, pela competência e dedicação com que exercem a sua função.

Aos professores da disciplina de odontopediatria da Faculdade de Odontologia da UERJ, que há 11 anos são grandes incentivadores do meu aprimoramento profissional.

A todos os meus colegas de curso, em especial às amigas Anna Maria Sales, Ilana Bezerra, Karine Boclin e Paula de Holanda Mendes, pela amizade, companheirismo e pelos momentos maravilhosos que passamos juntas.

A Juliana Ferreira de Almeida, pela valiosa contribuição na leitura e seleção dos resumos deste trabalho.

A todos os funcionários do Instituto de Medicina Social da UERJ, em especial aos membros da Secretaria Acadêmica e da Biblioteca, pelo apoio técnico-administrativo.

A todos os amigos e familiares que torceram por mim e, de alguma forma, me ajudaram nessa jornada.

À FAPERJ e ao CNPq, pelo apoio financeiro que viabilizou a realização deste trabalho.

DEDICATÓRIA

Ao amor da minha vida

RESUMO

SANTOS, Ana Paula Pires dos. *Efeito do dentifrício fluoretado na incidência de cárie na dentição decídua e fluorose na dentição permanente: revisões sistemáticas e metanálises*. 2011. 156f. Tese (Doutorado em Saúde Coletiva) - Instituto de Medicina Social, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2011.

Apesar do potencial anticárie do dentifrício fluoretado na dentição permanente estar bem estabelecido, existe uma lacuna no conhecimento em relação ao seu efeito na dentição decídua; não existe consenso quanto à concentração ideal de fluoreto no dentifrício capaz de maximizar o benefício anticárie na dentição decídua e simultaneamente minimizar o risco de desenvolver fluorose clinicamente importante na dentição permanente. O artigo 1 desta tese avaliou o efeito dos dentifrícios de concentração baixa (menos de 600 ppm) e padrão (1000 a 1500 ppm) de fluoreto comparados com placebo ou nenhuma intervenção e o artigo 2 comparou diretamente o efeito do dentifrício de concentração baixa de fluoreto com o de concentração padrão. Foi realizada uma revisão sistemática de ensaios clínicos randomizados ou quasi-randomizados. Dois examinadores leram, de forma independente, 1932 resumos ou citações e 159 estudos na íntegra. As discordâncias foram resolvidas por um terceiro examinador. Oito estudos foram incluídos no artigo 1 e cinco no artigo 2. Para avaliar o efeito dos dentifrícios fluoretados sobre o número de dentes e superfícies dentárias cariadas, perdidas por cárie e obturadas, e sobre o número de crianças com cárie e fluorose, foram estimados frações prevenidas (FP) e riscos relativos (RR) combinados, respectivamente. Quando os dentifrícios de concentração padrão de fluoreto foram comparados com placebo ou nenhuma intervenção, houve reduções significativas de cárie no nível de superfície (FP= 31%; IC 95% 18 – 43), dente (FP= 16%; IC 95% 7 – 24) e indivíduo (RR= 0,86; IC 95% 0,81 – 0,93). Quando os dentifrícios de concentração baixa de fluoreto foram comparados com nenhuma intervenção, houve redução significativa de cárie apenas no nível de superfície (FP= 40%; IC 95% 5 – 75) (artigo 1). Os dentifrícios de concentração baixa de fluoreto, comparados diretamente com os de concentração padrão, aumentaram significativamente o risco de cárie na dentição decídua (RR= 1,13; IC 95% 1,07 – 1,20) e não reduziram significativamente o risco de fluorose clinicamente importante nos dentes permanentes anteriores superiores (RR= 0,32; IC 95% 0,03 – 2,97). Houve uma redução significativa de cárie no nível de dente quando o dentifrício com concentração padrão de fluoreto foi comparado com o de baixa concentração (FP=14%; IC 95% 6 – 21). Porém, não houve diferença no nível de superfície, apesar de ter havido uma tendência favorecendo os dentifrícios com concentração padrão de fluoreto e pH neutro (FP= 13%; IC 95% -4 – 30) e os de concentração baixa de fluoreto e pH ácido (FP= -5%; IC 95% -22 – 11) (artigo 2). Os dentifrícios de concentração padrão de fluoreto foram mais efetivos na redução de cárie na dentição decídua de pré-escolares do que os de concentração baixa, placebo ou nenhuma intervenção. Os dentifrícios de concentração padrão de fluoreto, em comparação com os de concentração baixa, não aumentaram significativamente o risco de fluorose clinicamente importante nos dentes permanentes anteriores superiores. São necessários mais estudos para confirmar se a redução do pH dos dentifrícios de concentração baixa de fluoreto pode ser considerada uma alternativa para aumentar o efeito anticárie e reduzir o risco de fluorose clinicamente importante.

Palavras-chave: Cárie dentária. Fluorose dentária. Dentição Primária. Dentição Permanente. Revisão. Metanálise.

ABSTRACT

Despite the well established anti-caries effect of fluoride toothpaste in the permanent dentition, there is a gap in the knowledge reagarding its effect on the primary dentition; there is no consensus on the optimal fluoride concentration in toothpaste capable of maximizing the anti-caries benefits in the primary dentition and simultaneously minimizing the risk of clinically relevant fluorosis in the permanent dentition. Paper 1 of this thesis assessed the effects of low (less than 600 ppm) and standard (1000 to 1500 ppm) fluoride toothpastes compared to placebo or no intervention, whereas paper 2 compared directly the effects of low and standard fluoride toothpastes. A systematic review of randomized or quasi-randomized clinical trials was carried out. Two examiners independently read 1932 abstracts or citations and 159 full-text articles. Disagreements were solved by a third examiner. Eight studies were included in paper 1 and five in paper 2. Pooled prevented fractions (PF) and relative risks (RR) were estimated in order to assess the effects of fluoride toothpastes on the number of decayed, missing due to caries and filled teeth and dental surfaces, and on the number of children developing caries and fluorosis, respectively. When standard fluoride toothpastes were compared to placebo or no intervention, significant caries reductions were observed at surface (PF= 31%; 95% CI 18 - 43), tooth (PF= 16%; 95% CI 7 - 24) and individual (RR= 0.86; 95% CI 0.81 - 0.93) level. When low fluoride toothpastes were compared to no intervention, significant caries reduction was observed only at surface level (PF= 40%; 95% CI 5 - 75) (paper 1). Low fluoride toothpastes, compared directly to standard fluoride toothpastes, significantly increased the risk of caries in primary dentition (RR= 1.13; 95% CI 1.07 - 1.20) and did not significantly reduce the risk of clinically relevant fluorosis in upper permanent anterior teeth (RR= 0.32; 95% CI 0.03 - 2.97). There was a significant caries reduction at tooth level when standard fluoride toothpastes were compared to low fluoride toothpastes (FP= 14%; 95% CI 6 - 21). However, at surface level, no significant difference was observed, even though there was a tendency favouring standard fluoride toothpastes with neutral pH (PF= 13%; 95% CI -4 - 30) and low fluoride toothpastes with acidic pH (PF= -5%; 95% CI -22 - 11) (paper 2). Standard fluoride toothpastes were more effective in reducing caries in the primary dentition of preschool children than low fluoride toothpastes, placebo or no intervention. Standard fluoride toothpastes, when compared to low fluoride toothpastes, did not significantly increase the risk of clinically relevant fluorosis in upper permanet anterior teeth. Further research is necessary to confirm whether the reduction in the pH of low fluoride toothpastes might be an alternative to increase the anti-caries effects and to reduce the risk of clinically relevant fluorosis.

Keywords: Dental caries. Fluorosis, dental. Primary dentition. Permanent dentition. Review. Meta-Analysis.

LISTA DE ABREVIATURAS E SIGLAS

F	Fluoreto
CaF_2	Fluoreto de cálcio
ppm	partes por milhão
MEDLINE	*Medical Literature Analysis and Retrieval System Online*
PubMed	*Public/Publisher MEDLINE*
CENTRAL/ CCTR	*Cochrane Central Register of Controlled Trials*
EMBASE	*Excerpta Medica*
LILACS	Literatura Latino-Americana e do Caribe em Ciências da Saúde
BBO	Bibliografia Brasileira de Odontologia
MesH	*Medical Subject Headings*
RCT	*Randomized Controlled Trial*
FP	Fração prevenida
RR	Risco relativo
IC	Intervalo de confiança
Dp	Desvio-padrão
χ^2	Teste qui-quadrado de homogeneidade
I^2	Índice de Higgins
NNTB	Número necessário a tratar para causar um desfecho benéfico adicional
NNTH	Número necessário a tratar para causar um desfecho danoso adicional
ceo-s	Número de superfícies cariadas, perdidas devido à carie e obturadas – dentição decídua
ceo-d	Número de dentes cariados, perdidos devido à carie e obturados – dentição decídua

TF	*The Thylstrup & Fejerskov Index of Fluorosis*
FAPERJ	Fundação Carlos Chaga Filho de Amparo à Pesquisa do Estado do Rio de Janeiro
CNPq	Conselho Nacional de Desenvolvimento Científico e Tecnológico
CAPES	Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
SISNEP	Sistema Nacional de Informação Sobre Ética em Pesquisa envolvendo Seres Humanos

SUMÁRIO

INTRODUÇÃO

Esta tese se insere em um programa de investigação sobre a promoção da saúde bucal de crianças baseada na melhor evidência científica disponível. A motivação para a implementação deste programa foi a identificação, na rotina clínica da Odontopediatria, de divergências sobre questões relacionadas à saúde bucal infantil. Pode-se especular que a origem dessas divergências seja a dificuldade de atualização do profissional, devido ao grande número de estudos publicados atualmente, aliada à falta de treinamento para avaliá-los criticamente, ou ainda a ausência de uma evidência forte sobre os benefícios e danos de diferentes práticas voltadas para a saúde bucal.

Os objetivos desse programa de investigação são identificar recomendações direcionadas à população, fornecidas por instituições governamentais e não governamentais, no Brasil e no exterior, sobre práticas visando à promoção de saúde bucal de crianças; avaliar a melhor evidência científica disponível sobre essas recomendações; realizar revisões sistemáticas e metanálises sobre temas cujas evidências sejam inconclusivas e promover a divulgação dos achados tanto para a população quanto para profissionais da área da saúde através da mídia impressa e eletrônica.

A primeira etapa deste programa de investigação consistiu em consultar associações científicas e profissionais e órgãos governamentais, nacionais e internacionais, da área da Odontologia e Medicina (Pediatria), com o objetivo de identificar materiais, como cartilhas, folhetos ou seções de sítios da Internet, contendo recomendações direcionadas aos pais e/ou responsáveis sobre orientações relacionadas à higiene bucal de crianças. Essas recomendações foram comparadas com a evidência científica obtida a partir de revisões sistemáticas disponíveis em *The Cochrane Library* e *MEDLINE* via *PubMed*. Observou-se que muitas recomendações apresentavam divergências importantes e não eram baseadas na melhor evidência científica disponível. Além disso, percebeu-se uma escassez de revisões sistemáticas sobre várias práticas recomendadas. Os resultados dessa primeira etapa foram publicados nos periódicos Cadernos de Saúde Pública e *International Journal of Paediatric Dentistry* e estão apresentados nos apêndices A (pág. 47) e B (pág. 59), respectivamente.

Dentre os vários aspectos relacionados à higiene bucal que apresentaram divergências nas recomendações e cujas evidências científicas foram consideradas inconclusivas, o uso de dentifrícios por crianças pré-escolares foi escolhido como tema desta tese. A tese será apresentada sob o formato de artigos científicos conforme recomendação do Programa de Pós-Graduação em Saúde Coletiva do Instituto de Medicina Social.

O primeiro artigo aborda os efeitos de dentifrícios fluoretados, em comparação com placebo ou nenhuma intervenção, na prevenção de cárie dentária na dentição decídua de pré-escolares. O segundo artigo é sobre os efeitos de dentifrícios de baixa concentração de fluoreto, comparados diretamente com os de concentração padrão, na prevenção de cárie dentária na dentição decídua de pré-escolares e fluorose dentária esteticamente indesejável na dentição permanente.

Os capítulos 1 e 2 contêm uma breve revisão sobre os temas cárie dentária e fluorose dentária e nos capítulos 3 e 4 são apresentados a justificativa e os objetivos desta tese. No capítulo 5 foram detalhados os aspectos metodológicos comuns aos dois artigos e nos capítulos 6 e 7 são apresentados os resumos em português de ambos os artigos e as conclusões da tese. Nos apêndices C (pág. 80) e D (pág. 115) são apresentadas as versões em inglês dos dois artigos que compõem esta tese.

O programa de investigação na qual se insere esta tese é financiado pelo Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq - Processo 472566/2010-5) e pela Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ - Processo E-26/102.248/2009).

1 CÁRIE DENTÁRIA

1.1 Considerações gerais

Apesar de ser uma doença induzida por microorganismos, a cárie dentária não é considerada uma doença infectocontagiosa, visto que os microorganismos envolvidos na sua etiologia são endógenos ao hospedeiro. A cárie é um processo dinâmico resultante de mudanças no equilíbrio da microbiota bucal na interface dente/biofilme provocadas por alterações nas condições locais que levam à queda de pH, o que por sua vez pode iniciar a desmineralização do esmalte dentário[1]. A presença de um biofilme microbiano não necessariamente resulta no desenvolvimento de uma lesão cariosa, mas é um fator essencial para a sua ocorrência, ou seja, o biofilme microbiano é causa necessária, mas não suficiente para o desenvolvimento da cárie[2].

Por ser uma doença de caráter multifatorial, a cárie não dispõe de um mecanismo causal simples. Quando a unidade de análise é a população e não o indivíduo, a quantidade de açúcar disponível constitui o fator de risco mais importante[3,4]. Destacam-se também características individuais como fluxo salivar, capacidade tampão da saliva, velocidade de remoção dos carboidratos pelo fluxo salivar, presença de defeitos de desenvolvimento do esmalte dentário, qualidade da higiene bucal, hábitos dietéticos e exposição a fluoretos[1,5,6]. Essas variáveis podem ser influenciadas pelas características sócio-econômicas e comportamentais da população[1,7-9].

A cárie dentária é uma doença onipresente em todas as populações ao redor do mundo e afeta cerca de 60 a 90% das crianças em fase escolar e a grande maioria da população adulta[10]. A cárie não é igualmente distribuída na população; pessoas mais pobres são mais acometidas pela doença[11,12]. No Brasil, 20% dos escolares concentram 60% da carga da doença[12]. Na infância, ela é a doença crônica mais prevalente, sendo cinco vezes mais comum que a asma e sete vezes mais comum que a rinite alérgica[11].

Na última década, crianças pré-escolares, ao contrário de outros grupos etários, apresentaram um pequeno, porém significativo aumento na prevalência de cárie[13,14] e, neste grupo populacional, a prevalência de lesões de cárie em dentina ainda é considerada alta. Na Escócia, cerca de 25% das crianças de três anos de

idade têm cárie[15] e esse percentual é de 28% nas crianças de dois a cinco anos de idade nos Estados Unidos[13]. Aos cinco anos de idade, a prevalência é de 30% na Dinamarca[16], 31% na Bélgica[17], 38% na Inglaterra[18], 59% no Brasil[19], 60% na China[20] e 94% nas Filipinas[21].

Apesar de alguns levantamentos de cárie incluírem lesões iniciais de esmalte, a adoção desse limiar de detecção não é necessariamente vantajosa. A inclusão de lesões iniciais pode aumentar o número de lesões falso-positivas e, consequentemente, levar a um excesso de tratamento, mesmo que não invasivo[22]. Além disso, muitas lesões iniciais de esmalte paralisam sem nenhuma intervenção[23, 24]. Portanto, a cárie em esmalte pode ser considerada um desfecho substituto inadequado ao passo que a cárie em dentina pode ser considerada um desfecho verdadeiro. O tratamento restaurador só é indicado quando a cárie atinge a dentina[25], pois se acredita que a cárie em dentina sem tratamento tenda a evoluir levando frequentemente à morte pulpar. Além disso, somente a partir deste ponto é que a cárie pode causar algumas interferências na vida das pessoas, tais como dor de dente e dificuldades de mastigação.

O impacto da cárie dentária na qualidade de vida das crianças é bem documentado na literatura. Pré-escolares acometidos por cárie podem sofrer de dor de dente, dificuldades para comer, beber e falar, distúrbios do sono, alterações no comportamento e queda no rendimento escolar[26-30]. Casos mais graves de cárie nesta faixa etária podem causar desnutrição e interferências na taxa de crescimento das crianças[31,32]. Pais de crianças com cárie também são afetados, pois muitas vezes precisam não só faltar ao trabalho devido a queixas odontológicas dos filhos como também custear um tratamento odontológico[26].

1.2 O papel do dentifrício fluoretado

O efeito anticárie do fluoreto foi descoberto na década de 30, quando se observou que, em áreas onde a água de abastecimento apresentava, naturalmente, um alto teor de fluoreto, a prevalência de cárie era baixa. Inicialmente, acreditava-se que o potencial preventivo do fluoreto se dava através da sua ação sistêmica no período pré-eruptivo, ou seja, o aumento da ingestão de fluoreto durante a formação dentária aumentaria a concentração desse íon no esmalte dentário e, consequentemente, este se tornaria mais resistente à dissolução ácida. Logo, o

fluoreto deveria ser administrado de forma sistêmica através da fluoretação da água de abastecimento ou através de suplementos como tabletes e pastilhas. Entretanto, observou-se que a quantidade de fluoreto incorporada ao esmalte de dentes mineralizados na presença de fluoreto era insuficiente para conferir uma proteção anticárie significativa[1,33]. Hoje, há um consenso de que o efeito predominante do fluoreto é o efeito terapêutico local e pós-eruptivo, sendo considerado importante o fluoreto que é mantido de forma constante na cavidade bucal e que é capaz de interferir na dinâmica do processo de cárie, reduzindo a quantidade de minerais perdidos durante a desmineralização e ativando a quantidade reposta durante a remineralização salivar[1,33-37]. O fluoreto, portanto, não inibe a ocorrência da lesão de cárie, mas atua diminuindo a velocidade de progressão da mesma[1,38].

O uso de produtos fluoretados resulta em reações químicas nas estruturas mineralizadas dos dentes que culminam na formação de compostos do tipo fluoreto de cálcio (CaF_2). Esses compostos de CaF_2 funcionam como reservatórios de fluoreto no meio bucal que são liberados durante as quedas de pH e que buscam manter níveis constantes de fluoreto no meio bucal. A formação de CaF_2 depende de uma série de fatores que podem ter implicação clínica no efeito do fluoreto. O aumento na formação de CaF_2 é diretamente proporcional ao aumento da concentração de fluoreto do agente fluoretado, por isso o efeito anticárie do fluoreto é considerando concentração dependente. O pH do agente fluoretado também interfere na formação de CaF_2, sendo os produtos ácidos mais reativos que os neutros[38,39].

Foi observado um efeito diferencial do fluoreto de acordo com a superfície dentária. Crianças de 15 anos de idade que viviam numa cidade com água fluoretada apresentaram 75% menos lesões cavitadas proximais do que crianças que viviam em uma cidade com água não fluoretada. Já nas lesões cavitadas oclusais, esta diferença foi de apenas 36%[40]. Além disso, as superfícies oclusais, quando expostas ao dentifrício fluoretado, se tornaram cariadas a uma velocidade três vezes maior que as superfícies lisas[23]. Essas observações poderiam sugerir que o fluoreto tem um efeito especial, mais forte, em superfícies lisas. Entretanto, as superfícies oclusais são mais susceptíveis à cárie do que as superfícies lisas[41,42], logo lesões nas superfícies oclusais são mais difíceis de serem evitadas. Populações com alto nível de cárie apresentam lesões tanto nas superfícies mais suscetíveis como nas menos suscetíveis. Com a redução na incidência de cárie,

lesões nas superfícies menos suscetíveis reduzem em maior proporção, ao passo que as superfícies mais suscetíveis reduzem em menor proporção, independentemente da presença de fluoreto[43]. Logo, outras estratégias de controle da cárie, tais como redução no consumo do açúcar e melhoria na higiene bucal, também terão mais efeito em superfícies lisas do que em superfícies oclusais. Esses achados questionam a visão de que o fluoreto apresenta um efeito especial em superfícies lisas.

Ensaios clínicos testando o efeito do fluoreto incorporado aos dentifrícios tiveram início nos anos 40. A princípio, devido à combinação do íon fluoreto com abrasivos incompatíveis que o tornavam inativo, não se observou um efeito anticárie[35]. Estudos subseqüentes, entretanto, confirmaram os benefícios da adição do fluoreto ao dentifrício e hoje não há dúvidas de que o dentifrício fluoretado foi um importante divisor de águas na Odontologia[1]. Essa forma de administração de fluoreto é considerada também a mais racional, pois ao mesmo tempo em que o biofilme dental é desorganizado pela regularidade da escovação, mantém-se fluoreto constante no meio ambiente bucal para interferir na progressão da cárie dentária[38]. O uso de dentifrícios fluoretados foi identificado como a razão principal para o declínio da cárie dentária constatado na maioria dos países desenvolvidos, desde a década de 70, visto que este foi o único método de prevenção comum a todos os países que apresentaram redução nos níveis da doença[44,45].

Na década de 90, os dentifrícios fluoretados correspondiam a mais de 90% do mercado de dentifrícios em vários países, como Estados Unidos, Canadá e Brasil[38,46]. Os dentifrícios fluoretados chamados convencionais ou com concentração padrão contêm uma concentração de fluoreto em torno de 1000 a 1500 partes por milhão (ppm), geralmente sob a forma de fluoreto de sódio ou monofluorfosfato de sódio[47]. Apesar de menos frequentes, há também dentifrícios a base de fluoreto estanhoso ou fluoreto de amina[38]. Os chamados dentifrícios infantis podem conter concentração padrão ou concentração baixa de fluoreto (menos de 600 ppm), sendo as concentrações de 250, 440, 500 e 550 ppm as mais comuns. Este tipo de dentifrício é disponibilizado em muitos países, sendo os Estados Unidos e o Canadá exceções [47,48]. Também é possível encontrar vários dentifrícios no mercado que não contêm fluoreto na sua fórmula.

Os efeitos do uso tópico de fluoretos sobre a prevenção da cárie dentária em crianças e adolescentes foram extensamente estudados através de uma sequência

de revisões sistemáticas *Cochrane*, cujas evidências, obtidas a partir de ensaios clínicos controlados, são consideradas consistentes e robustas[49-51]. Foi demonstrado que o uso de dentifrícios fluoretados oferece proteção contra a cárie dentária tanto quanto outras formas tópicas de fluoreto, como géis, bochechos e vernizes, sendo que a aceitabilidade do dentifrício tende a ser maior. A partir da avaliação de 70 ensaios clínicos envolvendo cerca de 42.300 crianças, concluiu-se que a escovação regular com dentifrício fluoretado reduz em aproximadamente 24% (21% - 28%) a incidência de cárie em crianças e adolescentes. Houve aumento na eficácia de acordo com o aumento no nível inicial de cárie, na concentração de fluoreto, na freqüência de uso e com a supervisão da escovação, mas não houve diferença na eficácia entre áreas fluoretadas ou não fluoretadas[52].

Twetman et al.[53] também realizaram uma revisão sistemática com o objetivo de avaliar o efeito do dentifrício fluoretado na prevenção da cárie. Mesmo com a exclusão de estudos publicados antes de 1975, os resultados foram similares aos encontrados na Revisão *Cochrane*: fração prevenida de 24,9% (± 11,5%) quando o uso de dentifrício fluoretado foi comparado ao uso de placebo na dentição permanente jovem, maior efeito preventivo de dentifrícios contendo 1500 ppm de fluoreto quando comparados aos de 1000 ppm e maior redução de cárie observada em estudos onde a escovação dentária foi supervisionada.

Outra metanálise[54] desenvolvida com o mesmo objetivo, porém mais restrita em termos de bases de dados consultadas (apenas MEDLINE e Lilacs) e período avaliado (de 1980 a 1998), concluiu, com base em 11 ensaios clínicos, que a escovação com dentifrício fluoretado foi responsável por uma redução de cárie de 29,1% (24% - 34%) quando comparada com a escovação com o dentifrício não fluoretado. O aumento da concentração de fluoreto esteve associado com o aumento do efeito e as maiores reduções de cárie foram encontradas nos estudos que utilizaram escovação supervisionada.

Outras revisões sistemáticas já realizaram comparações diretas entre dentifrícios contendo diferentes concentrações de fluoreto. Os benefícios do aumento da concentração de fluoreto foram confirmados em relação a concentrações maiores ou iguais a 1000 ppm. Os autores sugerem que dentifrícios com baixa concentração de fluoreto podem não ser apropriados, apesar de enfatizarem a imprecisão das estimativas obtidas. Não foi detectado, no entanto, um

efeito superior quando o dentifrício foi utilizado de forma supervisionada ou em populações com níveis de cárie iniciais mais altos[55].

Ammari et al.[56] avaliaram o efeito anticárie de dentifrícios com baixa concentração de fluoreto em relação aos dentifrícios com concentração padrão de fluoreto. Os resultados demonstraram um menor efeito de dentifrícios com concentração de 250 ppm em relação aos de 1000 ppm na prevenção da cárie dentária. No entanto, não foi possível concluir sobre o efeito dos dentifrícios contendo 500 ppm de fluoreto em virtude da escassez de estudos.

Em metanálise conduzida por Steiner et al.[57], cujo objetivo foi estimar o efeito de dentifrício com 1000 ppm de fluoreto em relação aos de 250 ppm, houve um decréscimo um pouco maior no incremento de cárie no primeiro grupo em comparação com o segundo.

Apesar do efeito do dentifrício fluoretado no controle da cárie já ter sido amplamente investigado na dentição permanente, há pouca informação a respeito do seu efeito na dentição decídua. A evidência em relação ao efeito do uso de dentifrício na dentição decídua não foi avaliada ou foi classificada como inconclusiva em todas as revisões sistemáticas já realizadas até então sobre esse tema[52-58]. Presume-se que o efeito do fluoreto observado na dentição permanente seja equivalente ao que seria observado na dentição decídua, entretanto, os dentes decíduos apresentam características que poderiam exercer alguma influência no efeito do dentifrício fluoretado. Há uma maior velocidade de progressão de lesões de cárie em esmalte e dentina na dentição decídua quando comparada à dentição permanente[59]. A progressão de cárie na superfície distal do segundo molar decíduo foi 2-3 vezes mais rápida do que na superfície mesial do primeiro molar permanente[60]. Em dentes decíduos, foram necessários em média 12 meses para uma lesão de cárie proximal progredir além da metade externa do esmalte e aproximadamente 10 a 12 meses para que ela progredisse além da metade interna do esmalte. Em dentes permanentes recém-erupcionados, a progressão para além das metades externa e interna do esmalte levou em média 19 a 28 meses e 38 a 41 meses, respectivamente[61]. A maior velocidade de progressão de cárie na dentição decídua se deve talvez à menor espessura da camada de esmalte do dente decíduo. Diferenças na composição química do esmalte dos dentes decíduos e permanentes também foram relatadas. Foi identificada uma maior concentração de carbonato no esmalte decíduo, o que aumentaria a sua solubilidade aos ácidos e poderia

contribuir para uma maior velocidade de progressão das lesões de cárie[38,62,63]. Até o momento, há dúvidas se tais características inerentes aos dentes decíduos podem ou não interferir no papel do fluoreto sobre o controle da cárie dentária na dentição decídua.

2 FLUOROSE DENTÁRIA

2.1 Considerações gerais

No início do século XX, dentistas americanos observaram que cerca de 90% das crianças da cidade de Colorado apresentavam uma imperfeição no esmalte dentário, que foi chamada de “manchamento dental do Colorado”. Condições similares àquela descrita no Colorado foram relatadas em outros estados norte-americanos, assim como na Inglaterra e na Itália. Suspeitou-se que a água de abastecimento poderia ser um importante fator etiológico, pois a condição acometia crianças nascidas em áreas geográficas específicas. A partir daí, uma série de pesquisas epidemiológicas foram conduzidas e uma clara relação dose-resposta foi identificada entre a prevalência e gravidade de fluorose e a concentração de fluoreto na água de abastecimento. As pesquisas concluíram que, em níveis de até aproximadamente 1 ppm de fluoreto, a extensão e a gravidade da fluorose provavelmente não representavam um impacto para a saúde pública[35].

A fluorose dentária é considerada uma forma de toxicidade crônica decorrente da ingestão de fluoreto durante o período de mineralização dos dentes. A composição química do esmalte não fluorótico é de aproximadamente 95% de minerais, 4% de água e 1% de proteínas; já o esmalte fluorótico apresenta uma quantidade maior de proteínas e, consequentemente, torna-se mais poroso. O aumento da porosidade se manifesta sob a forma de linhas brancas transversais na coroa dos dentes (opacidades) e essas linhas podem se fundir fazendo com que toda a coroa adquira um aspecto branco-calcário. Nos casos mais graves de fluorose o esmalte está sujeito a pigmentações pós-eruptivas e fraturas[38,64].

O período de risco para o desenvolvimento de fluorose dentária compreende todo o período de formação do esmalte, que, com exceção dos terceiros molares, vai do nascimento até aproximadamente 8 anos de idade[65]. Entretanto, considerando que os dentes mais comprometidos esteticamente seriam os incisivos centrais superiores, a faixa etária de 20 a 36 meses é considerada crítica em termos de ingestão de fluoreto[22,38,66,67]. Nessa fase, as crianças deglutem, em média, de 57% a 72% do dentifrício colocado na escova[68-72].

No entanto, uma metanálise que avaliou a relação entre os períodos de risco associados ao desenvolvimento de fluorose nos incisivos centrais superiores revelou

que nenhum período pode ser classificado como mais crítico em termos de risco de desenvolvimento de fluorose. A duração da exposição ao fluoreto seria o fator que melhor explicaria o desenvolvimento de fluorose nesses dentes, ou seja, a exposição ao fluoreto por mais de dois anos durante os primeiros quatro anos de vida aumentaria o risco de desenvolver fluorose nos incisivos centrais superiores permanentes[73].

Além da duração da exposição, a gravidade da fluorose depende também da dose de fluoreto a qual a criança é submetida[38,66,73]. Há uma relação linear dose-efeito entre mg F/dia/kg de peso corpóreo, o que significa que qualquer ingestão de fluoreto pode resultar em fluorose[38,66]. Não há um nível de ingestão de fluoreto abaixo do qual a fluorose não ocorra[64]. Estima-se que 0,05 a 0,07 mg F/ dia/kg de peso corporal deva ser o limite máximo a que uma criança pode ser submetida para garantir que a fluorose não atinja grau que comprometa a estética dentária. Entretanto, estudos longitudinais têm mostrado que a quantidade de fluoreto ingerida por uma criança jovem pela dieta e pelo dentifrício fluoretado não corresponde ao nível de fluorose observado posteriormente, sendo a fluorose sempre de menor prevalência e gravidade do que o esperado[38,66]. Isto se deve ao fato de que os níveis de exposição ao fluoreto geralmente são superestimados; ou porque a freqüência de escovação é superestimada, ou porque o cálculo da dose de exposição é feito pela quantidade de fluoreto ingerida e não pela quantidade absorvida. O fluoreto é absorvido no estômago; logo, a escovação dentária após as refeições pode diminuir a sua absorção em até 40%[38].

Vários índices já foram descritos para avaliar a presença de fluorose[74-77], sendo que os mais comumente utilizados são os índices de Dean[74] e o índice de Thylstrup e Fejerskov (TF)[77]. O índice de Dean é baseado na aparência clínica dos dentes e classifica a fluorose como questionável, muito leve, leve, moderada ou grave. O índice de TF é uma extensão do índice de Dean e corresponde a uma escala ordinal composta de 10 escores (0 a 9) e que classifica os dentes de acordo com características clínicas e histopatológicas. A partir do escore 3, a fluorose é considerada moderada ou grave.

Segundo o levantamento nacional sobre as condições de saúde bucal na população brasileira (Projeto SB Brasil 2003), a prevalência de fluorose no Brasil aos 12 anos é 8,6%, sendo 0,7% quando considerados apenas os casos de fluorose moderada ou grave[19]. Em países como Escócia, Austrália, Suécia, México e

Inglaterra, a prevalência de fluorose varia de 18 a 54%[78-82]. Entretanto, a grande maioria dos casos é do tipo muito leve ou leve. Casos moderados e graves são incomuns em regiões não fluoretadas ou com nível ótimo de fluoreto na água de abastecimento[78-89].

Nas últimas décadas, tem sido relatado um aumento na incidência de fluorose[90,91]. Comparando os períodos de 1986-1987 e 1999-2004, a prevalência de fluorose aos 12 anos de idade nos Estados Unidos aumentou de 22,6% para 40,7%, ao passo que a prevalência de fluorose moderada ou grave aumentou de 1,3% para 3,6%[92]. Por outro lado, na Austrália, quando avaliadas as coortes nascidas em 1989/1990, 1991/1992 e 1993/1994, foi observado um declínio na prevalência de fluorose de 35% para 22% (quando considerados todos os casos de fluorose) e de 18% para 8% (quando excluídos os casos muito leves e considerados apenas os leves e moderados)[93].

A presença de fluorose não necessariamente afeta a satisfação das crianças com a aparência[94]. É importante diferenciar casos de fluorose muito leves e leves (TF 1 e 2) dos moderados e graves (TF≥3). O TF3 foi apontado, por adolescentes, o nível a partir do qual a estética dentária é comprometida[86,95] e o tratamento odontológico é considerado necessário[86]. O efeito da fluorose na qualidade de vida relacionada à saúde bucal tem sido avaliado em crianças com fluorose. Em alguns estudos as crianças avaliam os próprios dentes e, em outros, são avaliadas fotografias de casos de fluorose. Casos muito leves ou leves não tiveram impacto na qualidade de vida, sendo que nenhum efeito negativo associado a esses tipos de fluorose foi relatado. Apenas casos graves de fluorose afetaram negativamente a qualidade de vida associada à saúde bucal de crianças[96]. Pais de crianças também se mostraram insatisfeitos apenas quando seus filhos apresentavam fluorose moderada ou grave[97]. Foi observado ainda um efeito positivo de casos leves de fluorose na qualidade vida associada à saúde bucal relatada por crianças e seus pais, provavelmente devido à presença de dentes mais brancos[98].

2.2 O papel do dentifrício fluoretado

O mecanismo de ação do fluoreto na fluorose, ao contrário do que ocorre em relação à cárie, é dose dependente, ou seja, ele depende não só da concentração do íon, mas também da quantidade[35,99]. Todas as fontes de fluoreto ingeridas

durante o período de mineralização dentária contribuem para o desenvolvimento de fluorose. No passado, a água de abastecimento era a única fonte significativa de fluoreto e, portanto, a sua ingestão era considerada o principal fator de risco para fluorose. No entanto, atualmente ela é apenas uma das muitas fontes disponíveis de fluoreto. Além da água, o fluoreto está presente em vários agentes terapêuticos (dentifrícios, géis, bochechos, vernizes, pastilhas), assim como em bebidas e alimentos, o que torna a identificação dos níveis de ingestão de fluoreto extremamente difícil. Começou-se a citar o dentifrício como possível causa para o aumento na incidência de fluorose, pois existe uma relação inversa entre a idade da criança e a quantidade de dentifrício deglutida, o que significa que as crianças que deglutem uma quantidade maior de dentifrício são justamente aquelas que estão no período de risco para desenvolvimento de fluorose esteticamente indesejável[33].

Algumas recomendações específicas em relação ao uso de dentifrícios fluoretados em pré-escolares têm sido sugeridas numa tentativa de minimizar a quantidade de fluoreto ingerida e, consequentemente, o risco de desenvolvimento de fluorose. Dentre elas, destacam-se a supervisão da escovação por parte dos pais e/ou responsáveis, o uso de pequena quantidade de dentifrício (tamanho de um grão de ervilha ou colocação do dentifrício na escova no sentido transversal) e o uso de dentifrícios sem fluoreto ou com concentração baixa de fluoreto[35,47,82,100-104].

A quantidade de dentifrício tem um impacto significativo na ingestão de dentifrício por pré-escolares; quanto maior a quantidade de dentifrício colocada na escova, maior a ingestão do mesmo[105,106]. O uso de pouca quantidade de dentifrício de baixa concentração de fluoreto (400 - 550 ppm) contribuiu para a diminuição do risco de desenvolvimento de fluorose na Austrália[107]. Já o sabor do dentifrício é uma questão mais controversa; já foram encontradas associações significativas e não significativas entre o sabor do dentifrício e o percentual de dentifrício ingerido[71,106,108]. Entretanto, considerando que só o fluoreto absorvido tem potencial de causar fluorose, métodos para avaliar a absorção ao invés da ingestão do dentifrício são mais apropriados. A concentração de fluoreto na urina pode ser considerada um biomarcador útil de exposição recente ao fluoreto em grupos de indivíduos. Já as unhas são indicadas para avaliar a exposição passada ao fluoreto e, por ser um método de coleta simples, a aceitabilidade é grande. No entanto, o potencial de predição de fluorose desses biomarcadores ainda precisa ser investigado em estudos epidemiológicos[109,110].

Hábitos de escovação também podem exercer alguma influência no desenvolvimento de fluorose. Resultados de um estudo caso-controle revelaram que a introdução do hábito de escovação dentária com dentifrício fluoretado durante o primeiro ano de vida e em uma freqüência maior do que uma vez ao dia aumentou o risco de desenvolvimento de fluorose em crianças vivendo em área não fluoretada[111]. Fluorose do tipo leve também se mostrou associada à ingestão de dentifrício fluoretado aos 24 meses de idade[101]. No entanto, associação similar não foi detectada em um estudo prospectivo que avaliou a ingestão de fluoreto em crianças de 19 a 39 meses de idade residentes em duas áreas fluoretadas e a ocorrência de fluorose nos incisivos centrais superiores permanentes e primeiros molares permanentes aos 7 - 9 anos de idade[112].

Outro fator a ser considerado é a quantidade de fluoreto solúvel nos dentifrícios, pois apenas o fluoreto solúvel é ativo e, portanto, com potencial de causar fluorose. Dentifrícios contendo concentração padrão de fluoreto de 1000 - 1100 ppm e cuja formulação combine o agente fluoreto de sódio com abrasivo a base de sílica, apresentam quantidade solúvel de fluoreto equivalente à quantidade total de fluoreto. Já nos dentifrícios que contêm concentrações mais altas de fluoreto (1450-1500 ppm) e cuja formulação combine o agente monofluorfosfato de sódio e abrasivo a base de carbonato de cálcio, a quantidade de fluoreto solúvel é inferior à quantidade total de fluoreto. Isso ocorre porque parte do fluoreto do agente se combina com parte do cálcio do abrasivo. Logo, crianças que escovam os dentes com dentifrícios convencionais contendo 1450 - 1500 ppm de fluoreto na forma de monofluorfosfato de sódio e cujo abrasivo seja a base de cálcio, estão expostas a quantidades similares de fluoreto solúvel quando comparadas a crianças que usam dentifrícios a base de fluoreto de sódio e sílica contendo 1000 - 1100pm de fluoreto, quer sejam infantis ou não. Crianças expostas a esses dois tipos de dentifrício teriam o mesmo risco de desenvolver fluorose, apesar da diferença na concentração de fluoreto dos dentifrícios[113].

A relação entre o uso tópico de fluoretos por crianças jovens e o risco de desenvolvimento de fluorose foi investigada através de uma revisão sistemática *Cochrane*[114]. Vinte e cinco estudos (dois ensaios clínicos, seis estudos caso-controle e dezesseis estudos seccionais) publicados entre 1988 e 2006 foram incluídos. Estudos caso-controle e seccionais mostraram uma redução significativa no risco de desenvolvimento de fluorose quando as crianças não usavam dentifrício fluoretado

antes dos 12 meses de idade, mas resultados conflitantes foram observados em relação ao uso de dentifrício a partir dos 24 meses. Não foram detectadas associações significativas entre freqüência de escovação e quantidade de dentifrício utilizada e fluorose. O uso de dentifrício com concentração maior ou igual a 1000 ppm esteve associado a um aumento na incidência de fluorose quando considerados os estudos experimentais, mas não quando considerados os estudos observacionais. Nessa revisão, não houve diferenciação entre os tipos de fluorose, ou seja, os resultados se baseiam no risco de desenvolver qualquer tipo de fluorose. Logo, não existe evidência disponível sobre o papel do dentifrício fluoretado na incidência de casos moderados e graves de fluorose.

3 JUSTIFICATIVA

Apesar do potencial anticárie do dentifrício fluoretado já estar bem estabelecido na dentição permanente, existe uma lacuna em relação ao seu efeito na dentição decídua. Não se sabe até que ponto o efeito anticárie dos dentifrícios fluoretados na dentição decídua é similar ao efeito relatado na dentição permanente, especialmente porque diferenças em relação à velocidade de progressão da cárie e à composição do esmalte já foram observadas entre as duas dentições.

A queda na prevalência de cárie observada nas últimas décadas vem sendo acompanhada por um aumento na prevalência de fluorose, e a razão para essa tendência tem sido atribuída ao uso do dentifrício fluoretado. Existe um debate acerca da concentração ideal de fluoreto no dentifrício a ser utilizado por pré-escolares, pois é nesta fase da vida, quando ocorre a mineralização dentária, que as crianças estão sob risco de desenvolver fluorose. Até o momento não foi identificada a concentração de fluoreto no dentifrício capaz de maximizar o benefício anticárie na dentição decídua e ao mesmo tempo minimizar o risco de desenvolver fluorose, com potencial de afetar a qualidade de vida relacionada à saúde bucal, na dentição permanente.

Diante disso, torna-se fundamental buscar todos os estudos relevantes já realizados sobre esse assunto e avaliar critica e sistematicamente a informação disponível na literatura. Assim, será possível contribuir para que as recomendações relacionadas aos riscos e benefícios do uso de dentifrício fluoretado em pré-escolares sejam baseadas na melhor evidência científica disponível.

4 OBJETIVOS

4.1 Objetivo geral

Avaliar o efeito do dentifrício fluoretado na prevenção de cárie dentária e fluorose dentária nas dentições decídua e permanente, respectivamente.

4.2 Objetivos específicos

- Avaliar o efeito de dentifrícios com diferentes concentrações de fluoreto, em comparação com placebo ou nenhuma intervenção, na prevenção de cárie dentária na dentição decídua de crianças pré-escolares.
- Avaliar o efeito de dentifrícios com concentração padrão de fluoreto (1000-1500 ppm), em comparação com dentifrícios baixa concentração de fluoreto (<600 ppm), na prevenção de cárie dentária na dentição decídua de crianças pré-escolares.
- Avaliar o efeito de dentifrícios com baixa concentração de fluoreto (<600 ppm), em comparação com dentifrícios com concentração padrão de fluoreto (1000-1500 ppm), na prevenção de fluorose dentária clinicamente importante na dentição permanente.

5 METODOLOGIA

5.1 Desenho dO estudo

Revisão sistemática com metanálise.

5.2 Critérios de elegibilidade dos estudos

5.2.1 Estudos

Ensaios clínicos randomizados ou quasi-randomizados, em que o nível de randomização tenha sido tanto o indivíduo como grupos de indivíduos. Outros tipos de estudos, como ensaios clínicos não randomizados, estudos observacionais, revisões de literatura e relatos de casos foram excluídos. Estudos com tempo de acompanhamento menor do que um ano também foram excluídos.

5.2.2 Participantes

Crianças na fase de dentição decídua no início do estudo, independentemente do nível inicial de cárie dentária. As crianças deveriam ter no máximo sete anos de idade na época da mensuração do desfecho cárie dentária. Foram excluídos estudos cujos participantes foram selecionados em função de condições especiais de saúde (geral ou bucal).

5.2.3 Intervenções

Para o artigo 1, a comparação de interesse foi dentifrício contendo qualquer concentração de fluoreto *versus* placebo ou nenhuma intervenção. Para o artigo 2, a comparação de interesse foi dentifrício contendo baixa concentração de fluoreto (<600 ppm) *versus* dentifrício contendo concentração padrão de fluoreto (1000-1500 ppm). Essas intervenções foram consideradas independentemente do agente usado na formulação do dentifrício (fluoreto de sódio, monofluorfosfato de sódio, fluoreto estanhoso ou fluoreto de amina), do tipo de abrasivo e do pH. Estudos cujas intervenções associaram outras medidas de aplicação tópica de fluoreto (gel, verniz,

bochecho) ou aplicação de agentes não fluoretados (clorexidina, xilitol, selantes) foram excluídos. Como a educação em saúde bucal não tem sido efetiva para a mudança de desfechos em saúde bucal como cárie dentária[115,116], ela não foi considerada uma co-intervenção com potencial de viés.

5.2.4 Desfechos

O desfecho cárie dentária foi avaliado através do incremento de cárie[a] em dentes decíduos erupcionados ou que erupcionaram durante o estudo. O incremento foi mensurado pelas diferenças observadas entre os exames final e inicial no número de superfícies cariadas, perdidas devido à cárie e obturadas (ceo-s) e no número de dentes cariados, perdidos devido à cárie e obturados (ceo-d). A presença de cárie dentária foi considerada nos níveis de detecção de esmalte e dentina, incluindo lesões cavitadas e não cavitadas, desde que o registro fosse feito separadamente. Para avaliar o risco de desenvolver cárie, foi considerada a proporção de crianças que desenvolveram novas lesões de cárie ao final do estudo.

O desfecho fluorose dentária foi avaliado através da proporção de crianças que desenvolveram fluorose dentária na dentição permanente. Apenas casos de fluorose esteticamente indesejável (formas moderada e grave) foram considerados.

5.3 Estratégia de busca

5.3.1 Busca eletrônica

5.3.1.1 Bases de dados

As seguintes bases de dados foram consultadas desde o ano inicial disponível *online* até janeiro de 2010: The Cochrane Central Register of Controlled Trials (CENTRAL/CCTR); MEDLINE via PubMed; Embase; Web of Science; Lilacs; BBO. Fontes adicionais incluíram o Banco de Teses da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), o registro de ensaios clínicos do Sistema Nacional de Informações sobre Ética em Pesquisa envolvendo

[a] Incidência total de cárie no nível do dente ou superfície.

Seres Humanos (SISNEP), além de dois registros internacionais de ensaios clínicos em andamento (Current Controlled Trials e ClinicalTrials.gov.).

5.3.1.2 Identificação dos estudos

A estratégia de busca foi desenvolvida para o MEDLINE (Apêndice E), utilizando a ferramenta *PubMed Advanced Search* e combinando termos livres e vocabulário controlado, de acordo com o *Medical Subjects Headings* (MesH). Essa busca foi adaptada para cada uma das outras bases de dados selecionadas, considerando as normas para sintaxe e uso de vocabulário controlado específicos de cada base.

As referências bibliográficas dos ensaios clínicos identificados e de revisões sistemáticas e narrativas sobre fluoretos foram verificadas. Não houve restrição de idioma. Quando necessário, estudos foram encaminhados para tradução.

Foi realizado contato por email com especialistas na área, buscando identificar estudos não publicados e estudos em andamento. Esses especialistas eram autores de estudos sobre fluoreto, além de professores e pesquisadores da área de odontologia e epidemiologia em saúde bucal.

5.3.2 Busca manual

A busca manual foi realizada por dois examinadores, de forma independente, nos seguintes periódicos: *Acta Odontologica Scandinavica*, *Archives of Oral Biology*, *British Dental Journal*, *Caries Research*, *Community Dental Health*, *Community Dentistry & Oral Epidemiology*, *European Archives of Paediatric Dentistry*, *European Journal of Oral Sciences*, *International Dental Journal*, *International Journal of Paediatric Dentistry*, *Journal of the American Dental Association*, *Journal of Clinical Pediatric Dentistry*, *Journal of Dental Research*, *Journal of Dentistry for Children*, *Journal of Public Health Dentistry*, *Pediatric Dentistry*. A Colaboração *Cochrane* organizou um grupo internacional responsável por realizar buscas manuais[117], que disponibiliza uma planilha com uma lista dos periódicos que estão sendo pesquisados e com a data da última atualização da busca em cada um dos periódicos. Quando um ensaio clínico é identificado, este é incorporado na base de dados CENTRAL/CCTR. A busca manual para esta tese foi realizada para cada um

dos periódicos citados acima a partir da data de atualização da busca pela Colaboração *Cochrane* até junho de 2010. Foi realizada também a busca manual de resumos apresentados nos congressos da *International Association for Dental Research* (2001-2011) e da *European Organisation for Caries Research* (1998-2011).

5.4 Coleta e análise de dados

5.4.1 Gerenciamento das referências bibliográficas

Os registros obtidos de cada base de dados foram importados para o software EndNoteX3® (Thomson Reuters, CA, EUA) o que possibilitou a eliminação de referências duplicadas.

5.4.2 Seleção de estudos

Dois examinadores leram, de forma independente, os títulos e resumos (quando disponíveis) de todos os registros identificados na busca. Não houve mascaramento em relação ao nome dos autores, periódicos e data de publicação dos artigos. Os artigos completos foram obtidos sempre que os estudos aparentemente preenchiam os critérios de inclusão, havendo ou não informação suficiente nos resumos. Também foram obtidos os artigos completos de estudo cujos títulos eram potencialmente relevantes, mas os resumos não estavam disponíveis. A razão para exclusão de cada um dos artigos nesta fase foi documentada e, em caso de discordâncias em relação à pertinência de um estudo, um terceiro examinador foi consultado e a decisão foi resolvida por consenso. Todos os estudos que preencheram os critérios de inclusão foram obtidos e lidos na íntegra.

5.4.3 Extração de dados

Dois examinadores realizaram a extração dos dados de forma independente, através de um formulário para extração de dados (Apêndice F). Em caso de discordâncias, um terceiro examinador foi consultado e a decisão foi resolvida por

consenso. Quando necessário, os autores dos estudos incluídos foram consultados para a obtenção de dados incompletos ou ausentes.

5.4.4 Avaliação do potencial de viés nos estudos incluídos

Cada estudo incluído foi avaliado em relação ao potencial de viés através da avaliação de nove critérios metodológicos, seguindo as recomendações do *Cochrane Handbook for Systematic Reviews of Interventions*[118]. Cada dimensão foi classificada como tendo risco de viés alto, baixo ou incerto. As dimensões avaliadas foram: geração da seqüência de alocação (alto risco de viés quando não houve alocação aleatória), ocultação da alocação (alto risco de viés quando não houve ocultação da alocação), mascaramento de participantes e avaliadores do desfecho (alto risco de viés quando não houve mascaramento dos avaliadores do desfecho), dados incompletos sobre o desfecho (alto risco de viés quando não houve estratégias para lidar com dados incompletos), relato seletivo do desfecho (alto risco de viés quando o estudo não relatava o desfecho cárie dentária através dos índices ceo-s e ceo-d e da proporção de crianças que desenvolveram cárie dentária), perdas de seguimento (alto risco de viés quando as perdas foram maiores do que 20%), confiabilidade de diagnóstico (alto risco de viés quando abaixo da classificação boa, de acordo com Landis e Koch[119]), comparabilidade entre os grupos na linha de base (alto risco de viés quando dados referentes à idade, sexo, nível sócio-econômico e nível de cárie não estavam balanceados entre os grupos) e contaminação (alto risco de viés na ausência de estratégias para evitar a contaminação entre os grupos). Quando o estudo não disponibilizava informações ou informações insuficientes sobre uma determinada dimensão, esta recebia a classificação de risco de viés incerto.

5.4.5 Análise Estatística

Para avaliar o efeito do tratamento na prevenção de cárie dentária mensurado pelos índices ceo-s e ceo-d, foi calculada a fração prevenida (FP), que corresponde à proporção de doença no grupo não intervenção que poderia ter sido prevenida caso a intervenção tivesse sido implementada[120]. No artigo 1, a FP corresponde à diferença entre o incremento médio de cárie no grupo que recebeu placebo ou

nenhuma intervenção e o incremento médio de cárie no grupo que recebeu o dentifrício fluoretado, dividida pelo incremento médio de cárie no grupo que recebeu placebo ou nenhuma intervenção. No artigo 2, a FP corresponde à diferença entre o incremento médio de cárie no grupo que recebeu o dentifrício de concentração baixa de fluoreto e o incremento médio de cárie no grupo que recebeu o dentifrício de concentração padrão de fluoreto, dividida pelo incremento médio de cárie no grupo que recebeu o dentifrício de concentração baixa de fluoreto.

Metanálises foram realizadas para estimar medidas de efeito combinadas. Para avaliar o efeito dos dentifrícios fluoretados sobre o número de dentes e superfícies dentárias cariadas, perdidas por cárie e obturadas, foram estimadas frações prevenidas (FP) combinadas. Os intervalos de confiança (IC) de 95% das FPs foram calculados a partir do método de *Fieller*[121]. Para avaliar o efeito dos dentifrícios fluoretados sobre a proporção de crianças que desenvolveram cárie e fluorose, foram estimados riscos relativos (RR) combinados.

A heterogeneidade dos estudos foi avaliada através da inspeção visual do gráfico *forest plot,* do teste qui-quadrado de homogeneidade (χ^2) e do índice de *Higgins* (I^2). Na presença de heterogeneidade (χ^2 com nível de significância <0.10 e I^2> 50%)[122], um modelo de efeitos aleatórios foi utilizado.

As metanálises foram realizadas no software Stata®11.1 (StataCorp LP, College Station, TX, EUA) utilizando o comando *metan* com três parâmetros (FP e limites inferior e superior do IC de 95%) ou quatro parâmetros (número de eventos e não eventos nos grupos teste e controle).

O número necessário a tratar para causar um desfecho benéfico adicional (NNTB) e o número necessário a tratar para causar um desfecho danoso adicional (NNTH) foram calculados aplicando as estimativas combinadas (FP e RR) a diferentes cenários de incidência de cárie[123]. Os ICs de 95% do NNTB e NNTH foram calculados utilizando os ICs de 95% das estimativas combinadas[124]. No artigo 1, foi calculado o NNTB correspondente ao número de crianças que têm que usar dentifrício de concentração padrão de fluoreto (em comparação com nenhuma intervenção) para evitar cárie em uma criança (ou seja, para evitar pelo menos uma lesão de cárie em dentina). No artigo 2, foi calculado o NNTB correspondente ao número de crianças que têm que usar dentifrício de concentração padrão de fluoreto (em comparação com o dentifrício de baixa concentração) para evitar um ceo-d (ou seja, para evitar que um dente tenha uma lesão de cárie em dentina, ou que seja

perdido devido à carie, ou que tenha uma obturação). Foi calculado também o NNTH correspondente ao número de crianças que têm que usar o dentifrício de baixa concentração de fluoreto (em comparação com o dentifrício de concentração padrão) para causar dano em uma criança (ou seja, para produzir pelo menos uma lesão de cárie em dentina).

Análises de metarregressão para avaliar a influência de características dos estudos no efeito do tratamento foram inviabilizadas devido ao pequeno número de estudos. Pela mesma razão, não foi possível averiguar a presença de viés de publicação.

As fórmulas utilizadas na análise estatística estão detalhadas no Apêndice G.

6 RESULTADOS

Nesta seção, são apresentados os resumos em português dos dois artigos. Os resultados detalhados encontram-se nas versões em inglês dos artigos (apêndices C e D).

6.1 Resumo em português do artigo 1

Objetivos: Avaliar o efeito do dentifrício fluoretado na prevenção de cárie na dentição decídua de crianças pré-escolares. Desenho do estudo: Revisão sistemática e metanálise. Métodos: Foi realizada uma busca por ensaios clínicos randomizados ou quasi-randomizados, sem restrição de idiomas, em seis bases de dados eletrônicas, registros de ensaios clínicos em andamento, resumos de congressos, periódicos de odontologia e referências de estudos potencialmente elegíveis. Dois examinadores leram, de forma independente, 1932 resumos ou citações e 159 estudos na íntegra. Dados referentes às características dos participantes, intervenções, desfechos, tempo de acompanhamento e potencial de viés foram extraídos por dois examinadores de forma independente. As discordâncias foram resolvidas por consenso após consultar um terceiro examinador. Frações prevenidas (FP) e riscos relativos (RR) combinados foram estimados para dentifrícios de concentração baixa (<600 ppm) e padrão (1000 - 1500 ppm) de fluoreto separadamente. Resultados: Oito estudos preencheram os critérios de inclusão, sendo que a maioria comparou dentifrícios fluoretados associados à educação em saúde bucal com nenhuma intervenção. Quando os dentifrícios de concentração padrão de fluoreto foram comparados com placebo ou nenhuma intervenção, reduções significativas de cárie foram observadas no nível da superfície (FP= 31%; IC 95% 18 – 43; 2644 participantes em cinco estudos), dente (FP= 16%; IC 95% 7 – 24; 2555 participantes em um estudo) e indivíduo (RR= 0,86; IC 95% 0,81 – 0,93; 2806 participantes em dois estudos). Dentifrícios de concentração baixa de fluoreto foram efetivos apenas no nível da superfície (FP= 40%; IC 95% 5 – 75; 561 participantes em dois estudos). Conclusões: os dentifrícios com concentração padrão de fluoreto são efetivos para a redução de cárie na dentição decídua de pré-escolares e, portanto, devem ser recomendados para esse grupo populacional.

6.2 Resumo em português do artigo 2

Contexto: Apesar do potencial anticárie do dentifrício com concentração padrão de fluoreto estar bem estabelecido, o seu uso em crianças pré-escolares tem gerado preocupações em relação ao desenvolvimento de fluorose, levando à indicação de dentifrícios com concentração baixa de fluoreto. Objetivo: Avaliar o efeito dos dentifrícios com concentração padrão e baixa de fluoreto na prevenção de cárie na dentição decídua de pré-escolares e fluorose na dentição permanente. Métodos: Foi realizada uma revisão sistemática de ensaios clínicos randomizados ou quasi-randomizados. Dois examinadores leram, de forma independente, 1932 resumos ou citações e 159 estudos potencialmente elegíveis na íntegra. Metanálises estimaram frações prevenidas (FP) e riscos relativos (RR) combinados. Resultados: Os dentifrícios de concentração baixa de fluoreto aumentaram significativamente o risco de cárie na dentição decídua (RR=1,13; IC 95% 1,07 – 1,20; 4634 participantes em três estudos) e não reduziram significativamente o risco de fluorose clinicamente importante nos dentes permanentes anteriores (RR=0,32; IC 95% 0,03 – 2,97; 1968 participantes em dois estudos). Houve uma redução significativa de cárie no nível do dente quando o dentifrício de concentração padrão de fluoreto foi comparado com o de baixa concentração (FP=14%; IC 95% 6 – 21; 4634 participantes em três estudos). Porém, não houve diferença no nível da superfície, apesar de ter havido uma tendência favorecendo os dentifrícios de concentração padrão de fluoreto e pH neutro (FP= 13%; IC 95% -4 – 30; 2272 participantes em dois estudos) e os de concentração baixa de fluoreto e pH ácido (FP= -5%; IC 95% -22 – 11; 742 participantes em dois estudos). Conclusões: Não há evidência que justifique o uso de dentifrícios com concentração baixa de fluoreto para a prevenção de cárie e fluorose.

7 CONCLUSÕES

Os dentifrícios de concentração padrão de fluoreto foram mais efetivos na redução de cárie na dentição decídua de crianças pré-escolares do que os dentifrícios de concentração baixa de fluoreto, placebo ou nenhuma intervenção.

Os dentifrícios de concentração padrão de fluoreto, em comparação com os de concentração baixa, não aumentaram significativamente o risco de desenvolver fluorose clinicamente importante nos dentes permanentes anteriores superiores.

São necessários mais estudos para investigar se a redução do pH dos dentifrícios de concentração baixa de fluoreto pode ser uma alternativa para aumentar o efeito anticárie e reduzir o risco de desenvolvimento de fluorose clinicamente importante.

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APÊNDICE A - Artigo publicado no periódico Cadernos de Saúde Pública

Citação: Santos APP, Nadanovsky P, Oliveira BH. Survey of Brazilian governmental health agencies shows conflicting recommendations concerning oral hygiene practices for children. Cad Saude Publica. 2010;26(7):1457-63.
DOI: 10.1590/S0102-311X2010000700025

Disponível em:
http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0102-311X2010000700025

Artigo submetido em 15 de setembro de 2009
Versão final submetida em 21 de abril de 2010
Artigo aprovado em 3 de maio de 2010

Title: Survey of Brazilian governmental health agencies shows conflicting recommendations concerning oral hygiene practices for children.

Título: Pesquisa com Secretarias de Saúde no Brasil revela recomendações divergentes relacionadas a práticas de higiene bucal em crianças.

Running title: Conflicting recommendations on oral hygiene practices for children.

Key-words: oral hygiene, dental care for children, evidence-based dentistry.

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A.P.P.Santos collected the materials provided by the health agencies. All three authors contributed to the study concept, design, interpretation, drafting and final editing of the manuscript.

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Abstract

The aims of this study were to detect whether recommendations concerning oral hygiene practices for children among Brazilian health agencies are consistent and to verify whether possible inconsistencies in these recommendations might be associated with an apparent gap in the scientific evidence. Fifty-four Brazilian health agencies were contacted by mail or electronic mail and they were asked to send any material containing recommendations on oral hygiene practices aimed at children. Then, a search was carried out at the Cochrane Oral Health Review Group and PubMed-Clinical Queries websites in order to assess the scientific evidence available on this subject. Forty (74%) agencies answered and 21 materials containing oral hygiene recommendations were obtained. Eleven pertinent systematic reviews were identified. This preliminary study detected some conflicting and not evidence-based oral hygiene messages, which emphasizes the need to carry out and disseminate systematic reviews on these controversial issues in order to bridge the gap between knowledge and practice.

Resumo

Os objetivos deste estudo foram verificar se as recomendações fornecidas por órgãos governamentais brasileiros sobre higiene bucal em crianças são consistentes e se possíveis inconsistências nessas recomendações estão associadas a uma aparente falta de evidência científica. Cinqüenta e quatro órgãos governamentais brasileiros foram contatados por endereço eletrônico ou postal. Foi solicitado que enviassem materiais contendo recomendações sobre práticas de higiene bucal para crianças. Em seguida, realizou-se uma busca nos sites Cochrane Oral Health Review Group e PubMed-Clinical Queries para avaliar a evidência científica disponível sobre o assunto. Quarenta (74%) órgãos governamentais responderam e 21 materiais contendo recomendações sobre higiene bucal foram obtidos. Foram identificadas 11 revisões sistemáticas pertinentes. Este estudo preliminar detectou algumas recomendações divergentes e não baseadas em evidência científica, ressaltando a necessidade de se realizar revisões sistemáticas da literatura sobre esses tópicos para aproximar a pesquisa científica da prática clínica.

Introduction

Health messages targeted at populations should be clear, consistent and based on the most reliable evidence currently available as polices based on flawed evidence may adversely affect public health. Often, conflicting health messages are a consequence of difficulties in closing the "knowledge-to-practice gap": knowledge is available, but healthcare professionals do not assess or apply it. Other times, conflicting health messages are a consequence of lack of or poor scientific evidence, or still, evidence may be available but has not been systematically summarized[1].

This preliminary study had two aims: 1) to detect whether recommendations on oral hygiene practices for children among Brazilian health agencies are consistent and 2) to verify whether possible inconsistencies in these recommendations might be associated with an apparent gap in the scientific evidence.

Methods

The following Brazilian governmental health agencies were contacted by electronic mail and/or mail: the National Oral Health Agency/ Ministry of Health, the 26 State Health Agencies, the 26 Municipal Health Agencies of Brazilian capitals and the State Health Agency of the Brazilian Federal District. A first round of emails was sent to each agency in September 2008. In case of no answer, four more attempts (2 emails and 2 letters) were made until April 2009. The emails and postal addresses were obtained either through Google™ or by making direct contact with the National Oral Health Agency/ Ministry of Health. The agencies were requested to send any and all educational materials such as brochures, leaflets or folders containing recommendations regarding children's oral hygiene practices aimed at the general public. They were also asked whether recommendations on this topic were disclosed on their websites.

The scientific evidence was obtained from systematic reviews available at the Cochrane Oral Health Review Group (http://www.ohg.cochrane.org/reviews.html) and at PubMed Clinical Queries, using the filter "Find Systematic Reviews" and the text words "oral hygiene" and "dentifrices" (http://www.ncbi.nlm.nih.gov/corehtml/query/static/clinical.shtml), accessed on July 19, 2009. The search and the selection of the systematic reviews were performed by

one author (APPS). Whenever there were any doubts about the pertinence of a review, another author (PN) was consulted and any disagreement was solved by consensus.

Results

Forty out of 54 (74%) governmental health agencies answered; 19 reported not producing the material requested, whereas 21 sent some kind of material, either in print or electronic format (Table 1). All the materials mentioned children's oral hygiene practices such as toothbrushing frequency, toothbrushing supervision, when to start and how long toothbrushing should last, toothbrush design and replacement, flossing, gums/teeth wiping, tongue cleaning, type and amount of toothpaste and advice on toothpaste ingestion (Table 2).

The search carried out at the Cochrane Oral Health Review Group website resulted in 91 systematic reviews, among which 5 were considered pertinent to the present study. The search carried out at the PubMed Clinical Queries website yielded 249 citations using the text word "oral hygiene" and 71 using the text word "dentifrices", and other 6 pertinent systematic reviews were identified. Only systematic reviews focusing on oral hygiene practices aimed at children were considered (Table 3).

Discussion

Gathering and disseminating reliable knowledge from systematic reviews plays a key role in evidence-based practice. However, systematic reviews yield not only evidence pro or against an intervention, but also the lack of scientific support for some current practices. Among the 11 systematic reviews included in this study, 8 highlighted the need for better quality studies to assess issues pertaining to adverse effects and the applicability of the results to different settings[2-6, 9,10,12]. Moreover, one review was unable to answer the core question due to insufficient evidence[10].

All Brazilian health agencies that replied to our request provided information on frequency of toothbrushing and the majority of them emphasized the need for toothbrushing before sleeping. However, recommendations on frequency of toothbrushing ranged from at least once a day to after every meal, feeding, sugar or

medication intake. Toothbrushing supervision was recommended for children up to 6 to 10 years of age or as soon as they develop the necessary skills. Three systematic reviews assessing the effects of fluoride toothpastes on caries incidence reported that their anti-caries potential is enhanced by daily or twice-daily supervised toothbrushing[3,6,7]. However, these conclusions have been drawn from studies that took place in schools or institutions and therefore it has yet to be established whether home supervised toothbrushing with an increased frequency behaves likewise. Such gap in the evidence may partly explain the conflicting messages conveyed.

Most materials did not disclose information on when toothbrushing should begin, how long it should last or how often toothbrushes should be replaced. There was agreement in regard to the use of soft-bristled toothbrushes, even though no evidence on this topic has been identified.

A systematic review of the effects of flossing on interproximal caries revealed that professional flossing during school days in children with poor oral hygiene habits and minimal exposure to fluoride is beneficial. On the other hand, no evidence of the effectiveness of self-flossing in the presence of topical fluoride was found. The authors pointed out that some of the trials included in this review were of poor quality and thus further studies assessing simultaneously the effects of fluoride toothpastes and flossing devices should be carried out to establish whether flossing can contribute to reducing interproximal caries when topical fluoride is available[12]. Despite this lack of evidence, 17 out of 21 health agencies suggested that children should have their teeth flossed.

Most materials emphasized the need for gums/teeth wiping. Some of them advised gums wiping before tooth eruption, others advised that wiping should last until the eruption of posterior teeth. Almost half of the materials also suggested that children should have their tongue cleaned. It is not clear whether these practices are recommended in order to prevent dental caries, halitosis or if it is believed that they are part of a comprehensive oral hygiene program that should be established early in children's lives, but neither are evidence-based practices.

Despite the scientific debate about optimal fluoride concentration in toothpastes aimed at children, only 8 agencies provided information on this issue. Some supported the use of non-fluoride toothpastes until the age of 3 or 4, possibly due to dental fluorosis concerns, although it has not been assessed yet to what extent dental fluorosis is attributable to fluoride toothpastes[3]. Additionally, there is a

substantial body of evidence emphasizing the anti-caries effect of fluoride toothpastes containing either sodium fluoride or sodium monofluorophosphate, as long as they are formulated with compatible abrasive systems[3,6,7,11]. Thus, the recommendation of non-fluoride toothpastes lacks scientific support and may have a detrimental effect on children's oral health. Other agencies advocated the use of standard fluoride toothpaste as soon as the first primary tooth breaks through and none of them mentioned the use of low fluoride toothpastes. Two systematic reviews comparing the effects of low versus standard fluoride toothpastes on caries prevention yielded conflicting results[3,6]. One review stated that 250ppm and 1,000ppm fluoride toothpastes achieved similar results, whereas the other reported that 250ppm fluoride toothpastes were not as effective as 1,000ppm ones. Moreover, the latter stated that it was not possible to draw any conclusion regarding 500ppm fluoride toothpastes. As for higher concentrations, it was shown that high-fluoride toothpastes provided lower caries increments in the permanent dentition than standard fluoride toothpastes[8].

Different amounts of toothpaste were recommended. However, apparently all materials supported the use of a small amount. No evidence regarding whether smaller amounts of toothpaste may affect fluoride efficacy was identified.

A thorough assessment of the current evidence was beyond the scope of this preliminary study and the educational materials evaluated may not completely reflect each agency's view concerning oral hygiene practices for children. In spite of that, this study showed several conflicting and not evidence-based oral hygiene messages. Thus, there is a need to carry out and disseminate systematic reviews on these controversial issues in order to bridge the gap between scientific knowledge and health agencies' recommendations. This will better address public health educational efforts and may help improve oral health practice.

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Table 1. Materials on children's oral hygiene practices provided by 21 Brazilian governmental agencies.

Governmental agency	**Material provided**
Ministry of Health	Brochure/folder sent by email/mail (*Caderneta de Saúde da Criança* and *Mantenha seu sorriso fazendo a higiene bucal corretamente*)
SHA* Amazonas	Oral health information available at the website (http://www.saude.am.gov.br/index.php?id=bucal)
SHA Maranhão	Folders sent by mail (*Saúde bucal um direito de todos, Inter-relação Odontologia/Pediatria* and *Saúde da boca e dos dentes*)
SHA Mato Grosso do Sul	Brochure sent by mail (*Saúde bucal em todas as idades*)
SHA Paraná	Folder sent by mail (*Dicas para você manter a sua saúde bucal*)
SHA Piauí	Folder sent by email (*Saúde Bucal - A caminho da Universalização***)**
SHA Rio de Janeiro	Oral health information available at the website (http://www.saude.rj.gov.br/guia_sus_cidadao/pg_32.shtml)
SHA Rio Grande do Sul	Folders sent by email (*Viva melhor com saúde bucal* and *Saúde bucal na primeira infância*)
SHA São Paulo	Folders sent by email (*Sorria toda vida, Auto-exame e autocuidados em saúde bucal* and *Turma da Mônica e a saúde bucal*)
MHA** Aracaju	Folders sent by mail (*O sorriso saudável ao alcance de todos* and *Dicas para um sorriso saudável*)
MHA Belém	Oral hygiene recommendations sent by email
MHA Belo Horizonte	Poster sent by email (*15 maneiras de cuidar da saúde bucal do bebê, criança e do adolescente*)
MHA Campo Grande	Folders sent by mail (*Prevenção em Odontologia para bebês*)
MHA Cuiabá	Folders sent by mail (*Geração cárie zero* and *A cidadania conquistada pelo sorriso*)
MHA Florianópolis	Folder sent by mail (*Cuide do seu sorriso e da sua saúde: previna a cárie e a doença periodontal*)
MHA Goiânia	Oral hygiene recommendations sent by email
MHA Manaus	Folder sent by email (*Programa de saúde bucal*)
MHA Natal	Folder sent by mail (*A saúde bucal no boca a boca*)
MHA Porto Velho	Oral hygiene recommendations sent by email
MHA Rio Branco	Folders sent by mail (*Saúde bucal*, *Cuide bem do seu sorriso* and *Saiba mais sobre creme dental*)
MHA Salvador	Oral hygiene recommendations sent by email

*SHA: State Health Agency

**MHA: Municipal Health Agency

Table 2: Oral hygiene recommendations aimed at children provided by 21 Brazilian governmental agencies.

Subject	Recommendation	Number of agencies
Toothbrushing		
Toothbrushing frequency*	Daily	1
	At least once a day	1
	3 times a day	6
	After meals	15
	After sugar intake	2
	After medication intake	2
	After breast/bottle feeding	7
	Before sleeping	15
	Subject not mentioned	--
Toothbrushing supervision*	Toothbrushing should be supervised	2
	Until 6 years of age	1
	Until 7 years of age	4
	Until 9 years of age	2
	Until 10 years of age	1
	Until the child is skilled	2
	From 3 to 7, parents should finish off children's toothbrushing	1
	Children brush on their own and parents finish off toothbrushing	2
	Parents should brush their children's teeth until 7 years of age	1
	Parents should brush their teeth in front of their children	4
	Subject not mentioned	8
When to start toothbrushing	When the first primary tooth emerges	5
	When the first primary molar emerges	2
	At 18 months of age	1
	Subject not mentioned	13
Time spent at toothbrushing	5-8 minutes	1
	10 seconds per 2 teeth	1
	Subject not mentioned	19
Toothbrush design*	Finger toothbrush (for babies)	1
	Small head	9
	Soft bristles	15
	Vertical bristles	2
	End-rounded bristles	2
	Straight handle	2
	Subject not mentioned	6
Toothbrush replacement*	Every 2-3 months	1
	Every 3 months	2
	Every 3-4 months	1
	When it becomes worn out	6
	Whenever children catch a cold or flu	1
	Subject not mentioned	15
Flossing	Children should have their teeth flossed	4
	Daily	13
	Subject not mentioned	4
Gums/teeth wiping	Until the first primary tooth emerges	8
	Until the first primary molar emerges	4
	Until one year and a half	1
	Subject not mentioned	8
Tongue cleaning	Children should have their tongue cleaned	10
	Subject not mentioned	11

Toothpaste		
Type of toothpaste*	Non-fluoride toothpaste until 3 years of age	1
	Non-fluoride toothpaste until 4 years of age	1
	Fluoride toothpaste, irrespective of age	6
	Toothpaste without abrasives	2
	Subject not mentioned	13
Amount of toothpaste*	Small amount	5
	¼ pea grain	1
	Pea grain	1
	Lentil grain	1
	Bean grain	1
	Corn grain	2
	Rice grain	6
	Subject not mentioned	8
Advice on toothpaste ingestion	Children should not swallow the toothpaste	6
	Children should have their mouth wiped after toothbrushing	1
	The tube of toothpaste should be kept out of children's reach	1
	Subject not mentioned	13

*The number of agencies does not add up to 21 as the same agency may provide more than one recommendation.

Table 3: Summary of systematic reviews focusing on oral hygiene practices aimed at children*.

Author/Year	Conclusions/Recommendations
Marinho et al.[2] (2003)	The benefits of topical fluorides have been firmly established. No conclusions about adverse effects could be reached.
Marinho et al.[3] (2003)	There is clear evidence that fluoride toothpastes are effective in preventing caries, regardless of water fluoridation. Higher effects were shown with higher baseline caries levels, increased fluoride concentration, increased frequency of use (twice x once/day) and supervised toothbrushing. No conclusions about adverse effects could be reached.
Marinho et al.[4] (2004)	Fluoride toothpastes, mouthrinses and gels reduce caries in children and adolescents to a similar extent but acceptance is likely to be greater for fluoride toothpaste. There is no strong evidence that varnishes are more effective than other types of topical fluoride. No conclusions about adverse effects could be reached.
Marinho et al.[5] (2004)	Topical fluorides (mouthrinses, gels or varnishes) used in addition to fluoride toothpaste achieve a modest reduction in caries compared to toothpaste used alone. However, combined use of topical fluorides and toothpaste may be considered for children at higher risk of caries. No conclusions about adverse effects could be reached.
Twetman et al.[6] (2003)	There is strong evidence for the caries preventive effect of daily use of fluoride toothpaste. Superior preventive effects were found with 1,500ppm F toothpastes and supervised toothbrushing. There is incomplete evidence regarding the effect of fluoride toothpaste in the primary dentition.
Chaves et al.[7] (2002)	Toothbrushing with fluoride toothpaste significantly decreases the incidence of dental caries. Higher caries reductions were observed when toothbrushing was supervised.
Bartizek et al.[8] (2001)	The use of a 2,800ppm F dentifrice showed significantly lower caries increments than the use of a 1,100ppm F dentifrice in school children. The 1,700ppm F and 2,200ppm F dentifrices showed some directional advantages over the 1,100ppm F dentifrice, though not statistically significant.
Steiner et al.[9] (2004)	Slightly lower caries increments were found in children using 1,000ppm fluoride toothpastes when compared to children using 250ppm fluoride toothpastes. The authors state that the 1,000ppm toothpaste's effects on fluorosis and the availability of fluoridated salt justify the use of 250ppm toothpastes for Swiss preschool children.
Ammari et al.[10] (2003)	Toothpastes containing 250ppm F were not as effective in caries prevention in permanent dentition as those containing 1,000ppm F. Data comparing 500ppm with 1,000ppm fluoride toothpastes were very limited and further research is required.
Proskin et al. [11] (1995)	Dentifrices containing fluoride as sodium fluoride or as sodium monofluorophosphate provide equivalent anticaries effectiveness.
Hujoel et al.[12] (2006)	Professional flossing in children with low fluoride exposure and poor toothbrushing habits is effective in reducing interproximal caries risk. Self-flossing has failed to show an effect. Studies assessing the effects of fluoride toothpastes and flossing devices are required.

* Source: Cochrane Oral Health Review Group (http://www.ohg.cochrane.org/reviews.html) and PubMed - Clinical Queries (http://www.ncbi.nlm.nih.gov/corehtml/query/static/clinical.shtml). Accessed on July 19, 2009.

Apêndice B - Artigo publicado no periódico *International Journal of Paediatric Dentistry*

Citação: Santos APP, Nadanovsky P, Oliveira BH. Inconsistencies in recommendations on oral hygiene practices for children by professional dental and paediatric organisations in ten countries. Int J Paediatr Dent. 2011;21(3):223-31. DOI: 10.1111/j.1365-263X.2011.01115.x

Artigo submetido em 12 de agosto de 2010
Versão final submetida em 24 de setembro de 2010
Artigo aprovado em 25 de novembro de 2010

Title: Inconsistencies in recommendations on oral hygiene practices for children by professional dental and paediatric organisations in ten countries.

Key words: oral hygiene, dental care for children, evidence-based dentistry

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Acknowledgments
The authors wish to thank all dental and medical organisations for providing the items assessed in this study. A. P. P. Santos receives a PhD scholarship from Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ); P. Nadanovsky receives financial support from the Brazilian National Research Council (CNPq - grant no. 305714/2006-6) and B. H. Oliveira receives financial support from FAPERJ (E-26/102.248/2009).

Summary

Background. Some of the basic dental health practices that are recommended to the public by professionals are not evidence-based. Incorrect oral health messages may adversely affect children's oral health behaviours.

Aim. To identify and list the recommendations concerning children's oral hygiene practices provided by dental and paediatric organisations, and to assess how these recommendations relate to the scientific evidence currently available.

Design. Cross-sectional. The authors contacted professional organizations in 10 countries requesting items (brochures, leaflets or folders) containing messages on children's oral hygiene practices. They then listed these recommendations and assessed how they related to scientific evidence obtained from systematic reviews available at PubMed and the Cochrane Library.

Results. Fifty-two out of 59 (88%) organisations responded to our request and 24 dental health education materials were submitted to the authors. They mentioned recommendations on oral hygiene practices for children, such as toothbrushing frequency, supervision and technique; when to start and how long toothbrushing should last; toothbrush design and replacement; flossing; gums/teeth wiping; tongue cleaning; type and amount of toothpaste and advice on toothpaste ingestion. The search at PubMed and the Cochrane Library resulted in 11 systematic reviews addressing these topics.

Conclusions. Several oral hygiene messages delivered by professional organisations showed inconsistencies and lacked scientific support.

Introduction

There is an ethical obligation of health professionals to ensure that materials disseminated to the public on dental health education must be evidence-based. Incorrect and conflicting messages may confuse people and hinder compliance with oral health practices which may eventually undermine their confidence in health professionals[1].

Conflicting health messages stem from lack of or poor scientific evidence, or evidence that has not been systematically summarized. These make it difficult to provide consistent evidence based recommendations. Practitioners then tend to fall back on tradition, experience or outdated evidence[2]. They may feel unsure about providing sound counselling in an environment of uncertainty[2-4].

Practitioners may find difficulty keeping up-to-date with emerging knowledge because of the increasing rate of dental publications and their lack of skills to critically appraise research quality[2, 5, 6]. Moreover, patients can obtain oral health information from multiple sources.[7] When taken together, these issues may substantially contribute to the dissemination of contradictory health messages.

The aims of this study were to identify and list the recommendations concerning children's oral hygiene practices provided by national dental and medical (paediatric) organisations aimed at the general public, and to assess how these recommendations relate to the scientific evidence currently available.

Material and Methods

Firstly, we selected countries that had a significant scientific output of dental research[8]: United States of America (USA), Canada, United Kingdom, Denmark, Finland, Norway, Sweden, Australia, Japan and Brazil. Secondly, we selected the national organisations according to their apparent international reputation and by browsing the websites of the World Dental Federation, the International Association of Paediatric Dentistry and the International Association of Paediatrics. Attempts were made to select at least one general dental organisation, one paediatric dentistry organisation and one paediatric (medical) organisation per country. Lastly, whenever an organisation did not produce the item requested but suggested we should contact another organisation, this other organisation was also included.

A first round of emails was sent to each organisation in September 2008. In case of no answer, four more attempts (2 emails and 2 letters) were made until April 2009. The postal addresses and emails of all organisations were obtained either by searching Google™ or at the websites of the international associations mentioned above. All organisations were requested to send any and all kind of items such as brochures, leaflets or folders containing recommendations on children's oral hygiene practices aimed at the general public. As some websites are more search-friendly than others and to avoid missing any information, we also asked the organisations whether information on this issue was disclosed on their websites.

Scientific evidence was obtained from systematic reviews available at the Cochrane Oral Health Review Group (http://www.ohg.cochrane.org/reviews.html)[1] and at PubMed (http://www.ncbi.nlm.nih.gov/sites/pubmedutils/clinical)[#], using the tool "Clinical Queries", the filter "Find Systematic Reviews" and the text words "oral hygiene" and "dentifrices", accessed on January 10, 2010. It was defined a priori that only mechanical oral hygiene practices would be assessed: toothbrushing, flossing and gums/tongue cleaning. The search and the selection of the systematic reviews were performed by one author (APPS). Whenever there were any doubts about the pertinence of a review, another author (PN) was consulted and any disagreement was solved by consensus.

Results

Recommendations provided by professional organisations

Of the 59 dental or medical organisations that were contacted by mail or electronic mail (Figure 1), 52 (88%) answered; 20 reported not producing the items requested, even though 1 disclosed information on the topic on its website; 22 sent the items requested either in print or electronic format and 10 sent items that were further excluded due to idiom constraints or because they were aimed at professionals or did not address the topic of interest. Among the 7 organisations that did not answer, 1 disclosed the information requested on their website, amounting to 24 items to be evaluated (Table 1). All items mentioned at least one aspect of children's oral hygiene practices such as toothbrushing frequency, supervision and

[1] Self-Archived at WebCite® on Jan 10, 2010 (http://www.webcitation.org/5mgBmSiOE)
[#] Self-Archived at WebCite® on Jan 10, 2010 (http://www.webcitation.org/5mgBzHGv1)

technique; when to start and how long toothbrushing should last; toothbrush design and replacement; flossing; gums/teeth wiping; tongue cleaning; type and amount of toothpaste and advice on toothpaste ingestion (Table 2).

Almost all organisations provided information on toothbrushing frequency, type of toothpaste and amount of toothpaste. On the other hand, many organisations failed to provide any recommendation concerning toothbrushing technique, the amount of time children should spend at toothbrushing, toothbrush replacement and tongue cleaning. Huge inconsistencies were detected concerning the most appropriate toothpaste for children and although the vast majority of organisations advocated toothbrushing supervision, there was no consensus about until what age this practice is needed.

Scientific evidence currently available

The search carried out at the Cochrane Oral Health Review Group retrieved 95 systematic reviews, 5 of which were considered pertinent to the present study. The search carried out at PubMed Clinical Queries yielded 258 citations using the text words “oral hygiene” and 72 using the text word “dentifrices”. Of these 330 citations, 6 were systematic reviews addressing the topic of interest. Only systematic reviews focusing on oral hygiene practices aimed at children were considered[9-19] (Table 3).

One systematic review assessed the role of flossing in the reduction of interproximal caries[12] whereas the other 10 addressed issues pertaining to fluoride toothpaste[9-11, 13-19]. Concerning the role of fluoride dentifrice in caries prevention, a significant increase of the preventive fraction was found when toothbrushing with fluoride dentifrice was performed twice daily in comparison with only once a day[14]. Also, 3 systematic reviews reinforced the need to supervise children’s toothbrushing as it probably results in a higher compliance and a higher frequency of fluoride dentifrice use[11, 14, 19]. Two systematic reviews about low fluoride dentifrice showed lower caries increments in children using 1,000ppm dentifrices in comparison to children using 250ppm dentifrices. One does not recommend the use of 250ppm dentifrices in areas where fluoride levels in water are low[9], whereas the other supports the use of 250ppm dentifrices when fluorosis is of concern[18].

Discussion

Other health professionals, apart from paediatric dentists, play a role in oral health education aimed at children. For instance, children are more likely to visit a paediatrician than a dentist in their first years of life. Despite limited knowledge of and little familiarity with basic oral health-related issues, most paediatricians acknowledge their role in identifying dental problems, counseling families on dental caries prevention and referring patients[20]. Therefore, in this study we gathered oral hygiene messages conveyed not only by paediatric dental associations, but also by other organisations that may, at least to some extent, provide counseling on oral health to the general public. The fact that there was no attempt to draw a representative sample of national or international organisations or to make comparisons across countries does not weaken the importance of our findings. Whenever dentists, oral health programs, academic institutions or the Internet deliver conflicting oral health messages to the public, confusion, scepticism and low acceptance of educational messages may arise[1, 7]. Thus, the existence of a certain level of disagreement among oral hygiene recommendations should be addressed despite the lack of representativeness.

Organisations that recommend twice-daily toothbrushing are in line with current available scientific evidence on frequency of toothbrushing. However, there is no evidence suggesting that higher frequencies of toothbrushing, i.e. more than twice a day, are beneficial. Hence, systematic reviews addressing head to head comparisons of different frequencies of toothbrushing are required.

There is general agreement on the importance of supervised toothbrushing, although recommendations differ on at what age children are able to brush their teeth on their own. This may give rise to doubts as to when parents should brush their children's teeth and when only supervision is required. It should be pointed out that the studies that assessed toothbrushing supervision were carried out in schools or similar settings. It remains unclear whether home toothbrushing supervision, as advised by dental and medical organisations, is capable of providing the same protection against dental caries as school-based supervised programs do.

Scant scientific evidence, implied by lack of systematic review, may partly explain why toothbrushing techniques, amount of time spent at toothbrushing and frequency of toothbrush replacement have been overlooked by most organisations.

Flossing is regarded as an integral part of tooth-cleaning as it disrupts and removes dental biofilm at interproximal surfaces and the biological plausibility of interproximal caries reduction due to flossing is widely accepted by lay people and professionals. The only systematic review on flossing we found failed to show interproximal caries risk reductions for self-flossing, although the authors acknowledged the presence of a moderate to high risk of bias in the trials evaluated.[12] However, dentists and health organisations should bear in mind that there is lack of evidence to support self-flossing as a measure to prevent interproximal caries, especially when people are exposed to fluoride.

Although the effectiveness of fluoride dentifrice in reducing the incidence of dental caries has already been established[11, 14, 19], no systematic review addressed its dental fluorosis risk. Nowadays, children may be exposed to different sources of fluoride, which arguably puts them at a higher risk of fluorosis, especially those aged 20 to 30 months-old, a critical period for sustaining aesthetic alterations in the permanent upper incisors[21]. Hence, dental and medical organisations agree that preschool children should not only use a small amount of dentifrice but also avoid swallowing it. Other strategies aimed at preschool children that have been adopted by a number of organisations include refraining from fluoride dentifrice and using low fluoride dentifrice. However, in light of current evidence, it seems unjustifiable to prevent preschool children from the well-established benefits of fluoride dentifrice. Regarding low fluoride dentifrice, both systematic reviews addressing this topic highlight important weaknesses in the trials included and most of these trials were performed in schoolchildren, whereas the target population for low fluoride dentifrice use comprises preschool children[9, 18]. Therefore, it seems premature to advise preschool children to brush their teeth with low fluoride dentifrice due to fluorosis concerns, especially because it has been suggested that mild fluorosis does not have a negative impact on the perception of dental appearance, self-rated oral health or child and parent perceptions of oral health-related quality of life[22].

The post-brushing behaviour is a source of controversy among organisations, as it is among researchers. We found two clinical trials on the topic showing different results[23, 24]. Hence, the evidence on to rinse or not to rinse with water after toothbrushing remains inconclusive.

Although there seems to be no apparent explanation for postponing the age children should start toothbrushing, some organisations do not recommend

toothbrushing soon after the eruption of the first tooth. Concerning wiping babies' gums prior to tooth eruption, although it is a widely recommended practice, its effectiveness has yet to be proved.

Items from 4 organisations stated the need for tongue cleaning, even though they were rather unclear about the benefits accrued from this behaviour. On the one hand, there is evidence that toothbrushes and tongue scrapers reduce the levels of volatile sulphur compounds and thus may be effective in the treatment of halitosis in adults[25]. Maybe the importance of tongue cleaning among children lies in the fact that acquiring this habit at an early age could result in its maintenance in adulthood and avoid halitosis in children and adults. On the other hand, the presence of *mutans streptococci* appears to be a predictive factor for dental caries risk in preschool children[26]. As it has been suggested that the tongue is a potential reservoir for these cariogenic species in young children[27], the act of tongue cleaning may have implications for dental caries prevention, although it is noteworthy that this intervention has not been tested in a clinical trial.

Several of the oral hygiene messages identified showed inconsistencies across the different organisations and although some of these messages are in line with the best currently available scientific evidence, most lack scientific support. This study raised some potential areas for future research, which can contribute to an appropriate incorporation of scientific evidence by dental and medical organisations and eventually reduce conflicting oral hygiene messages delivered to the general public.

Bullet points

What this paper adds

- This paper reports that there exist serious differences in the dental health education messages that dental professional organisations disseminate to the public.

Why this paper is important for paediatric dentists

- This paper highlights the need to provide the public with evidence-based recommendations regarding oral hygiene practices.

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Figure 1. Number of dental and medical organisations in each country that were contacted, answered and sent items containing oral hygiene messages.

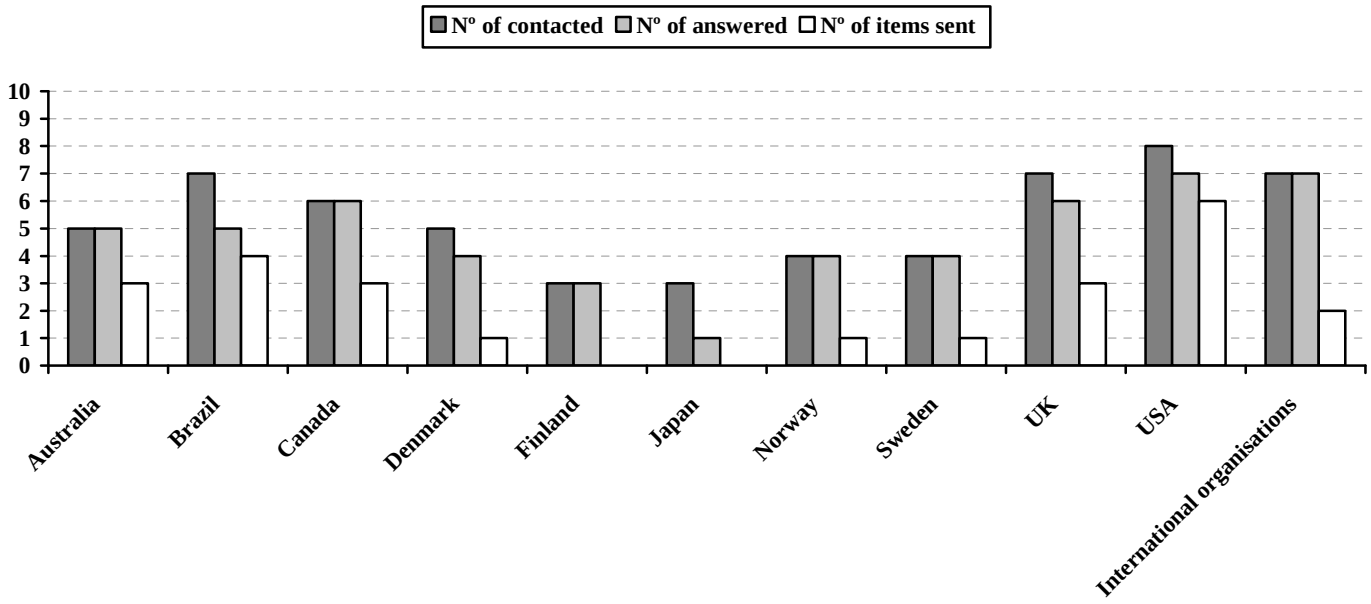

Table 1. Dental and medical (paediatric) organisations that responded and sent dental health materials on children's oral hygiene practices

Organisation	Item provided
Australia	
Australian Dental Association	*Oral hygiene for babies and toddlers* (http://www.webcitation.org/5mevLBvmr)*
Australian and New Zealand Society for Paediatric Dentistry	*Preventive care for children* (http://www.webcitation.org/5mevfbJXZ)*
Australian Research Centre for Population Oral Health	*Oral health promotion for infants, and preschool and school children* (http://www.webcitation.org/5mex16SNb)*
Brazil	
Association of Dental Surgeons of the State of São Paulo[#]	Information sent by email
Brazilian Association of Health Promotion Dentistry	*Sorriso em todas as idades* (http://www.webcitation.org/5mevxeEAd)*
Brazilian Dental Association	Folder sent by mail (*Educação em saúde bucal*)
National Oral Health Council, Ministry of Health	*Caderneta de saúde da criança* (http://www.webcitation.org/5mf56jJOT)* and *Mantenha seu sorriso fazendo a higiene bucal corretamente* (http://www.webcitation.org/5mf5vxYJA)*
Canada	
Canadian Dental Association	*Dental Care for Children* (http://www.webcitation.org/5mexNdyM7)*

Canadian Paediatric Society	*Healthy teeth for children* (http://www.webcitation.org/5mexbqs3K)*
Health Canada	*Health living - oral health* (http://www.webcitation.org/5meyyiaYY)*
Denmark	
Danish Society of Pediatric Dentistry	Information sent by email
Norway	
Norwegian Association for Promotion of Oral Health	Folder sent by email (*Veiviser til god tannhelse*)
Sweden	
Swedish National Board of Health and Welfare	Folder sent by email (*Folktandvården - the Dental Public Service in Stockholm*)
United Kingdom	
British Dental Association	*BDA Smile - Infants & Children* (http://www.webcitation.org/5mexHmlE9)*
Department of Health	*Dental care for babies and children* (http://www.webcitation.org/5meyZz24C)*
Scottish Intercollegiate Guidelines Network	*Prevention and management of dental decay in the pre-school child* (http://www.webcitation.org/5mezrjQmy)*

United States of America	
American Academy of Pediatrics	*Children's health topics - oral health* (http://www.webcitation.org/5metIHAHn)*
American Academy of Pediatric Dentistry	*Parent Education Brochures* (http://www.webcitation.org/5metnDAV1)*
American Dental Association	Folders sent by mail (*Happiness is a healthy smile, Healthy smiles for mother & baby, Your child's teeth, Why baby teeth are important*)
Centers for Disease Control and Prevention	*Brush Up on Healthy Teeth* (http://www.webcitation.org/5mf4ewHar)*
National Institute of Dental and Craniofacial Research	*A Healthy mouth for your baby* (http://www.webcitation.org/5mezLkkWc)*
National Maternal and Child Oral Health Resource Center	*Head Start - FAQs* (http://www.webcitation.org/5mezWwwld)*
International organisations	
European Academy of Paediatric Dentistry	*A guide to oral health for the prospective mothers and their infants* (http://www.webcitation.org/5meyhGWyd)*
International Association of Paediatric Dentistry	*Parents - Let me ask you, Doc* (http://www.webcitation.org/5mezCrWJQ)*

* Self-Archived at WebCite® on Jan 9, 2010.
# Despite named "São Paulo", it is in reality a national organisation.

Table 2. Oral hygiene recommendations aimed at children provided by 24 dental and medical (paediatric) organisations

Subject	Recommendation	Number of organisations
Toothbrushing		
Toothbrushing frequency*	Subject not mentioned	7
	At least once a day	4
	Twice a day	14
When to brush*	Subject not mentioned	7
	After meals	8
	After sugar intake	2
	After medication intake	2
	After breast/bottle feeding	4
	Before sleeping	11
Toothbrushing supervision*	Subject not mentioned	5
	Toothbrushing should be supervised	4
	Until 6 years of age	2
	Until 7 years of age	2
	Until 8 years of age	4
	Until 9 years of age	3
	Until 10 years of age	2
	Until 11 years of age	2
	Until the child is skilled	5
	Children brush on their own and parents finish off toothbrushing	5
	Parents should brush their children’s teeth until 2 years of age	1
	Parents should brush their children’s teeth until 3 years of age	2
	Parents should brush their children’s teeth until 4 years of age	1
	Parents should brush their children’s teeth until 6 years of age	1
	Parents should brush their children’s teeth until 7 years of age	2
	Parents should brush their children’s teeth until 12 years of age	1
	Parents should brush their teeth in front of their children	4

Toothbrushing technique*	Subject not mentioned	16
	Gentle motions	6
	Small circular motions	5
	Short back and forth motions at chewing surfaces	5
	Do not scrub	3
	Angle the bristles towards the gums at 45 degrees	2
	Jiggle the toothbrush from the gum line towards the tip of the tooth	2
	Avoid flicking and circular motions	1
	Three or two teeth at a time	2
	One tooth at a time	1
	Use a disclosing solution	3
When to start toothbrushing*	Subject not mentioned	4
	When the first primary tooth emerges	13
	When the first primary molar emerges	5
	After the eruption of the incisors	2
	At 18 months of age	2
	At 24 months of age	1
Time spent at toothbrushing	Subject not mentioned	21
	At least one minute	1
	2 minutes	2
Toothbrush design*	Subject not mentioned	8
	Finger toothbrush	2
	Child toothbrush	5
	Small head	10
	Soft bristles	14
	End-rounded bristles	2
	Bulky handle	1
	Powered toothbrush	4
Toothbrush replacement*	Subject not mentioned	19
	Every 3-4 months	4
	When it becomes worn out	2

Flossing*	Subject not mentioned	13
	At least twice a week	2
	Daily	3
	Daily, whenever teeth have contact	5
	When children are two and a half years of age	1
	Parents should floss until 8-10 years of age	3
	Parents should supervise flossing until 10-11 years of age	1
	Floss with fluoride toothpaste	1
Gums/teeth wiping*	Subject not mentioned	8
	Until the first primary tooth emerges	4
	Until the first primary molar emerges	5
	Until one year and a half	1
	Until the second birthday	1
	Using gaze pad or wet cloth	14
	Using a soft-bristled toothbrush	6
	Using a finger toothbrush	3
Tongue cleaning	Subject not mentioned	20
	Children should have their tongue cleaned	4
Toothpaste		
Type of toothpaste*	Subject not mentioned	3
	Non-fluoride toothpaste until 18 months of age	1
	Non-fluoride toothpaste until 2 years of age	5
	Non-fluoride toothpaste until 3 years of age	4
	Non-fluoride toothpaste until 4 years of age	2
	Low fluoride toothpaste until 6 years of age	3
	Fluoride toothpaste, irrespective of age	9
Amount of toothpaste*	Subject not mentioned	3
	Small amount	1
	Smear	10

	Pea grain	14
	Rice grain	2
	Bean grain	1
	Child’s little finger nail	1
	Transversal technique	1
Advice on toothpaste ingestion*	Subject not mentioned	7
	Keep the tube of toothpaste out of children’s reach	5
	Do not swallow toothpaste	15
	Do not eat or lick toothpaste	1
	Do not rinse after toothbrushing	6
	Do not rinse after toothbrushing with lots of water	1
	Rinse after toothbrushing	1
	Rinse well after toothbrushing	1

*The number of organizations does not add up to 24 as the same organization may provide more than one recommendation.

Table 3. Summary of systematic reviews* focusing on oral hygiene practices aimed at children

Title	Author/Year	Conclusions/Recommendations
Systematic review of studies comparing the anti-caries efficacy of children's toothpaste containing 600ppm of fluoride or less with high fluoride toothpastes of 1,000ppm or above.	Ammari et al.[10] (2003)	Toothpastes containing 250ppm F were not as effective in caries prevention in permanent dentition as those containing 1,000ppm F. Data comparing 500ppm with 1,000ppm fluoride toothpastes were very limited and further research is required.
Reduction in dental caries with four concentrations of sodium fluoride in a dentifrice: a meta-analysis evaluation.	Bartizek et al.[11] (2001)	The use of a 2,800 ppm F dentifrice showed significantly lower caries increments than the use of a 1,100 ppm F dentifrice in school children. The 1,700 ppm F and 2,200 ppm F dentifrices showed some directional advantages over the 1,100 ppm F dentifrice, though not statistically significant.
Anticaries effectiveness of fluoride toothpaste: a meta-analysis.	Chaves et al.[12] (2002)	Toothbrushing with fluoride toothpaste significantly decreases the incidence of dental caries. Higher caries reductions were observed when toothbrushing was supervised.
Dental flossing and interproximal caries: a systematic review.	Hujoel et al.[13] (2006)	Professional flossing in children with low fluoride exposure and poor toothbrushing habits is effective in reducing interproximal caries risk. Self-flossing has failed to show an effect. Studies assessing the effects of fluoride toothpastes and flossing devices are required.
Topical fluoride (toothpastes, mouthrinses, gels or varnishes) for preventing dental caries in children and adolescents.	Marinho et al.[14] (2003)	The benefits of topical fluorides have been firmly established. No conclusions about adverse effects could be reached.
Fluoride toothpastes for preventing dental caries in children and adolescents.	Marinho et al.[15] (2003)	There is clear evidence that fluoride toothpastes are effective in preventing caries, regardless of water fluoridation. Higher effects were shown with higher baseline caries levels, increased fluoride concentration, increased frequency of use (twice x once/day) and supervised toothbrushing. No conclusions about adverse effects could be reached.
Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus single topical fluoride for preventing dental caries in children and adolescents.	Marinho et al.[16] (2004)	Topical fluorides (mouthrinses, gels or varnishes) used in addition to fluoride toothpaste achieve a modest reduction in caries compared to toothpaste used alone. However, combined use of topical fluorides and toothpaste may be considered for children at higher risk of caries. No conclusions about adverse effects could be reached.
One topical fluoride (toothpastes, or mouthrinses, or gels, or varnishes) versus	Marinho et al.[17]	Fluoride toothpastes, mouthrinses and gels reduce caries in children and adolescents to a similar extent but acceptance is likely to be greater for fluoride

another for preventing dental caries in children and adolescents.	(2004)	toothpaste. There is no strong evidence that varnishes are more effective than other types of topical fluoride. No conclusions about adverse effects could be reached.
Comparison of the anticaries efficacy of dentifrices containing fluoride as sodium fluoride or sodium monofluorophosphate.	Proskin et al. [18] (1995)	Dentifrices containing fluoride as sodium fluoride or as sodium monofluorophosphate provide equivalent anticaries effectiveness.
Effect of 1,000ppm relative to 250ppm fluoride toothpaste. A meta-analysis.	Steiner et al.[19] (2004)	Slightly lower caries increments were found in children using 1,000ppm fluoride toothpastes when compared to children using 250ppm fluoride toothpastes. The authors state that the 1,000ppm toothpaste's effects on fluorosis and the availability of fluoridated salt justify the use of 250ppm toothpastes for Swiss preschool children.
Caries-preventive effect of fluoride toothpaste: a systematic review.	Twetman et al.[20] (2003)	There is strong evidence for the caries preventive effect of daily use of fluoride toothpaste. Superior preventive effects were found with 1,500 ppm F toothpastes and supervised toothbrushing. There is incomplete evidence regarding the effect of fluoride toothpaste in the primary dentition.

* Self-Archived at WebCite® on January 10, 2010. Cochrane Oral Health Review Group: http://www.webcitation.org/5mgAGHLGp; PubMed using the text words "oral hygiene": http://www.webcitation.org/5mgB6zESt; PubMed using the text word "dentifrices": http://www.webcitation.org/5mgBBZjLf

APÊNDICE C - Artigo 1

Title:

A systematic review and meta-analysis of the effects of fluoride toothpastes on the prevention of dental caries in the primary dentition of preschool children

Running head:

Fluoride toothpastes and caries in the primary dentition

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Abstract

Objectives: To assess the effects of fluoride (F) toothpastes on the prevention of dental caries in the primary dentition of preschool children. Study design: Systematic review and meta-analysis. Methods: A search for randomized or quasi-randomized clinical trials was carried out, without idiom restraints, in six electronic databases, registers of ongoing trials, meeting abstracts, dentistry journals and reference lists of potentially eligible studies. The search yielded 1932 records and 159 full-text articles were independently read by two examiners. Data regarding characteristics of participants, interventions, outcomes, length of follow-up and potential of bias were independently extracted by two examiners on the basis of predetermined criteria. Any disagreement was solved by a third examiner. Pooled prevented fractions (PF) and relative risks (RR) were estimated separately for studies testing low F toothpastes (<600 ppm) and those testing standard F toothpastes (1000 - 1500 ppm). Results: Eight clinical trials fulfilled the inclusion criteria and most of them compared F toothpastes associated with oral health education against no intervention. When standard F toothpastes were compared to placebo or no intervention, significant caries reduction at surface (PF= 31%; 95% CI 18 – 43; 2644 participants in five studies), tooth (PF= 16%; 95% CI 7 – 24; 2555 participants in one study) and individual level (RR= 0.86; 95% CI 0.81 - 0.93; 2806 participants in two studies) were observed. Low F toothpastes were effective only at surface level (PF= 40%; 95% CI 5 – 75; 561 participants in two studies). Conclusion: Standard F toothpastes are effective in reducing dental caries in the primary teeth of preschool children and thus their use should be recommended to this age group.

Introduction

Despite significant improvements in children's oral health status over the past decades, dental caries still remains a major oral health problem, especially among socio-economically deprived groups (1). Preschool children, in contrast to other age groups, have experienced a significant increase in caries prevalence in the primary dentition (2, 3) and, once caries develops in young children, adverse outcomes such as dental pain and the need for extraction are common (4). Children with caries have an incidence of new cavities 5-6 times greater than those without caries, irrespective of when they developed the disease (5), and those with caries in their primary teeth are three times more likely to develop caries in their permanent teeth (6).

The role of fluoride (F) toothpastes in the control of dental caries is well established and beyond dispute. Systematic reviews have shown that the use of standard F toothpastes (1000 - 1500 ppm) reduce approximately 24 to 29% the incidence of dental caries in children's permanent teeth (7-9). However, little information has been provided regarding the effects of F toothpastes in the primary dentition and the lack of evidence of this intervention in preschool children has been highlighted previously (8-10).

Higher rates of caries progression have been detected in primary teeth in comparison with young permanent teeth (11-15) and this is probably due to the thinner enamel layer in primary teeth. Differences in carbonate contents between primary and permanent teeth may also contribute to the faster caries progression in primary teeth (16, 17). Although it would be reasonable to expect a similar effect of F in both dentitions, it is still unclear whether the differences mentioned above could interfere with F anti-caries potential.

The aim of this study was to assess the effects of F toothpastes on the prevention of caries in the primary dentition of preschool children.

Materials and Methods

Study design: systematic review and meta-analysis.

Criteria for considering studies for this review

Studies: individual or cluster randomized or quasi-randomized clinical trials. Non-randomized clinical trials, observational studies and studies with a follow-up period shorter than one year were excluded.

Participants: children in the primary dentition phase at the beginning of the study, irrespective of baseline caries levels. Children should be no older than seven years old when the outcome was assessed. Studies whose participants had special general or oral health conditions were excluded.

Interventions: F toothpastes in contrast to placebo or no intervention. F toothpastes were considered irrespective of F concentration, F agent, abrasive system and pH. Studies whose interventions included other F products (gel, varnish, mouthrinse) or other non-F products (chlorhexidine, xilitol, dental sealants) were excluded.

Outcomes: dental caries increment in the primary dentition, measured by the number of decayed, missing due to caries and filled teeth and surfaces (dmft and dmfs indices, respectively) and proportion of children developing dental caries in the primary dentition. Caries was assessed at the enamel and dentine level of diagnosis, at both cavitated and non-cavitated stages, as long as they were recorded separately, which means that studies that recorded all levels of diagnosis and stages of caries as a whole were excluded.

Search strategy

Electronic search: The following databases were consulted from date of online availability to January 2010: The Cochrane Central Register of Controlled Trials (CENTRAL/CCTR), MEDLINE via PubMed, WEB OF SCIENCE, EMBASE, LILACS and BBO. Additional sources included a Brazilian database of thesis and dissertations (*Banco de Teses CAPES*), a Brazilian register of ethically approved projects involving human beings (SISNEP) and two international registers of ongoing trials (Current Controlled Trials and ClinicalTrials.gov). The search strategy included controlled vocabulary and free terms. It was developed for MEDLINE (Appendix 1) and adapted for the other databases. Meeting abstracts of the International

Association for Dental Research (2001-2011) and the European Organisation for Caries Research (1998-2011) were also searched.

Reference lists: References of eligible trials and systematic and narrative reviews on the subject of F toothpastes were checked in order to detect potential studies.

Idioms: There were no idiom restraints. When necessary, studies were translated.

Correspondence: Specialists in the field were contacted by email. These included authors of studies on the subject of F and dental/oral epidemiology professors/researchers.

Handsearch: Sixteen dentistry journals were chosen to be handsearched: Acta Odontologica Scandinavica, Archives of Oral Biology, British Dental Journal, Caries Research, Community Dental Health, Community Dentistry & Oral Epidemiology, European Archives of Paediatric Dentistry, European Journal of Oral Sciences, International Dental Journal, International Journal of Paediatric Dentistry, Journal of the American Dental Association, Journal of Clinical Pediatric Dentistry, Journal of Dental Research, Journal of Dentistry for Children, Journal of Public Health Dentistry and Pediatric Dentistry. The Cochrane Collaboration has organized a worldwide handsearching programme (18), which covers all the above-mentioned journals. Once a clinical trial is identified, it is incorporated into CENTRAL database. We checked the date of last handsearching update for each journal in the Cochrane Master List of Journals Being Searched and handsearching was complemented until June 2010 by two independent examiners.

Data collection and analysis

Management of references: References were imported to the software EndNote X3® (Thomson Reuters, CA, USA), enabling the identification of duplicates.

Selection of studies: Two examiners read the titles and abstracts (when available) of all studies identified in the electronic search. No blinding was performed regarding authors' names, journals and publication date. Whenever there was not enough information available, the full-text article was obtained. Any disagreement was solved by a third examiner.

Data extraction: Two examiners independently extracted the data by means of a data extraction form. Any disagreement was solved by a third examiner. Attempts were made to contact the authors to check for incomplete data. Missing standard deviations (sd) were calculated according to Higgins et al.(19).

Assessment of risk of bias in included studies: We used the Cochrane Collaboration's tool for assessing risk of bias (20). The following domains were assessed: generation of allocation sequence, allocation concealment, blinding of participants and outcome assessors, incomplete outcome data and selective outcome reporting. Each domain was classified as having low, high or uncertain risk of bias. For this review, non-blinding of participants was judged as unlikely to introduce bias so single-blinded studies, as long as the outcome assessors were blinded, were considered as having low risk of bias. Also, studies were considered to be free of selective outcome reporting and thus having low risk of bias when the outcomes included caries increment at both surface and tooth level and the proportion of children developing caries. Other possible sources of bias, defined by the authors of this review, included: losses to follow-up (low risk of bias when less than 20%); diagnosis reliability (low risk of bias when good, according to Landis and Koch (21)); baseline balance (low risk of bias when data showed baseline balance regarding age, gender, socioeconomic status and caries levels) and contamination (low risk of bias when strategies to avoid contamination between groups were reported).

Statistical analysis: Data skewness prevented a meta-analysis of the difference in means. Instead, meta-analyses of prevented fractions (PF) were performed in order to assess the effect of fluoride toothpaste on the number of decayed, missing due to caries and filled teeth (dmft) and dental surfaces (dmfs). PFs were calculated by subtracting the mean caries increment in the test group (F toothpaste) from the mean caries increment in the control group (placebo or no intervention) and then dividing by the mean caries increment in the control group; they correspond to the proportion of disease in the control group that could have been prevented had the intervention been implemented (22). Confidence intervals (CI) of PFs were calculated using Fieller's method (23).

Meta-analyses were also performed in order to obtain a pooled relative risk (RR) to assess the effect of F toothpastes on the proportion of children developing caries. Number needed to treat for an additional beneficial outcome (NNTB), which

corresponds to the number of children that need to use standard F toothpaste, as opposed to no intervention, in order to prevent caries in one child, was derived by applying the pooled RR to three different scenarios of caries incidence (24); 95% CIs were derived by applying the 95% CIs of the pooled RR (25).

Heterogeneity of studies was assessed by visual inspection of forest plots, chi-square homogeneity test (χ^2) and Higgins index (I^2). A random effects model was used in the presence of heterogeneity (χ^2 with significance level < 0.10 and I^2 > 50%).

The meta-analyses contain trials that reported the mean increment of caries as well as the final levels of caries, which is not considered problematic (26). They were carried out separately for low (< 600 ppm) and standard (1000 - 1500 ppm) F toothpastes, using the software Stata®11.1 (StataCorp LP, College Station, TX, USA), by means of the *metan* command with three parameters (PFs and the lower and upper limit of 95% CI) or four parameters (number of events and nonevents in the test and control groups). The paucity of studies prevented the use of meta-regression to assess the influence of study characteristics on the treatment effect, as well as the assessment of publication bias.

Results

Search

After excluding duplicates, 1932 records were retrieved from the electronic search. Handsearching and the search for ongoing trials yielded no additional reports. One hundred and fifty four reports were considered relevant and the full-text articles were obtained. After checking the references of these articles, five more potentially eligible full-text articles were also obtained. Three articles in German were translated. Eight articles corresponding to eight studies were included. Figure 1 shows a flow diagram of the reports that were identified, screened, assessed for eligibility, excluded and included in the review.

Included studies

The characteristics of included studies are described in Appendix 2.

Risk of bias in included studies

Figure 2 shows the risk of bias in the included studies, according to nine different domains. Crucial aspects, such as sequence generation and allocation concealment, have not been reported adequately and thus were judged as unclear in half of the studies. The studies have also failed to provide enough information on diagnosis reliability, baseline balance and contamination and, in all studies, except for one, selective outcome reporting was present.

Interventions

The interventions tested in the studies are detailed in Table 1. It can be noted that they differed markedly across studies; test groups used different F concentrations, whereas control groups received either a placebo or no intervention. In most studies oral health education was part of the intervention.

Outcomes

dmfs increment

Information on the number of decayed, missing due to caries and filled primary dental surfaces is detailed in Table 2. Figure 3 shows that the meta-analysis of two studies (27, 28) comparing low F toothpastes and no intervention yielded a pooled PF of 40% (95% CI 5 - 75), whereas the meta-analysis of five studies (29-33) comparing standard F toothpastes and placebo or no intervention yielded a pooled PF of 31% (95% CI 18 - 43).

dmft increment

Information on the number of decayed, missing due to caries and filled primary teeth is detailed in Table 3. Figure 4 shows that the meta-analysis of two studies (27, 34) comparing low F toothpastes and no intervention yielded a pooled PF of 24% (95% CI -17 – 66). Table 3 and Figure 4 show data regarding the only study comparing standard F toothpaste and no intervention that reported caries incidence by means of the dmft index (34). This study showed that 12-month-old children that used 1450 ppm F toothpaste for approximately 5½ years had mean caries levels at final examination of 2.15 (±2.96) whereas those receiving no intervention had mean caries levels at final examination of 2.57 (±3.16); the prevented fraction was 16% (95% CI 7 – 24).

Proportion of children developing dental caries

Two studies comparing low F toothpastes and no intervention (27, 34) and two comparing standard F toothpaste and no intervention (32, 34) reported the proportion of children who developed dental caries. Regarding the comparison between low F toothpastes and no intervention, the pooled RR was not statistically significant (0.87; 95% CI 0.65 – 1.17); on the other hand, the studies comparing standard F toothpastes and no intervention yielded a statistically significant pooled RR (0.86; 95% CI 0.81 – 0.93) (Figure 5). NNTBs were 11 (95% CI 7 - 20), 15 (95% CI 10 - 28) and 37 (95% CI 26 - 59) for scenarios of high, medium and low caries incidence, respectively.

Discussion

This systematic review and meta-analyses assessed the role of F toothpastes in reducing dental caries in the primary teeth of preschool children and their results support the findings from previous reviews on the anti-caries potential of F toothpastes in the permanent teeth of schoolchildren (7-9). Preschool children who brushed their teeth with standard F toothpastes experienced a significant reduction in the mean number of primary decayed, missing due to caries and filled dental surfaces and teeth. They also had a significant lower risk of developing dental caries than those who received no intervention. In populations with high 5-year-caries incidence (e.g. 70%), 11 preschool children need to use standard F toothpaste (as opposed to no intervention) in order to avoid caries in one preschool child. In populations with medium (e.g. 50%) and low (e.g. 20%) 5-year-caries incidence, NNTBs would be 15 and 37, respectively. Even the higher NNTB obtained in a scenario of low caries incidence can be considered highly beneficial when it is taken into account that standard F toothpaste is a simple, safe, non-invasive and relatively inexpensive population intervention.

The evidence on the effectiveness of low F toothpastes on the prevention of dental caries is somewhat equivocal. Overall, 1000 ppm F toothpastes provide a higher caries preventive effect in comparison with 250 ppm F toothpastes (35-37) and a lack of a statistically significant additional benefit of 500 ppm F toothpastes compared with 250 ppm F toothpastes or of 1000 ppm F toothpastes compared with 500 ppm F toothpastes has been reported (37). A recent meta-analysis, which has compared the effects of low and standard F toothpastes on the reduction of caries in

the primary teeth of preschool children, showed that using low F toothpastes increased the risk of developing caries when compared with standard F toothpastes (38).

In our review, only when the dmfs index was considered has the comparison between low F toothpastes and oral health education against no intervention yielded a statistically significant PF. Meta-analyses at tooth and individual level failed to show statistically significant differences between the group who received low F toothpastes associated with oral health education and the group who received no intervention at all (it should be noted that few studies were included and there was considerable heterogeneity). Strangely, though, among all the studies included in this review (irrespective of F concentration), the higher PFs at both tooth and surface level were found in a trial testing a low F toothpaste (27). However, this trial was poorly reported: among the nine domains of methodological quality assessment, six were judged as unclear, including sequence generation, allocation concealment and blinding, which are important safeguards against bias. Trials with inadequate or unclear sequence generation and allocation concealment tend to yield exaggerated estimates of intervention effects (20, 39, 40). Lack of blinding of outcome assessors in randomized trials has also been associated with more exaggerated estimated intervention effects (40), even when the outcome is objective, like dental caries at cavitated level. As this trial has contributed data to all meta-analyses regarding low F toothpastes (surface, tooth and individual level), the pooled estimates of these meta-analyses may be overestimated. Overall, the studies included in this review have not performed satisfactorily on the methodological quality assessment. This finding emphasizes that the reporting of clinical trials has yet to be improved, regardless of the widespread advocacy of the Consolidated Standards of Reporting Trials statement (39).

The effectiveness of F toothpastes has been much more extensively studied in the permanent dentition than in the primary dentition. Three systematic reviews that assessed the capacity of F toothpastes to reduce dental caries in permanent teeth of children based their conclusions on 22 (7), 54 (9) and 70 (8) clinical trials. However, only eight clinical trials fulfilled the inclusion criteria of this review. The paucity of studies precluded further analyses on the influence of study characteristics, such as baseline caries levels and the use of placebo, on the differences observed in the estimates of treatment effect across the studies.

Four out of the five trials included in the meta-analysis comparing the effects, at surface level, of standard F toothpastes associated with oral health education against placebo or no intervention, were carried out in China. Among these, two provided a placebo toothpaste to the control group whereas in the others it was reported that, despite receiving no intervention, children from the control group used non-F toothpaste, which was the toothpaste widely used in China. The pooled PF was 31% but it is noteworthy that the prevalence of dental caries in preschool children in China is high (41-44) and a higher beneficial effect of F toothpastes is to be expected with increased baseline caries levels (8). Thus, the findings from these trials should be cautiously interpreted when considering other scenarios.

One shortcoming of this review is that the majority of studies compared F toothpastes associated with oral health education against no intervention and therefore it could be argued that the effect measure obtained cannot be ascribed to the F toothpaste per se but to the joint effect of F toothpastes and oral health education. However, there is no evidence that oral health education is effective in changing oral health outcomes such as caries (45-47). School-based programs have improved oral hygiene levels in the short term, but the impact of such programs on caries incidence is open to question. Furthermore, all programs involving oral health education that have proved to be effective in caries reduction have included F therapy (48). Thus, oral health education should not be considered as a co-intervention with potential of bias and the significant caries reduction observed in the meta-analyses may be attributed to the use of F toothpastes.

Moreover, as most control groups received no intervention instead of a placebo, it is not possible to assure which toothpaste, if any, children from the control groups were using, except for the trials carried out in China, where F toothpastes were not readily available at the time the studies were conducted (31, 32). Therefore, contamination between groups cannot be ruled out. Also, no intervention control groups may overestimate the caries preventive effect (49).

Evidence on the effects of F toothpastes has been underpinned by trials carried out mainly between the sixties and the eighties, when it was unusual to include preschool children in caries assessment. During this period, only one trial assessed the caries incidence rate in the primary dentition by reporting the number of new decayed or filled teeth per 100 observed primary teeth (50). This trial found a prevented fraction of 37% ($p<0.001$), but this study was not included in the present

review as its focus was not on primary teeth of preschool children, but of schoolchildren. All the studies included in this review were conducted in the last two decades, when the anti-caries potential of F toothpastes had already been established, thus it is not surprising that, due to ethical concerns, just those studies carried out in countries where using non-F toothpastes was the norm compared F toothpaste with a placebo. Hence, it is unlikely that new evidence on the effects of F toothpastes in the primary dentition will accrue from placebo-controlled trials.

When children have cavitated caries lesions, the treatment of choice is to place a restoration (51). It is known that invasive treatment to young children can be distressful to children, parents and dentists (52) and thus it may be disappointing to confirm that studies have given little consideration to primary teeth. On the other hand, the need for restorative treatment in primary teeth has been questioned in England when studies have shown that very few carious primary teeth left unrestored went on to cause pain and required treatment or extraction whereas the vast majority remained symptomless until natural exfoliation (53, 54). According to the authors, these results should be cautiously interpreted and other factors, such as a sound clinical judgment, should be taken into account in the decision of restoring primary teeth. Nonetheless, these findings have triggered debate and stimulated further investigations, some of which have not supported the policy of non-intervention for primary carious teeth. Filling primary teeth has increased the likelihood of exfoliation without the need for an extraction (55) and Scottish data have suggested that not treating carious primary teeth has increased the risk of dental sepsis occurrence (56). From these data it seems clear that caries preventive strategies in the primary dentition, such as F toothpastes, are highly welcomed.

Despite the small number of clinical trials and the fact that some of them lacked important methodological details, the present meta-analyses provided new evidence on the effects of F toothpastes on caries reduction in the primary dentition of preschool children. It reinforces the anti-caries potential of standard F toothpastes and the need to support their use by children, regardless of age.

Acknowledgements

The authors wish to thank Juliana Ferreira Almeida for her valuable contribution to the reading of reports and selection of studies. A. P. P. Santos

receives a PhD scholarship from the Research Support Foundation of the State of Rio de Janeiro (FAPERJ); P. Nadanovsky receives financial support from the Brazilian National Research Council (CNPq - grant no. 305714/2006-6) and B. H. Oliveira receives financial support from FAPERJ (E-26/102.248/2009).

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Table 1. Characteristics of the interventions in the included studies

		Test group		Control group	
Study/Country	**Year**	**Toothpaste**	**Oral health education**	**Toothpaste**	**Oral health education**
Andruskeviciene/ Lithuania	2008	500 ppm[a]	Theoretical instruction and visual material demonstration about oral hygiene and fluoride to teachers and parents	-	-
Whitlle/ England	2008	440 ppm	Dental health advice and leaflet on oral hygiene, fluoride and diet to parents	-	-
Davies/ England	2002	440 and 1450 ppm	Leaflets encouraging parents to brush their child's teeth twice daily using use a pea-sized amount of toothpaste	-	-
Schwarz/ China	1998	1000 ppm[a]	Oral health education to teachers, who taught dental health knowledge to children	[b]	-
You/ China	2002	1100 ppm[a]	Education to teachers and children about oral hygiene through videotape and audiotape supplemented with pictures	placebo	-
Rong/ China	2003	1000 ppm[a]	Oral health sessions to teachers, who educated the parents about the importance of oral hygiene and maintaining healthy teeth using video, audiotape and pictures	[b]	-
Jackson/ England	2005	1450 ppm[a]	-	-	-
Fan/ China	2008	1500 ppm	Presentation of educational films and lectures at school about toothbrushing	placebo	Presentation of educational films and lectures at school about toothbrushing

[a] Supervised by teachers
[b] Although children in the control group did not receive a placebo toothpaste, the authors stated that they brushed their teeth with non-F toothpaste

Table 2. Mean number and standard deviations (sd) of baseline and final decayed, missing due to caries and filled dental surfaces (dmfs), mean and sd of caries increment, p values for the difference in caries increment between test and control groups and prevented fractions.

Study	Year	Test group n	Test group dmfs baseline (sd)	Test group dmfs final (sd)	Test group mean increment (sd)	Control group n	Control group dmfs baseline (sd)	Control group dmfs final (sd)	Control group mean increment (sd)	p value	prevented fraction
Low F toothpaste											
Andruskeviciene	2008	152	1.42 (1.85)[a]	2.3 (3.08)[a]	0.88 (1.11)[a]	133	1.86 (2.77)[a]	3.78 (3.34)[a]	1.92 (0.92)[a]	0.000[b]	54%
Whitlle	2008	147	0	3.99 (6.49)[a]	-	129	0	4.84 (8.40)[a]	-	0.353	18%
Standard F toothpaste											
Schwarz	1998	152	-	-	3.6 (5.55)[a]	99	-	-	6.3 (7.56)[a]	0.002	43%
You	2002	457	6.24 (8.06)	-	4.07 (5.30)[a]	395	6.24 (7.95)	-	4.85 (6.12)[a]	0.046	16%
Rong	2003	258	5.24 (7.08)	-	2.47 (4.09)	256	5.96 (7.74)	-	3.56 (5.30)	0.009	31%
Jackson	2005	181	7.34 (10.54)[a]	9.76 (11.63)[a]	2.43 (5.25)[a]	189	5.41 (10.45)[a]	8.18 (11.54)[a]	2.76 (5.23)[a]	0.001	12%
Fan	2008	329	3.54 (5.34)	-	2.75 (4.33)	328	3.60 (6.07)	-	4.73 (5.17)	0.000[b]	42%

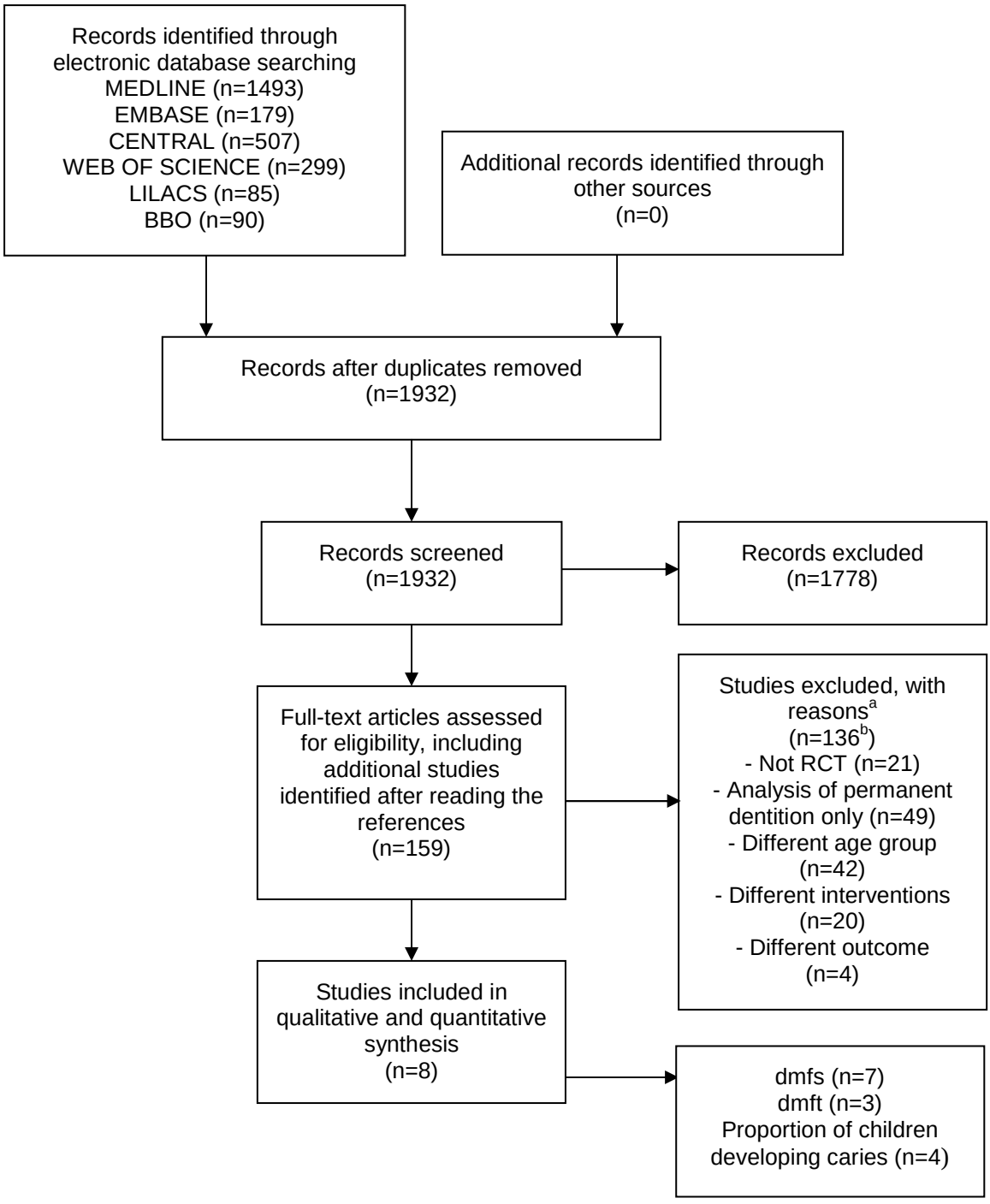
[a] Other measures of dispersion reported; sd calculated by the authors of this review according to Higgins et al.(19)
[b] Calculated by the authors of this review using *t* test with unequal variances

Table 3. Mean number and standard deviations (sd) of baseline and final decayed, missing due to caries and filled teeth (dmft), mean and sd of caries increment, p values for the difference in caries increment between test and control groups and prevented fractions.

Study	Year	Test group n	Test group dmft baseline (sd)	Test group dmft final (sd)	Test group mean increment (sd)	Control group n	Control group dmft baseline (sd)	Control group dmft final (sd)	Control group mean increment (sd)	p value	prevented fraction
Low F toothpaste											
Davies	2002	1176	0	2.49 (3.16)	-	1369	0	2.57 (3.16)	-	≅ 1.0	3%
Andruskeviciene	2008	152	1.33 (2.12)[a]	2.1 (2.71)[a]	0.77 (0.62)[a]	133	1.59 (2.22)[a]	3.0 (2.65)[a]	1.41 (0.92)[a]	0.000[b]	45%
Standard F toothpaste											
Davies	2002	1186	0	2.15 (2.96)	-	1369	0	2.57 (3.16)	-	0.002	16%

[a] Standard errors reported; sd calculated by the authors of this review according to Higgins et al. (19)
[b] Calculated by the authors of this review using *t* test with unequal variances

Fig 1. Flow diagram showing the process of identifying, screening, assessing for eligibility, excluding and including studies.



[a] The reasons for exclusion were those firstly or most easily obtained. For instance, a study that was excluded because of a different age group (the first or easiest clue) could also have been excluded because of a different intervention.
[b] The number of excluded studies does not add up to 151 (159 full-text articles assessed for eligibility minus the 8 included studies) because the results of some studies were published in more than one article.

Fig. 2: Ascertainment of the risk of bias in the included studies.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete oucome data addressed?	Free of selective reporting?	Losses to follow-up < 20%?	Adequate diagnosis reliability?	Baseline balance?	Free of contamination?
Andruskeviciene et al. (27)	?	?	?	-	+	+	?	?	?
Whittle et al. (28)	+	+	+	-	-	-	?	?	?
Davies et al. (34)	+	+	+	+	-	-	?	?	?
Schwarz et al. (32)	-	-	-	-	-	+	?	-	?
You et al. (33)	?	?	+	+	-	-	?	?	+
Rong et al. (31)	+	+	+	+	-	-	+	+	+
Jackson et al. (30)	?	?	+	+	-	-	+	-	?
Fan et al. (29)	?	?	+	-	-	+	+	?	+

Yes (+), No (-), Unclear (?)
The darker the shade of grey the higher the risk of bias

Fig 3. Comparison between F toothpaste and placebo or no intervention regarding dental caries increment at surface level (dmfs prevented fraction).

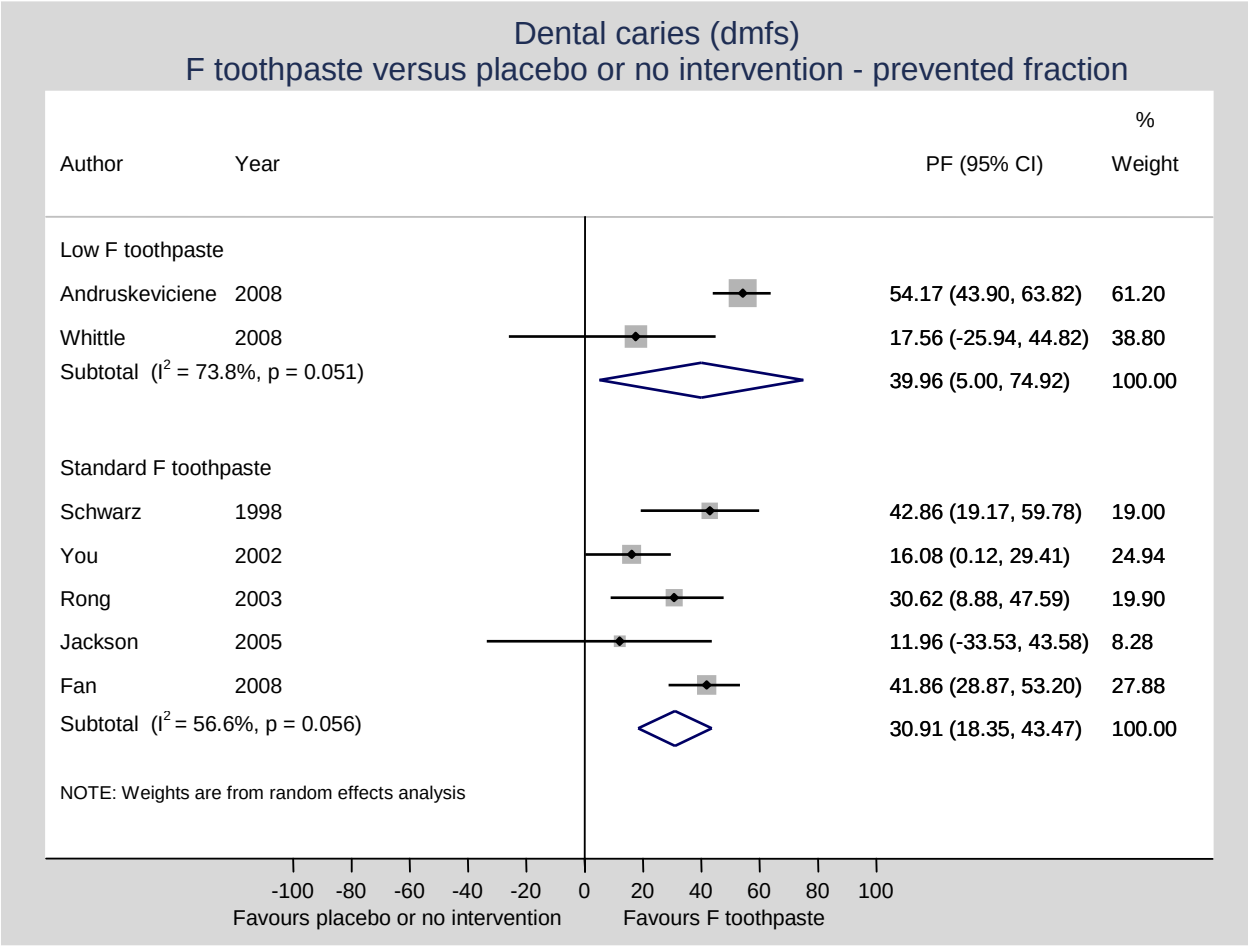


Fig 4. Comparison between F toothpaste and no intervention regarding dental caries increment at tooth level (dmft prevented fraction).

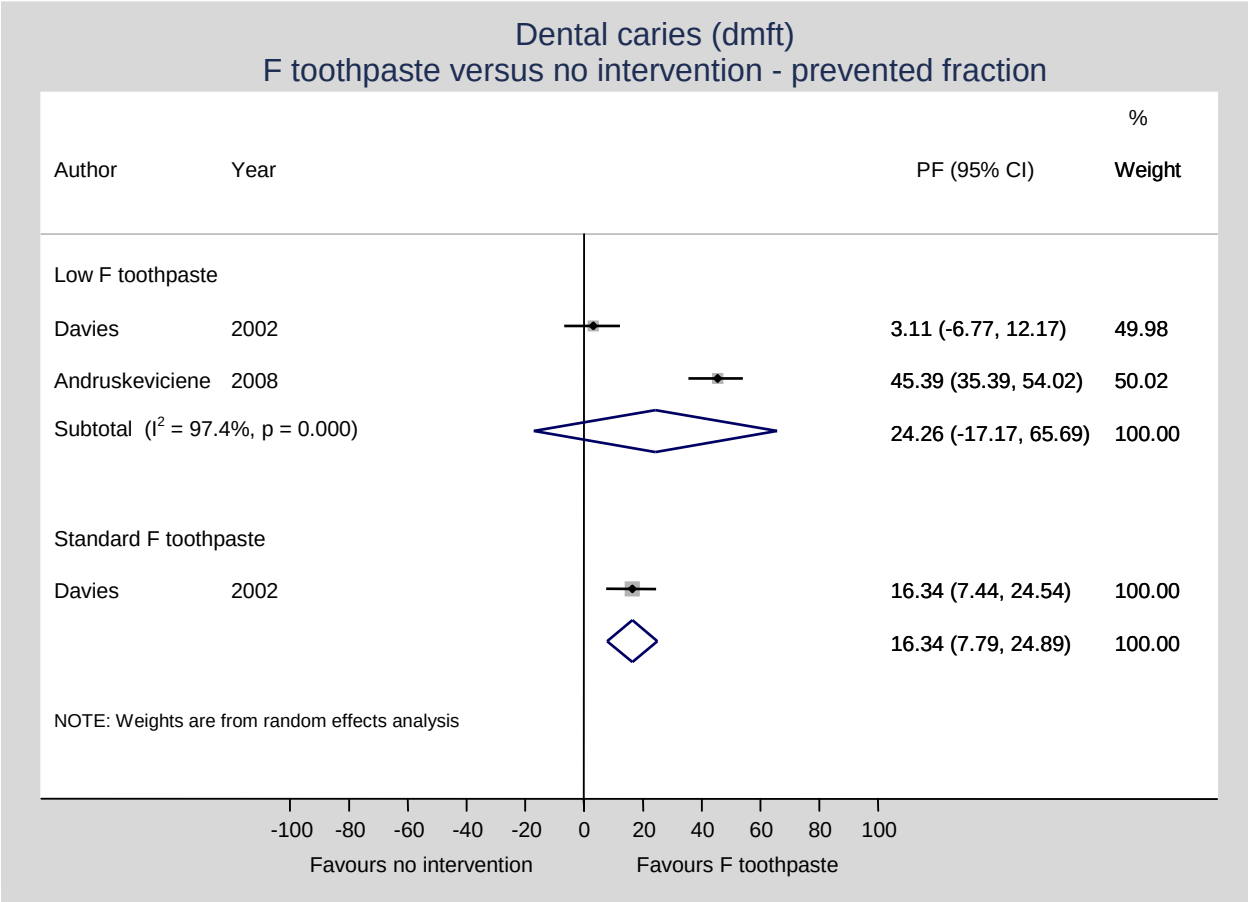
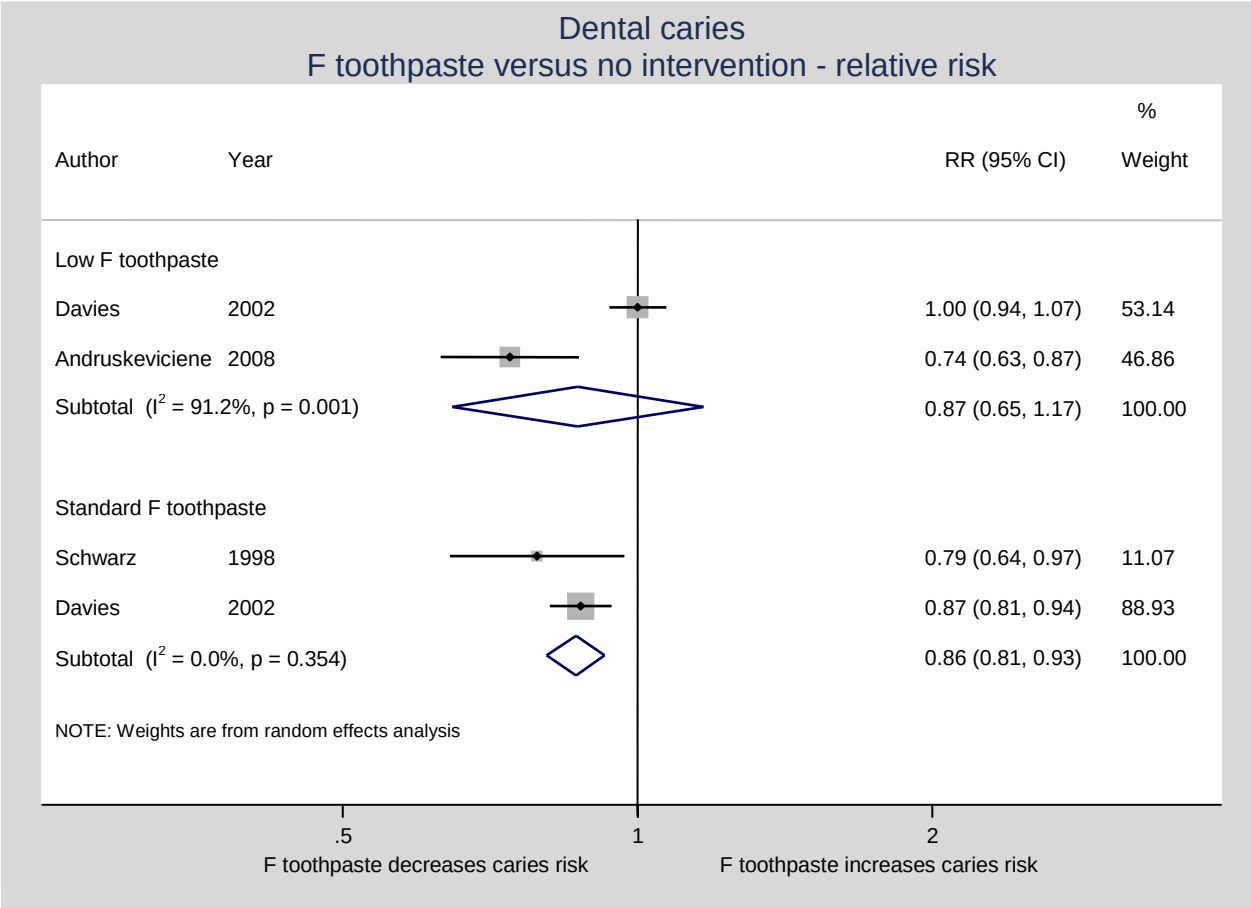


Fig 5. Comparison between F toothpaste and no intervention regarding the proportion of children developing caries (relative risk).



Appendix 1. Search strategy for MEDLINE via PubMed

#1 DENTAL CARIES [mh]
#2 TOOTH DEMINERALIZATION [mh]
#3 DMF INDEX [mh]
#4 (dmft or dmfs or dft or dfs)
#5 ((tooth or teeth or dent*) and (caries or carious or decay or deminerali* or cavit*))
#6 #1 or #2 or #3 or #4 or #5
#7 FLUORIDES [mh]
#8 FLUORIDES, TOPICAL [mh]
#9 CARIOSTATIC AGENTS [mh]
#10 (fluor* or cariost*)
#11 #7 or #8 or # 9 or #10
#12 TOOTHPASTES [mh]
#13 TOOTHPASTE [mh]
#14 (dentifric* or toothpaste* or tooth paste*)
#15 #12 or #13 or #14
#16 #6 and #11 and #15

Appendix 2. Characteristics of included studies.

Andruskeviciene et al. (27)		
Participants	1656 children (878 boys and 778 girls) aged from 3 to 7 years who were attending 16 kindergartens in Kaunas city, Lithuania	
Interventions	Test group (156 children allocated): 500 ppm toothpaste, twice a day, supervised toothbrushing at the kindergarten in the morning and at home in the evening. Kindergarten personnel and the children's parents underwent theoretical instruction and visual material demonstration about the importance of oral hygiene and fluoride Control group (137 children allocated): no intervention Another test group not considered	
Outcomes	mean caries increment (dmft and dmfs) and proportion of children developing caries	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Comment: allocation strategy not mentioned Quote: "a group of 411 3-year-old children were selected as participants in the prevention programme that began in 2003. Test group A (n=156), test group B (n=118), and the control group (n=137) were defined for the study. These groups were homogeneous with respect to oral health status"
Allocation concealment?	Unclear	Comment: allocation strategy not mentioned, thus it is not possible to assess allocation concealment
Blinding?	Unclear	Comment: blinding not mentioned
Incomplete outcome data addressed?	No	Comment: the study does not provide information about incomplete outcome data assessment
Free of selective outcome reporting?	Yes	Comment: mean caries increment (dmft and dmfs) and proportion of children developing caries reported
Losses to follow-up less than 20%?	Yes	Comment: 2.6% test group and 2.9% control group Quote: "after 3 years, 397 participants were re-examined. There was a drop-out of 14 participants (4 in test group A, 6 in test group B, and 4 in the control group) owing to the children leaving the kindergarten"
Diagnosis reliability?	Unclear	Comment: the study does not mention the number of examiners or the intra-examiner reliability; inter-examiner reliability substantial Quote: "the inter-examiner agreement of dmf-t scores was measured by applying the kappa index. A kappa value of 0.8 for the inter-examiner agreement was considered satisfactory"
Baseline characteristics balanced?	Unclear	Comment: the study does not provide information about baseline socio-demographic characteristics; baseline caries levels (dmft and dmfs) were not significantly different between test and control groups

Free of contamination?	Unclear	Comment: no strategies to avoid contamination between groups were reported; it is not clear whether children attending the same kindergarten were allocated to the same intervention

Whittle et al. (28)		
Participants	8 month-old children attending a distraction-hearing test at a health centre in Burnley, Pendle and Rossendale (England)	
Interventions	Test group (250 children allocated): 440 ppm toothpaste given to parents and dental health advice to parents based on that recommended by the Health Education Authority Control group (251 children allocated): no intervention; parents received no dental input other than the level of dental advice currently provided by health visitors in the area	
Outcomes	mean dmfs	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "parents were allocated to either the intervention or control group (in balanced blocks, stratified by ethnicity and location, using sealed envelopes prepared by Lancaster University)"
Allocation concealment?	Yes	Comment: sealed envelopes
Blinding?	Yes	Comment: single-blind Quote: "an experienced dental examiner…carried out the dental examinations. This dentist did not know to which group the children belonged"
Incomplete outcome data addressed?	No	Comment: the study does not provide information about incomplete outcome data assessment
Free of selective outcome reporting?	No	Comment: dmft and proportion of children developing caries not reported
Losses to follow-up less than 20%?	No	Comment: 41,4% test group and 48,4% control group Quote: "501 children were recruited to the study, 251 in the control group and 250 in the intervention group. At three years 171 (68.1%) and 181 (72.4%) children in the respective groups were examined"; "in the 2003/04 census survey 2,529 children were examined at school. One hundred and twenty nine (51.4%) of these had been in the control group, 147 (58.8%) in the intervention group and 2,253 other children (the census group)."
Diagnosis reliability?	Unclear	Comment: information on diagnosis reliability not reported
Baseline characteristics balanced?	Unclear	Comment: information on baseline characteristics not reported

Free of contamination?	Unclear	Comment: no strategies to avoid contamination between groups were reported. Quote: “the study indicated that the randomised control trial might not be the best way to evaluate oral health promotion programmes because it is not possible to restrict information to the intervention group”

Davies et al. (34)		
Participants	Children born in nine health districts in the north west of England, where the prevalence of caries in 5-year-olds was high. They were 12 months-old at baseline and 5½ years-old at outcome assessment	
Interventions	Test group 1 (2472 children allocated): 440 ppm F toothpaste (Colgate 0-6 Gel) Test group 2 (2488 children allocated): 1450 ppm F toothpaste (Colgate Great Regular Flavour) Control group (2462 children allocated): no intervention In both test groups, leaflets encouraged parents to use a pea-sized amount of the toothpaste and to brush their child's teeth twice daily	
Outcomes	mean dmft (primary outcome), mean mt and prevalence of caries experience (dmft>0)	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: “within each of the nine districts children were given an identity number and centrally allocated to either one of the two test groups or a control group using random number tables”
Allocation concealment?	Yes	Quote: “centrally allocated”
Blinding?	Yes	Comment: single-blind Quote: “dental examinations were conducted under blind conditions but as *off the shelf* toothpaste (without over wrapping or repackaging) was delivered to the participants, subjects and their families were aware of which toothpaste they were using”
Incomplete outcome data addressed?	Yes	Quote: “a further two analyses were performed for the primary outcome dmft to try to estimate the population effect. The first included data from all children who were clinically examined and were originally part of the study population but included those who did not complete the study. The second also included subjects initially randomised but not examined clinically by imputing the means and standard deviations from the control group”
Free of selective reporting?	No	Comment: dmfs not reported
Losses to follow-up less than 20%?	No	Comment: withdrawals in both intervention groups of 32%; children were excluded after randomization. Quote: “children were withdrawn from test and control groups if toothpaste or questionnaires were returned by the post office as undeliverable”; “reply paid cards were returned by

		the parents of 641 test children, indicating that they did not wish their children to participate and during the five years of the study 1,432 children moved away from the area. Five children withdrew from the 1450 ppm F toothpaste group, one because the dentist advised this, three because of concerns about fluorosis and one because of an allergy to the toothpaste"
Diagnosis reliability?	Unclear	Comment: the study does not mention the number of examiners or the intra and inter-examiner reliability Quote: "in each district the clinical examinations were undertaken by trained, standardized and calibrated examiners according to the standards set by BASCD"
Baseline characteristics balanced?	Unclear	Comment: the study does not provide information about baseline socio-demographic characteristics. Also, children were not examined at baseline; it was assumed that all children were caries-free at the beginning of the trial
Free of contamination?	Unclear	Comment: no strategies to avoid contamination between groups were reported; it is not possible to rule out contamination at home or school as the randomization was performed within each district

Schwarz et al. (32)		
Participants	289 children (94% were 3 years old, 4% were not yet 3, and 2% were 4 years old) from the Conghua County, southern part of China; mainly rural areas	
Interventions	Test group (1 kindergarten and 168 children allocated): 1000 ppm F toothpaste (Colgate MFP), daily after lunch, supervision of a teacher, amount of toothpaste was the size of a child's little finger nail, 2-3 min, simple miniscrub, rinse with water; oral health education Control group (2 kindergartens and 121 children allocated): no intervention; no dental health education or other information or activities were provided for the control	
Outcomes	dmfs and proportion of children developing caries	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	No	Comment: non-random allocation Quote: "the children in the largest kindergarten constituted the test group (n=168) and those in the two other kindergartens (n=121) formed the control group"
Allocation concealment?	No	Comment: non-random allocation prevents allocation concealment
Blinding?	No	Quote: "the ideal protocol including masking of examiners was not considered logistically possible in this community and within the available resources of the project"
Incomplete outcome data addressed?	No	Quote: "Only those children who were present at baseline and all subsequent examinations were included in this analysis."

Free of selective outcome reporting?	No	Comment: dmft not reported
Losses to follow-up less than 20%?	Yes	Comment: 10% test group and 19% control group Quote: "The dropout rate of the test children was 10 percent; i.e., 152 out of the 168 children remained in the trial at year 3. The corresponding figure for the control children was 19 percent; i.e., 99 out of the 121 children remained."
Diagnosis reliability?	Unclear	Comment: two examiners; intra-examiner reliability not reported Quote: "interexaminer reliability for caries status calculated at the tooth surface level and expressed by kappa statistics was consistently about 0.90 for all four examinations"
Baseline characteristics balanced?	No	Comment: baseline caries status significantly different between test and control groups; information on other baseline characteristics not mentioned Quote: "the dmfs of all the test children was 4.9 dmfs (SE=0.56) at baseline and for all the control children 6.8 dmfs (SE=0.75)"
Free of contamination?	Unclear	Comment: contamination avoided at kindergartens due to the allocation scheme; control teachers were aware of the interventions Quote: "no dental health education or other information or activities were provided for the control kindergarten teachers. They were, however, aware of the ongoing activities"

You et al. (33)		
Participants	A population of 1,334 preschool children, approximately three years of age, from 24 kindergarten classes in Huairou and Miyun counties, China	
Interventions	Test group (682 children allocated): 1,100 ppm sodium fluoride toothpaste; twice a day, supervision of teachers; pea size (0.48g); 60 seconds; oral health education to teachers and children Control group (652 children allocated): placebo toothpaste for *ad libitum* use at home and no school program Both dentifrices had the same excipient ingredients (hydrated silica, flavor system, coloring agents, humectants, suspending agents, and buffers) with only minor differences in humectant level to adjust for the different fluoride levels	
Outcomes	dmfs increment	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Comment: the method of randomization is not mentioned Quote: "classrooms were stratified based on mean baseline dmfs scores derived from the visual-tactile baseline examination, and randomly assigned to one of two treatment groups"
Allocation concealment?	Unclear	Comment: as it is not possible to know which method of randomization was used, allocation concealment cannot be

		assessed
Blinding?	Yes	Comment: double-blind Quote: "subject blindness to product and examiner blindness to treatment and product were maintained throughout the study"
Incomplete outcome data addressed?	Yes	Quote: "the overall results for the *all subjects* analyses of the two year increment data were generally consistent with the *final subject subset* results"
Free of selective outcome reporting?	No	Comment: dmft and proportion of children developing caries not reported
Losses to follow-up less than 20%?	No	Quote: "during the two years of the study, there was a 31.3% subject attrition rate, with 916 subjects re-examined at the year-two exams."
Diagnosis reliability?	Unclear	Comment: two examiners, one of which was unavailable for participation at the year-one exams; intra and inter-examiner reliability not mentioned
Baseline characteristics balanced?	Unclear	Comment: the groups were similar regarding age, gender and baseline caries levels (dmfs); socioeconomic status not assessed
Free of contamination?	Yes	Comment: contamination avoided at kindergartens due to the allocation scheme; contamination at home unlikely as children received toothpastes for *ad libitum* use at home Quote: test group: "toothpaste and toothbrushes were supplied to the children for *ad libitum* use at home at night, during holidays, and on weekends"; control group: "children randomized to schools receiving the placebo dentifrice were supplied with toothbrushes and dentifrice for ad libitum use at home"

Rong et al. (31)		
Participants	3-year-old children from the 10 biggest kindergartens in the central township of Miyun County, Beijing, China; mainly rural areas	
Interventions	Test group (4 kindergartens and 361 children allocated): 1000 ppm F toothpaste (Crest sodium fluoride); twice a day during school days; supervision of teachers; pea-size (0.5g), 1 min; oral health education to teachers and parents Control group (6 kindergartens and 370 children allocated): no intervention; control children were provided with the most common nonfluoridated toothpaste	
Outcomes	dmfs increment	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "the kindergartens were first stratified into three stratums according to the general socioeconomic background of the children i.e. high, average and low, and then randomly assigned to either the test or the control groups by drawing lots"

Allocation concealment?	Yes	Comment: drawing lots
Blinding?	Yes	Comment: double-blind Quote: "the participants and the examiner were not aware of the assignment of the toothpaste"
Incomplete outcome data addressed?	Yes	Comment: all children examined at baseline were compared to those who completed the study regarding children's background (age and sex) and baseline caries status (mean dmft and mean dmfs); information reported on Table 1 Quote: "no statistically significant differences between groups"
Free of selective outcome reporting?	No	Comment: dmft and proportion of children developing caries not reported
Losses to follow-up less than 20%?	No	Comment: 29% test group and 31% control group Quote: "During the 2-year program, the dropout rates of the subjects in the test and control groups were 29 and 31%, respectively. The main reasons were transfer to other kindergartens and absence from kindergarten on the day of examination"
Diagnosis reliability?	Yes	Comment: one examiner Quote: "duplicate examinations were carried out of every 10 children. Results showed that intraexaminer reproducibility was good (Kappa>0.84)"
Baseline characteristics balanced?	Yes	Comment: children's background (age and sex) and baseline caries status (mean dmft and mean dmfs) balanced; kindergartens were stratified into 3 stratums according to socioeconomic background before random allocation
Free of contamination?	Yes	Comment: contamination avoided at kindergartens due to the allocation scheme; contamination at home not probable Quote: "a set of toothbrush and toothpaste was given to each child every 3 months for use at home. The children's parents were asked to ensure that their children brushed their teeth before going to bed"

Jackson et al. (30)		
Participants	517 five-year-old children in the first term of their first year of primary school in North West London; neighbourhoods of social deprivation and high ethnic population	
Interventions	Test group (259 children allocated): 1,450 ppm sodium fluoride toothpaste (Crest Decay Prevention - Mildmint; Procter and Gamble plc); school days, supervison of teachers; there was no concurrent dental health education and no toothpaste was provided for home use Control group (258 children allocated): no intervention	
Outcomes	mean dmfs	
Risk of bias		
Item	**Authors' judgement**	**Description**

Adequate sequence generation?	Unclear	Comment: the method of randomization is not mentioned Quote: "in total 517 5-year-old children were recruited into this 21-month study. The schools were randomised such that there were approximately equal numbers of children in the intervention group and in the non-intervention group"
Allocation concealment?	Unclear	Comment: as it is not possible to know which method of randomization was used, allocation concealment cannot be assessed
Blinding?	Yes	Comment: single-blind Quote: "randomised, single-blind, parallel group clinical trial"; "the children were examined clinically when they were 5–6 years old by an examiner who was blind to individual children's group allocation"
Incomplete outcome data addressed?	Yes	Comment: baseline characteristics (age, gender, mean dmfs) of children who entered the study were compared to baseline
Free of selective outcome reporting?	No	Comment: dmft and proportion of children developing caries not reported
Losses to follow-up less than 20%?	No	Comment: 30.1% test group and 16.7% control group Quote: "a total of 147 (28%) did not attend the final examination"
Diagnosis reliability?	Yes	Comment: two examiners Quote: "examiner reliability for caries assessment was determined, and the kappa values obtained were over 0.75 indicating excellent agreement"
Baseline characteristics balanced?	No	Comment: baseline caries levels not balanced; socioeconomic characteristics apparently similar Quote: "differences in initial mean caries incidence between the intervention (7.34) and non-intervention groups (5.41) occurred since the groups were not balanced for caries prevalence at baseline"; "the children in the present study all attended schools with catchment areas from neighbourhoods of social deprivation and high ethnic population"
Free of contamination?	Unclear	Comment: strategies to avoid contamination between groups not reported

Fan et al. (29)	
Participants	Four-year-old children from the Chengdu area of China
Interventions	Test group (329 children allocated): 1.14% SMFP calcium carbonate-based toothpaste (Colgate® Anticavity Toothpaste) Control group (328 children allocated): no-fluoride calcium carbonate-based dentifrice (ZhongHua Toothpaste) A positive control group not considered After treatment assignment, study participants were instructed to brush their teeth at least twice daily
Outcomes	dfs increment
Risk of bias	

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Comment: the method of randomization is not mentioned Quote: "qualifying subjects were stratified according to age and sex, and were randomly assigned to one of the three dentifrice groups"
Allocation concealment?	Unclear	Comment: as it is not possible to know which method of randomization was used, allocation concealment cannot be assessed
Blinding?	Yes	Comment: double-blind Quote: "this two-year clinical study employed a double-blind, parallelgroup, three-treatment design"; "the dentifrices were packaged in white tubes or over-wrapped with white tape so as to mask their identity"
Incomplete outcome data addressed?	No	Comment: missing data unlikely to introduce bias Quote: "subjects who did not complete the study dropped out for reasons unrelated to the use of the treatments"
Free of selective outcome reporting?	No	Comment: dmft and proportion of children developing caries not reported
Losses to follow-up less than 20%?	Yes	Quote: "nine-hundred and ninety-eight (998) subjects completed the entire two-year study (16.84% dropout)"
Diagnosis reliability?	Yes	Comment: one examiner and two back-up examiners Quote: "the Kappa statistic for the reproducibility of the examiners for caries scores was greater than 0.9, indicating a high level of agreement within and between the examiners"
Baseline characteristics balanced?	Unclear	Comment: the groups were similar regarding age, gender sex and baseline caries levels (dfs); socioeconomic status not assessed
Free of contamination?	Yes	Comment: contamination at home unlikely Quote: "multiple subjects in the same household were all assigned to the dentifrice randomly allocated to the first among them"; "the dentifrices were provided to the study subjects four times per year, along with two commercially available youth-size, soft-bristled toothbrushes. When new tubes of the dentifrices were delivered, subjects returned their previous tubes so that compliance with dentifrice use could be monitored"

APÊNDICE D - Artigo 2

Title: Effects of low and standard fluoride toothpastes on caries and fluorosis: systematic review and meta-analysis

Short title: Fluoride toothpastes, caries and fluorosis

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Keywords: dental caries; fluorosis, dental; fluoride; toothpastes; dentition, primary; dentition, permanent; review; meta-analysis

Financial disclosure
A. P. P. Santos receives a PhD scholarship from the Research Support Foundation of the State of Rio de Janeiro (FAPERJ); B. H. Oliveira receives financial support from FAPERJ (E-26/102.248/2009) and P. Nadanovsky receives financial support from the Brazilian National Research Council (CNPq - grant no. 310807/2009-3).

Conflict of interest
The authors declare no conflict of interest.

Acknowledgments
The authors wish to thank Juliana Ferreira Almeida for her valuable contribution to the reading of reports and selection of studies.

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Contributor's statement:

A. P. P. Santos carried out the search, selected the studies, extracted and analyzed the data. B. H. Oliveira extracted the data. P. Nadanovsky solved any disagreement about study selection and data extraction. All authors contributed to the study conception, design, interpretation, drafting and final editing of the manuscript.

Abstract

Context: Although the anti-caries effects of standard fluoride (F) toothpastes are well-established, their use by young children has given rise to concerns regarding the development of dental fluorosis. Thus, a widespread support of low F toothpastes has been observed. Objective: To assess the effects of low and standard F toothpastes on the prevention of caries in the primary dentition of preschool children and fluorosis in the permanent teeth. Methods: Systematic review of clinical trials. Two examiners independently screened 1932 records and read 159 potentially eligible full-text articles Pooled prevented fractions (PF) and relative risks (RR) were estimated. Results: Low F toothpastes significantly increased the risk of caries in primary teeth (RR= 1.13; 95% CI 1.07 – 1.20; 4634 participants in three studies) and did not significantly decrease the risk of aesthetically objectionable fluorosis in the upper anterior permanent teeth (RR= 0.32; 95% CI 0.03 – 2.97; 1968 participants in two studies). There was a significant caries reduction at tooth level when standard F toothpastes were compared to low F toothpastes (PF= 14%; 95% CI 6 – 21; 4634 participants in three studies). However, at surface level, no significant differences were observed, even though there was a tendency favouring standard F toothpastes with neutral pH (PF= 13%; 95% CI -4 – 30; 2272 participants in two studies) and low F toothpastes with acidic pH (PF= -5%; 95% CI -22 – 11; 742 participants in two studies). Conclusions: There is no evidence to support the use of low F toothpastes by preschool children regarding caries and fluorosis prevention.

Introduction

Dental caries is the most prevalent chronic childhood disease[1]. Despite the dramatic decline in its incidence over the past decades, a small but significant increase among preschool children has been observed recently[2,3] and the prevalence in this age group is still high, ranging from 25% to 94%[2-8].

Children suffering from caries and severe caries may experience dental pain, irritability, difficulties in eating and drinking, low growth rate and body weight, malnourishment, sleep disturbances, embarrassment among other children, absence from school and diminished ability to learn[9-14]. Parental distress due to children's caries status or severity has also been reported as parents have to spend time and money to provide their children with dental treatment[9].

The role of topical fluorides in reducing dental caries in children and adolescents has been extensively studied[15] and, among these, fluoride (F) toothpastes are more likely to be used owing to their higher acceptability as toothbrushing with F toothpaste is culturally approved and widespread[16-18]. Three systematic reviews have shown that standard F toothpastes, which contain from 1000 to 1500 parts per million (ppm) of F, reduce approximately 24 to 29% of dental caries in permanent teeth when compared to a placebo and that larger reductions were associated with an increase in F concentration[19-21]. On the other hand, it has been reported that the use of toothpastes with a standard F concentration by young children was significantly associated with an increase in dental fluorosis in the permanent anterior teeth[22].

Dental fluorosis is a disturbance on tooth formation caused by a cumulative ingestion of F during amelogenesis, which results in a more porous and opaque dental enamel. Severe forms of fluorosis can be subject to post-eruptive staining and mechanical breakdown of the surface. Once there is F intake from any sources during tooth development, a certain level of fluorosis will always exist[23]. In recent years, both an increase and a decrease in the prevalence of fluorosis have been reported[24-27]; however, there is general agreement that moderate to severe forms of fluorosis in areas with non-fluoridated or optimally fluoridated drinking water are uncommon[24,25,28-32]. Also, mild forms of fluorosis are of little concern for parents and have little or no effect on children's oral health-related quality of life[33-36].

Much concern has been raised regarding the use of F toothpastes by young children as they tend to swallow from 60 to 72% of the toothpaste applied to the toothbrush[37-40], which would arguably put them at a higher risk of developing fluorosis. Dental and medical associations recommend different strategies to address this issue[41,42], among which is the reduction in the F concentration of the toothpaste[41]. However, the anti-caries potential of low F toothpastes (< 600 ppm) remains inconclusive; whereas those containing 250 ppm F have shown to be less effective when compared to 1000 ppm ones[43-45], it was not possible to draw any definite conclusion concerning other low F toothpastes (440/500/550 ppm) due to the paucity of studies and the uncertainty of the estimates obtained[43,45].

As low F toothpastes are targeted at young children in order to reduce the occurrence of fluorosis, it is more important to assess their effectiveness specifically in these younger children, who are at risk of developing it, than to assess their effectiveness in children in general, as has been the case in previous reviews. Moreover, as mild forms of fluorosis are not considered aesthetically objectionable, the question that has yet to be answered is the extent to which the anti-caries benefits of low F toothpastes in young children outweigh the theoretically smaller risks of developing moderate to severe forms of fluorosis.

The aim of this study was to evaluate the effects of low and standard F toothpastes on the prevention of dental caries in the primary dentition of preschool children and moderate to severe forms of dental fluorosis in the permanent dentition.

Materials and Methods

Study design: systematic review and meta-analysis.

Criteria for considering studies for this review

Studies: individual or cluster randomized or quasi-randomized clinical trials. Non-randomized clinical trials, observational studies and studies with a follow-up period shorter than one year were excluded.

Participants: children in the primary dentition at the beginning of the study, irrespective of baseline caries levels. Children should be no older than seven years

old when the outcome dental caries was assessed. Studies whose participants had special general or oral health conditions were excluded.

Interventions: low F toothpastes (<600 ppm) and standard F toothpastes (1000-1500 ppm), irrespective of F agent, abrasive system and pH. Studies whose interventions included other F products (gel, varnish, mouthrinse) or other non-F products (chlorhexidine, xilitol, dental sealants) were excluded. As there is no evidence that oral health education is effective in changing oral health outcomes[46], this co-intervention was not considered a potential source of bias.

Outcomes: dental caries increment in the primary dentition, measured by the number of decayed, missing due to caries and filled teeth and dental surfaces (dmft and dmfs indices, respectively), proportion of children developing dental caries in the primary dentition and proportion of children developing dental fluorosis in the permanent dentition. Caries was assessed at the enamel and dentine level of diagnosis and only moderate to severe forms of fluorosis were considered.

Search strategy

Electronic search: The following databases were consulted from date of online availability to January 2010: The Cochrane Central Register of Controlled Trials (CENTRAL/CCTR), MEDLINE via PubMed, EMBASE, WEB OF SCIENCE, LILACS and BBO. Additional sources included a Brazilian database of thesis and dissertations (*Banco de Teses CAPES*), a Brazilian register of ethically approved projects involving human beings (SISNEP) and two international registers of ongoing trials (Current Controlled Trials and ClinicalTrials.gov). The search strategy included controlled vocabulary and free terms. It was developed for MEDLINE (Appendix 1) and adapted for the other databases. Meeting abstracts of the International Association for Dental Research (2001-2011) and the European Organisation for Caries Research (1998-2011) were also searched.

Reference lists: References of eligible trials and systematic and narrative reviews on the subject of F were checked in order to detect potential studies.

Idioms: There were no idiom restraints. When necessary, studies were translated.

Correspondence: Specialists in the field were contacted by email. These included authors of studies on the subject of F and dental/oral epidemiology professors/researchers.

Handsearch: Sixteen dentistry journals were chosen to be handsearched: Acta Odontologica Scandinavica, Archives of Oral Biology, British Dental Journal, Caries Research, Community Dental Health, Community Dentistry & Oral Epidemiology, European Archives of Paediatric Dentistry, European Journal of Oral Sciences, International Dental Journal, International Journal of Paediatric Dentistry, Journal of the American Dental Association, Journal of Clinical Pediatric Dentistry, Journal of Dental Research, Journal of Dentistry for Children, Journal of Public Health Dentistry and Pediatric Dentistry. The Cochrane Collaboration has organized a worldwide handsearching programme, which covers all the above mentioned journals; whenever a clinical trial is found it is incorporated into the CENTRAL/CCTR[47]. We checked the date of last handsearching update for each journal in the Cochrane Master List of Journals Being Searched and handsearching was complemented until June 2010 by two independent examiners.

Data collection and analysis

Management of references: References were imported to the software EndNote X3® (Thomson Reuters, CA, USA), enabling the identification of duplicates.

Selection of studies: Two examiners read the titles and abstracts (when available) of all studies identified in the electronic search. No blinding was performed regarding authors' names, journals and publication date. Whenever there was not enough information available, the full-text article was obtained. Any disagreement was solved by a third examiner.

Data extraction: Two examiners independently extracted the data by means of a data extraction form. Any disagreement was solved by a third examiner. Attempts were made to contact the authors to check for incomplete data. Missing standard deviations (sd) were calculated according to Higgins et al.[48].

Assessment of risk of bias in included studies: Risk of bias was assessed according to the *Cochrane Handbook for Systematic Reviews of Interventions*[49]. The following domains were assessed: sequence generation, allocation concealment, blinding of participants and outcome assessors, incomplete outcome data and

selective outcome reporting. Each domain was classified as having low, high or uncertain risk of bias. For this review, non-blinding of participants was unlikely to introduce bias; therefore, single-blinded studies (when only the outcome assessors were blinded) were considered as having low risk of bias. Also, studies were considered to be free of selective outcome reporting and thus having low risk of bias when the outcomes included dental caries increment at both surface and tooth level and the proportion of children developing dental caries. Other possible sources of bias, defined by the authors of this review, included: losses to follow-up (low risk of bias when less than 20%); diagnosis reliability (low risk of bias when good, according to Landis and Koch[50]); baseline balance (low risk of bias when data showed baseline balance regarding age, gender, socioeconomic status and caries levels) and contamination (low risk of bias when strategies to avoid contamination between groups were reported).

Statistical analysis: For the assessment of the effect of F toothpaste on the prevention of caries and fluorosis as measured by the proportion of children who developed caries in primary teeth and aesthetically objectionable fluorosis in permanent teeth, pooled relative risks (RR) and 95% confidence intervals (CI) were calculated. Number needed to treat for an additional harmful outcome (NNTH), which corresponds to the number of children that needed to use low F toothpaste, as opposed to standard F toothpaste, in order for one child to be harmed, i.e., to develop at least one dentine caries lesion, was derived by applying the pooled RR of caries to three different scenarios of caries incidence[51]; 95% CIs were derived by applying the 95% CIs of the pooled RR[52].

For the assessment of the effect of F toothpaste on the prevention of dental caries as measured by dmfs and dmft indices, no meta-analysis of the difference in means was performed as data were highly skewed[53]. Instead, meta-analyses of prevented fractions (PF) were performed. PFs were calculated by subtracting the mean caries increment in the standard F toothpaste group from the mean caries increment in the low F toothpaste group and then dividing by the mean caries increment in the low F toothpaste group; PFs correspond to the proportion of disease in the control group that could have been prevented had the intervention been implemented[54]. Positive PFs mean that using standard F toothpastes decreased the mean caries increment, whereas negative PFs mean that using standard F toothpastes increased the mean caries increment. Confidence intervals of PFs were

calculated according to the Fieller method[55]. Numbers needed to treat for an additional beneficial outcome (NNTB) in order to prevent one dmft were calculated based on the pooled dmft PF and on three different caries increments at tooth level; 95% CIs were derived by applying the 95% CIs of the pooled dmft PF[52].

Heterogeneity of studies was assessed by visual inspection of forest plots, chi-square homogeneity test (χ^2) and Higgins index (I^2). A random effects model was used in the presence of heterogeneity (χ^2 with significance level < 0.10 and I^2 > 50%).

The meta-analyses contain trials that reported the mean increment of caries as well as the final levels of caries, which is not considered problematic[56]. All analyses were carried out in Stata®11.1 (StataCorp LP, College Station, TX, USA), using the command *metan* with four parameters (number of events and nonevents in test and control groups) or three parameters (PFs and the lower and upper limit of 95% CIs). The paucity of studies prevented the use of meta-regression to assess the influence of study characteristics on the treatment effect, as well as the assessment of publication bias.

Results

Search

After excluding duplicates, 1932 records were retrieved from the electronic search. Handsearching and the search for ongoing trials yielded no additional reports. One hundred and fifty four reports were considered relevant and the full-text articles were obtained. After checking the references of these articles, five more potentially eligible full-text articles were obtained. Three articles in German were translated. Nine articles, which corresponded to five studies, were included. Figure 1 shows a flow diagram of the reports that were identified, screened, assessed for eligibility, excluded and included in the review.

Included studies

The characteristics of included studies are described in Appendix 2.

Risk of bias in included studies

Figure 2 shows the risk of bias in the included studies, according to nine different domains of methodological quality. The domain judged as having the lower

risk of bias was blinding, whereas high rates of losses to follow-up posed a threat to the validity of the majority of the studies. Ascertainment of baseline characteristics balance was unclear in all studies.

Interventions

Although all the interventions consisted of comparisons between low and standard F toothpastes, several differences were observed concerning the formulations of the toothpastes (Table 1).

Outcomes

Proportion of children developing dental caries

Three studies contributed data to this analysis[57-59]. One of them was a cluster randomized trial which was analyzed as an individual randomized trial[58]. An extern estimate of an intraclass correlation coefficient was used to obtain the design effect[60]. Then, the number of events and non events in both groups of this study were divided by the design effect in order to obtain the effective sample size[61]. Figure 3 shows the Mantel-Haenzel pooled RR (1.13; 95% CI 1.07 - 1.20). NNTHs were 11 (95% CI 7 - 20), 15 (95% CI 10 - 28) and 38 (95% CI 25 - 71) for scenarios of high, medium and low incidence of caries, respectively.

Caries increment at tooth level (dmft index)

Table 2 shows the four studies that reported caries incidence by means of the dmft index[57-59,62]. All the means were smaller than twice the standard deviations, suggesting that data were highly skewed[53]. Figure 4 shows the meta-analysis excluding one trial that tested low F toothpaste with acidic pH. The pooled PF was statistically significant (13.71%; 95% CI 6.03 - 21.38). In populations with a caries increment of 5 dmft per at least two years, this PF is equivalent to a NNTB of 1 (95% CI 1 - 3), which means that 1 child needs to use standard F toothpastes, as opposed to low F toothpastes, in order to prevent 1 dmft. When considering populations with lower dmft increments (e.g. 3 and 1), this PF corresponds to NNTBs of 2 (95% CI 2 - 6) and 7 (95% CI 5 - 17), respectively.

Caries increment at surface level (dmfs index)

Table 3 shows the four studies that reported caries incidence by means of the dmfs index[58,59,62,63]. Again, all the means were smaller than twice the standard deviations, suggesting that data were highly skewed. Meta-analyses showed no

statistically significant differences in the PF when only low F toothpastes with neutral pH were considered (PF= 12.88%; 95% CI -3.96 – 29.73) or when only low F toothpastes with acidic pH were considered (PF= -5.36%; 95% CI -22.01 – 11.29) (Figure 5).

Proportion of children developing dental fluorosis

Two clinical trials[57,59] that assessed the incidence of dental caries in the primary dentition also provided data of the assessment of dental fluorosis in the upper permanent anterior teeth[64,65]. Both studies were carried out in England and in non-fluoridated areas or areas where levels of F were below optimal levels. Holt et al.[64] assessed fluorosis by means of the Dean's index and the Thylstrup and Fejerskov Fluorosis Index (TF), whereas Tavener et al.[65] used only the TF index. For the present analysis, only data regarding the TF index was considered. The comparison consisted of children who developed no fluorosis or mild fluorosis (TF= 0, 1 or 2) and children who developed aesthetically objectionable dental fluorosis (TF≥ 3). Although the study of Tavener et al.[65] reported the results separately for deprived and less deprived districts, in this review data were analyzed as a whole. Figure 6 shows the DerSimonian and Laird pooled RR (0.32; 95% CI 0.03 - 2.97).

Discussion

Children are more likely to visit a pediatrician than a dentist at an early age. Thus, not only are pediatricians instrumental in providing anticipatory guidance regarding the benefits of F toothpastes for caries prevention but also in referring patients to dental care[66]. It is important, therefore, that they have access to the best scientific evidence currently available regarding the benefits and risks of toothpastes with different F concentrations. Low F toothpastes have been marketed to young children in many countries, such as Australia, Brazil, Switzerland, United Kingdom, among others, and there is considerable support to the use of this type of toothpaste[44,67], even in countries where they are not available, such as the United States[68].

To the best of our knowledge, this is the first systematic review that focuses on the effects of F toothpastes on the prevention of caries in primary teeth of children at risk of developing fluorosis. The rationale behind the advocacy of low F toothpastes to young children is to reduce the risk of fluorosis development. Thus, evidence

accrued from trials that assessed the effectiveness of low F toothpastes in primary or permanent teeth of schoolchildren does not help decision-making as these children are no longer at risk of developing aesthetically objectionable dental fluorosis and can benefit from the well established anti-caries effects of standard F toothpastes. Furthermore, although it has been reported that standard F toothpastes are associated with an increased risk of developing fluorosis[22], this review has specifically addressed the effects of F toothpastes on the occurrence of aesthetically objectionable fluorosis. Several studies have confirmed that, unless children are exposed to above-optimal fluoridated water, moderate to severe forms of fluorosis are not commonly found[24,25,28-32]. Cases of very mild and mild fluorosis, which account for the vast majority of all fluorosis cases, do not have a negative impact on children's oral health-related quality of life[33-36].

The results of this review showed that children who brushed their teeth with low F toothpastes had an increased risk of developing caries at dentinal level in the primary teeth. In populations with high 5-year-caries incidence (e.g. 70%), 11 preschool children need to use low F toothpaste (as opposed to standard F toothpaste) in order to harm one preschool child (i.e., for one preschool child to develop at least one dentine caries lesion). In populations with medium (e.g. 50%) and low (e.g. 20%) 5-year-caries incidence, NNTHs would be 15 and 38, respectively.

Among the trials that assessed caries increment at tooth (dmft) and surface (dmfs) level, two tested low F toothpastes with acidic pH. It is known that reducing the pH of a topical F agent increases the formation of calcium fluoride-like material (CaF_2), which acts like a F reservoir to be released during cariogenic challenges[69]. We found it prudent to carry out separate meta-analyses for low F toothpastes with neutral and acidic pH otherwise the acidic pH could compensate for the lower F concentration and artificially attenuate the difference in effect when low F toothpastes were compared with standard F toothpastes. A significant caries reduction was observed at tooth level in children using standard F toothpastes. At surface level, no significant differences were found when low F toothpastes were compared with standard F toothpastes, even though there was a tendency favouring standard F toothpastes with neutral pH and low F toothpastes with acidic pH. The reduction in the pH of low F toothpastes as an alternative to improve their anti-caries effectiveness is still open to question, and no definite conclusion can be drawn before

further research confirms this findings. In spite of the fact that low F toothpastes with acidic pH resulted in lower fingernails F concentration[63], the potential of such biomarkers of F intake to predict fluorosis has yet to be investigated[70,71].

Some aspects related to the methodological quality assessment of the trials included in this review that might have influenced its results should be noted. Firstly, most studies had more than 20% losses to follow up. Although it is important to assess the extent to which these losses were related to the outcome considered, losses of this magnitude are bound to affect the power of the study to detect significant differences between interventions. The study by Sonju-Clasen et al[58], for instance, is a cluster randomized trial but was analyzed as an individual one. After estimating the effective sample size, the sample was reduced nearly by half, which may have had a substantial impact on the power of the study. The weight of this study on the caries meta-analyses is negligible when compared to the weights of the other studies. Secondly, it was not possible to evaluate the baseline balance regarding caries levels, age, gender and socioeconomic status as either the studies have not presented data regarding these aspects or they have failed to perform, according to our judgment, a thorough assessment of all the characteristics to be considered. Thirdly, two studies lasted less than two years[58,63], despite the recommendation that trials should last at least two years in order to allow a significant number of lesions to develop at the cavitation level[72]. Finally, of the five studies, one was considered a quasi-randomized controlled trial as the interventions were allocated according to the children's month of birth[62]. Non-random methods of allocation presumably yield biased results due to the inability to conceal the allocation scheme adequately[73].

Although in this review we sought information on the increment of dental caries at both enamel and dentine levels of diagnosis, all the included studies assessed dental caries at the dentine level. Our search identified one clinical trial evaluating both active and inactive enamel and dentine lesions, which showed that, in children with active caries, low F toothpaste was less effective than standard F toothpaste[74]. However, this study was excluded from our review as the increment of enamel and dentine lesions were not recorded separately. Enamel or initial lesions, also called white spot lesions, are the first clinical manifestation of caries. These lesions can be arrested by means of non-invasive treatment, such as F therapy, but once caries has reached the dentine, the treatment of choice is to place a

restoration[75,76]. Besides, only after reaching the dentine can dental caries produce interferences on patients´ daily lives (e.g. dental pain and difficulty in chewing). For these reasons, dentine caries can be regarded as a true outcome whereas enamel caries would be considered a surrogate endpoint. Another reason for the importance of recording enamel and dentine lesions separately is the role of F in controlling the rate of caries progression; F does not prevent caries initiation, rather it delays or avoids the progression of caries from enamel through the dentine Therefore, when both enamel and dentine lesions are considered together, there may be virtually no difference in caries incidence between groups exposed and unexposed to F, whereas when only dentine lesions are considered, there is a marked reduction in caries incidence[77,78].

Regarding dental fluorosis, it can be noted that very few cases of aesthetically objectionable fluorosis were reported in the two trials included in the meta-analysis. One trial included 2 year-old children, lasted 3 years and compared 500 and 1000 ppm F toothpastes[64], whereas the other included 12 month-old children, lasted 5 years and compared 440 and 1450 ppm F toothpastes[65]. It could be argued that both the longer study duration and the higher F concentration in the toothpaste tested in the latter are likely to increase the risk of developing fluorosis. It should be noted, however, that the F agent of the 1450 ppm toothpaste is a combination of sodium monofluorophosphate and sodium F in a calcium-based abrasive system. In such formulations, part of the F is bound to combine with the calcium[79], which means that it is unlikely that all the F of this 1450 ppm toothpaste was available in its ionic form and therefore with potential to cause fluorosis. Our results showed that, in non-fluoridated areas, the use of low F toothpastes did not protect young children from developing moderate to severe forms of fluorosis in upper permanent anterior teeth. There is no information regarding the effects in optimally-fluoridated areas.

Conclusions

There is no evidence to support the use of low F toothpastes by preschool children as they increase the risk of caries in the primary dentition, at tooth and individual level, and do not decrease the risk of aesthetically objectionable fluorosis in upper permanent anterior teeth.

Clinical implication

As the mechanism of action of F on caries control is concentration dependent and on fluorosis development it is dose dependent[80], it seems that the best strategy to maximize the anti-caries potential of F toothpaste and minimize the risk of developing fluorosis is to recommend preschool children to use a small amount of standard F toothpaste under parental supervision. The role of low F toothpastes with acidic pH in caries and fluorosis prevention requires further research, especially in fluoridated areas.

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TABLE 1. Characteristics of the toothpastes tested in the included studies.

Study	Low fluoride toothpaste			Standard fluoride toothpaste		
	ppm	pH	F agent and abrasive	ppm	pH	F agent and abrasive
Davies[a]	440	neutral	NaF; silica	1450	neutral	1000 ppm SMFP + 450 ppm NaF; dicalcium phosphate dihydrate
Gerdin	250	5.5	KF; no abrasive	1000	6.5	NaF; no abrasive
Sonju-Clasen	250	6.5	NaF; silica	1450	6.8	NaF; silica
Vilhena[a]	550	4.5	NaF; silica	1100	7.0	NaF; silica
Winter	550	not reported	SMFP + NaF; calcium glycerophosphate	1055	not reported	SMFP; calcium glycerophosphate

[a] Complete information was obtained after consulting the authors
F= fluoride
KF= potassium fluoride
NaF= sodium fluoride
SMFP= sodium monofluorophosphate

TABLE 2. Mean and standard deviations (sd) of baseline and final decayed, missing due to caries and filled teeth (dmft); mean and sd of caries increment; p values for the difference in caries increment between low and standard fluoride groups and prevented fraction.

	Low fluoride toothpaste				Standard fluoride toothpaste					
Study	**n**	**dmft baseline (sd)**	**dmft final (sd)**	**mean increment (sd)**	**n**	**dmft baseline (sd)**	**dmft final (sd)**	**mean increment (sd)**	**p value**	**Prevented fraction**
Davies	1176	0	2.49 (3.16)	-	1186	0	2.15 (2.96)	-	0.02	13.65%
Gerdin	108	2.31 (1.78)	-	3.22 (2.81)	105	2.28 (1.82)	-	3.49 (3.16)	0.51[c]	-8.38%
Sonju-Clasen	46[a]	1.0 (2.2)	-	1.2 (2.2)	49[a]	1.2 (2.8)	-	0.8 (1.4)	0.30[c]	33.33%
Winter	1104	0	1.48 (2.62)[b]	-	1073	0	1.29 (2.62)[b]	-	0.09[c]	12.84 %

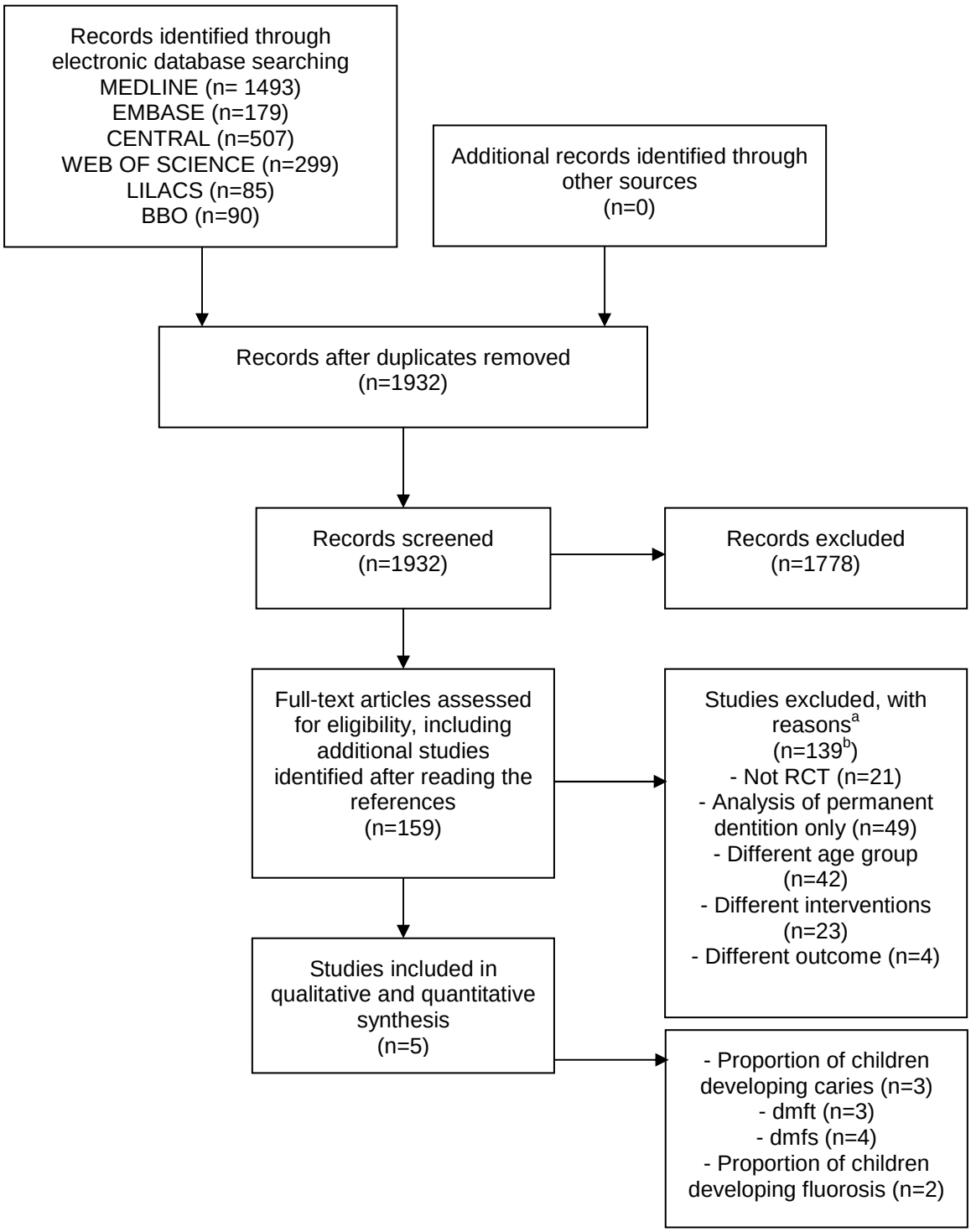
[a] This is the effective sample size. Original sample size was 83 (low F toothpaste) and 89 (standard F toothpaste)
[b] Other measure of dispersion reported; sd calculated by the authors of this review according to Higgins et al.[48]
[c] Calculated by the authors of this review using *t* test with unequal variances

TABLE 3. Mean and standard deviation (sd) of baseline and final decayed, missing due to caries and filled surfaces (dmfs); mean and sd of caries increment; p values for the difference in caries increment between low and standard fluoride groups and prevented fraction.

	Low fluoride toothpaste				Standard fluoride toothpaste					
Study	**n**	**dmfs baseline (sd)**	**dmfs final (sd)**	**mean increment (sd)**	**n**	**dmfs baseline (sd)**	**dmfs final (sd)**	**mean increment (sd)**	**p value**	**Prevented fraction**
Gerdin	108	2.87 (2.41)	-	3.83 (3.21)	105	2.95 (2.32)	-	4.23 (3.53)	0.39[c]	-10.44%
Sonju-Clasen	46[a]	2.0 (5.5)	-	2.9 (5.1)	49[a]	2.4 (6.6)	-	1.7 (3.2)	0.18[c]	41.38%
Vilhena	259	5.24 (5.37)	7.29 (7.27)	2.05 (2.79)	270	5.05 (4.89)	7.13 (6.35)	2.08 (2.34)	0.89[c]	-1.46%
Winter	1104	0	2.45 (5.36)[b]	-	1073	0	2.21 (5.36)[b]	-	0.296[c]	9.80%

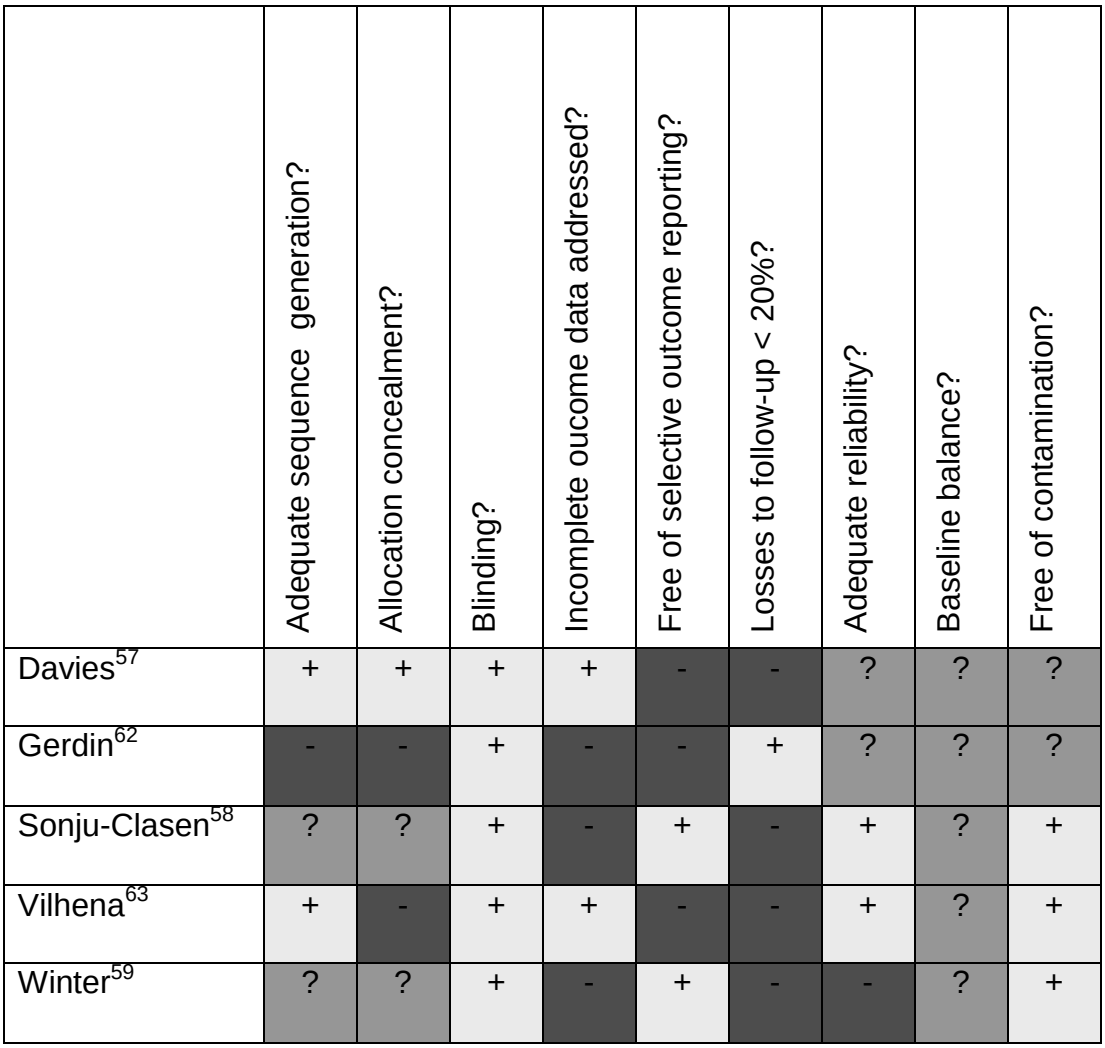
[a] This is the effective sample size. Original sample size is 83 (low F toothpaste) and 89 (standard F toothpaste)
[b] Other measure of dispersion reported; sd calculated by the authors of this review according to Higgins et al.[48]
[b] Calculated by the authors of this review using *t* test with unequal variances

FIGURE 1. Flow diagram showing the process of identifying, screening, assessing for eligibility, excluding and including studies.



[a] The reasons for exclusion were those firstly or most easily obtained. For instance, a study that was excluded because of a different age group (the first or easiest clue) could also have been excluded because of a different intervention.
[b] The number of excluded studies does not add up to 154 (159 full-text articles assessed for eligibility minus the 5 included studies) because the results of some studies were published in several articles.

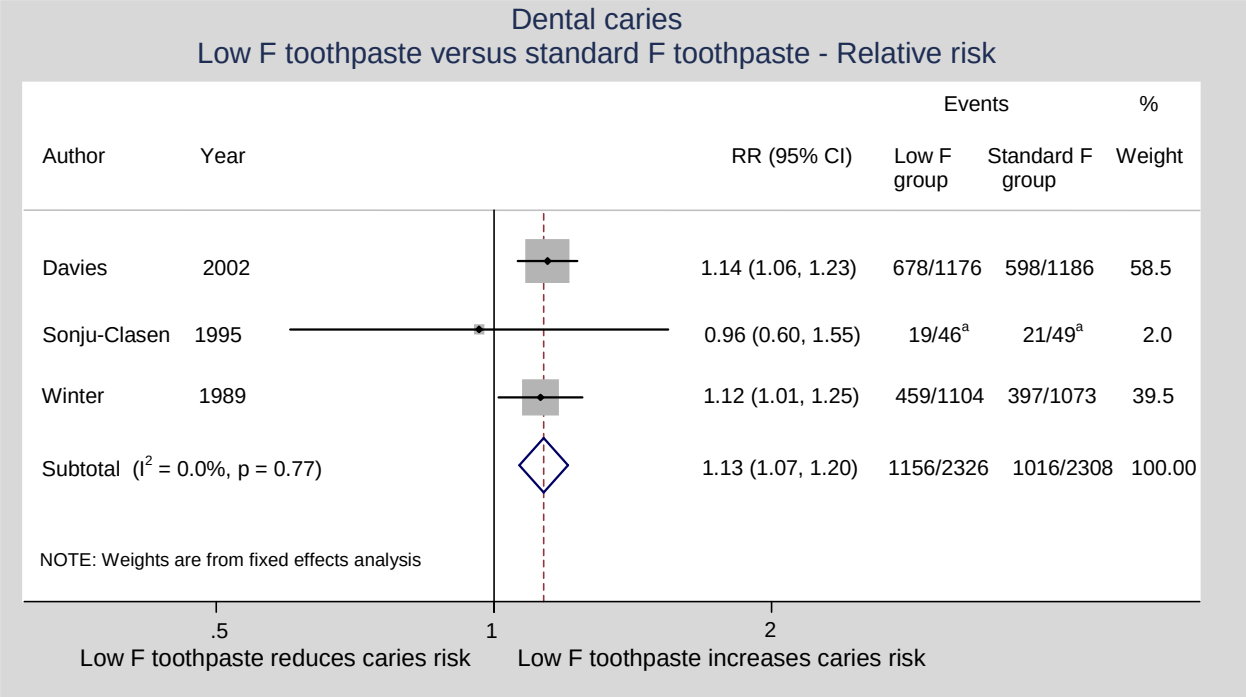
FIGURE 2. Ascertainment of the risk of bias in the included studies.



	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete oucome data addressed?	Free of selective outcome reporting?	Losses to follow-up < 20%?	Adequate reliability?	Baseline balance?	Free of contamination?
Davies[57]	+	+	+	+	-	-	?	?	?
Gerdin[62]	-	-	+	-	-	+	?	?	?
Sonju-Clasen[58]	?	?	+	-	+	-	+	?	+
Vilhena[63]	+	-	+	+	-	-	+	?	+
Winter[59]	?	?	+	-	+	-	-	?	+

Yes (+), No (-), Unclear (?)
The darker the shade of grey the higher the risk of bias

FIGURE 3. Comparison between low fluoride toothpaste and standard fluoride toothpaste regarding the proportion of children developing caries in the primary dentition.



[a] This is the effective sample size. Original numbers were 35/83 (low F group) and 38/89 (standard F group)

FIGURE 4. Comparison between low fluoride toothpaste and standard fluoride toothpaste regarding the number of decayed, missing due to caries and filled primary teeth (dmft). One trial testing low fluoride toothpastes with acidic pH was excluded.

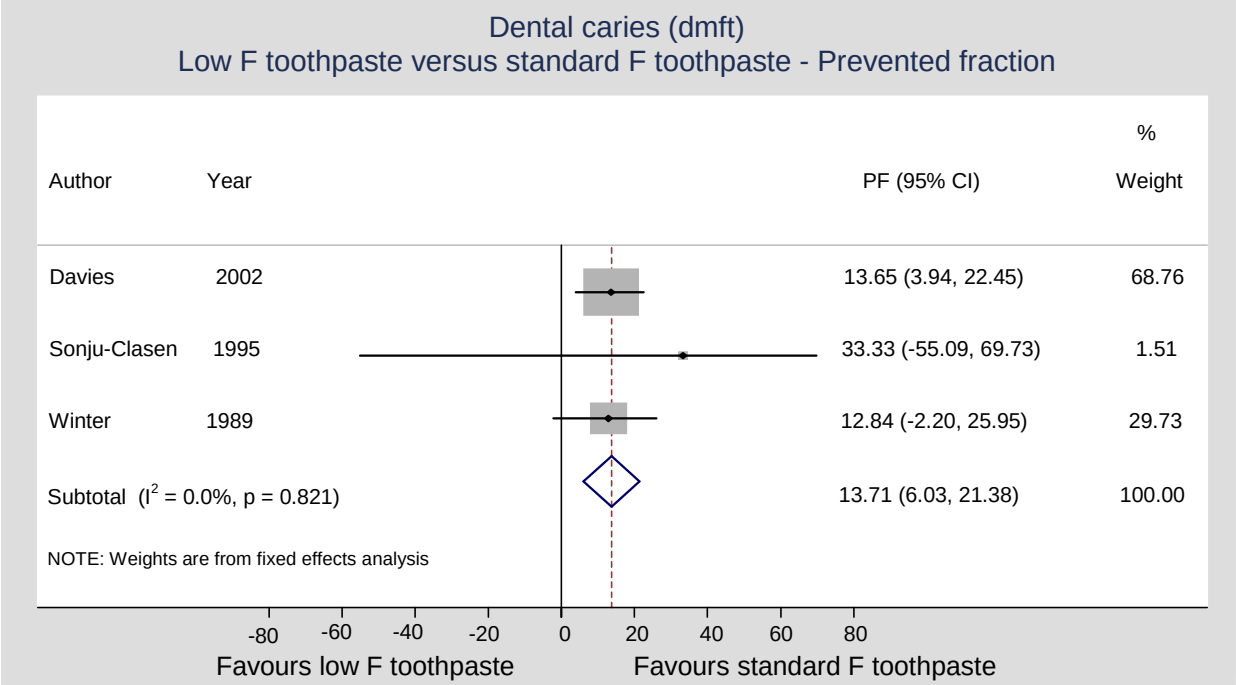


FIGURE 5. Comparison between low fluoride toothpaste and standard fluoride toothpaste regarding the number of decayed, missing due to caries and filled primary dental surfaces (dmfs).

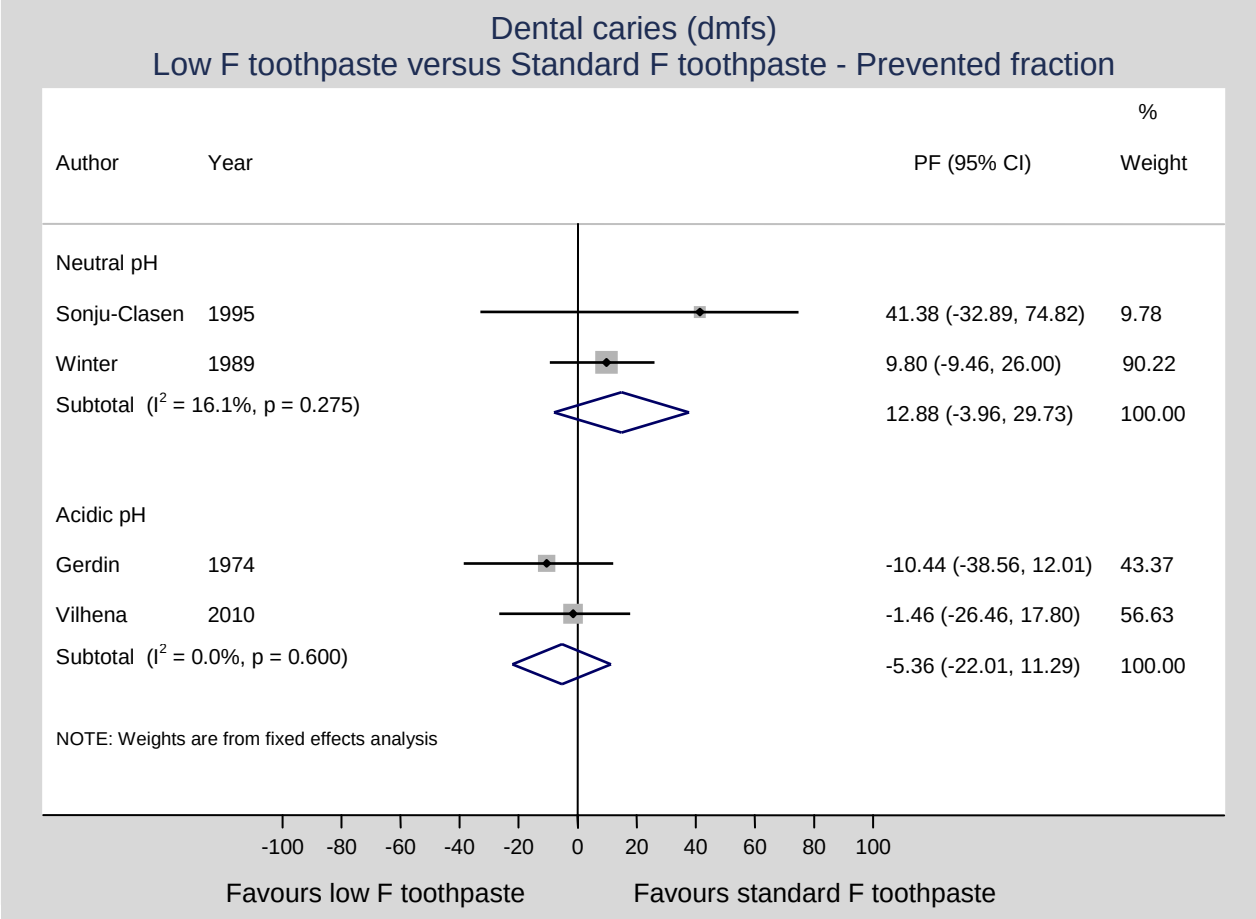
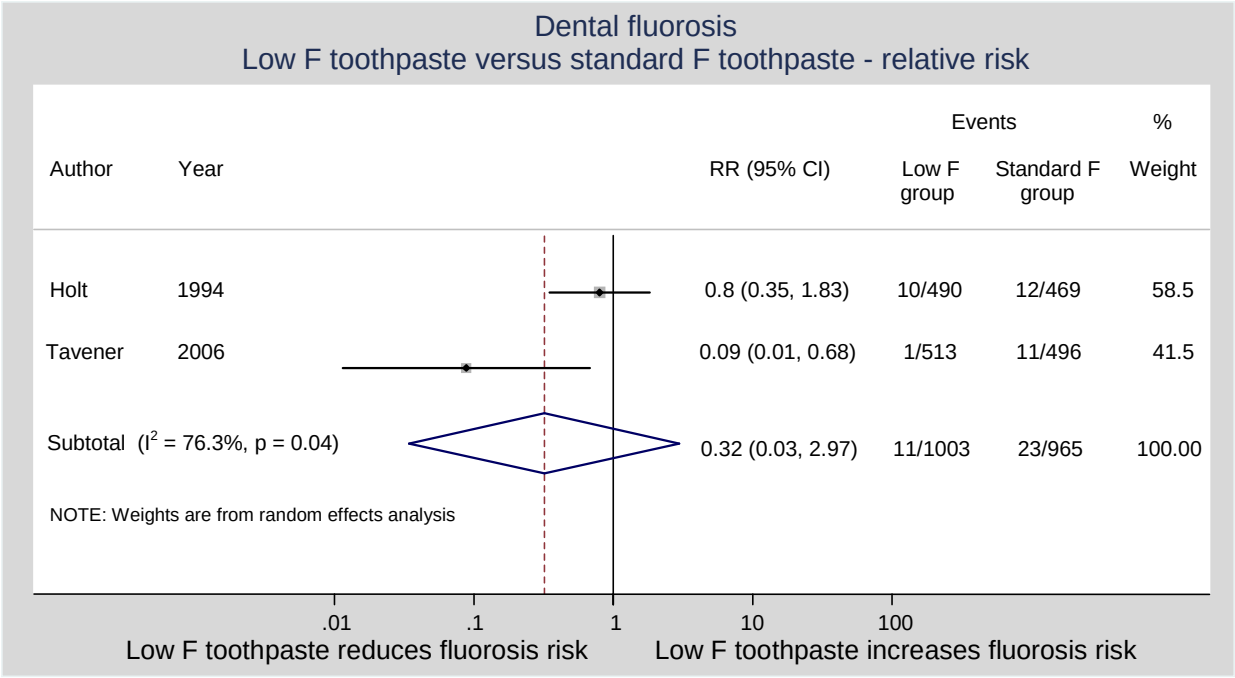


FIGURE 6. Comparison between low fluoride toothpaste and standard fluoride toothpaste regarding the proportion of children developing moderate to severe fluorosis in upper permanent anterior teeth.



APPENDIX 1. Search strategy for MEDLINE via PubMed

#1 DENTAL CARIES [mh]
#2 TOOTH DEMINERALIZATION [mh]
#3 DMF INDEX [mh]
#4 (dmft or dmfs or dft or dfs)
#5 ((tooth or teeth or dent*) and (caries or carious or decay or demineral* or cavit*))
#6 #1 or #2 or #3 or #4 or #5
#7 FLUORIDES [mh]
#8 FLUORIDES, TOPICAL [mh]
#9 CARIOSTATIC AGENTS [mh]
#10 (fluor* or cariost*)
#11 #7 or #8 or # 9 or #10
#12 TOOTHPASTES [mh]
#13 TOOTHPASTE [mh]
#14 (dentifric* or toothpaste* or tooth paste*)
#15 #12 or #13 or #14
#16 #6 and #11 and #15

APPENDIX 2. Characteristics of included studies.

Davies et al.[57]		
Participants	Children born in nine health districts in the north west of England, where the prevalence of caries in 5-year-olds was high. They were 12 months-old at baseline and 5½ years-old at outcome assessment	
Interventions	Test group (2472 children allocated): 440 ppm F toothpaste (Colgate 0-6 Gel) Control group (2488 children allocated): 1450 ppm F toothpaste (Colgate Great Regular Flavour) Another control group not considered Leaflets encouraged parents to use a pea-sized amount of the toothpaste and to brush their child's teeth twice daily	
Outcomes	mean dmft (primary outcome), mean mt and prevalence of caries experience (dmft>0)	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "within each of the nine districts children were given an identity number and centrally allocated to either one of the two test groups or a control group using random number tables"
Allocation concealment?	Yes	Quote: "centrally allocated"
Blinding?	Yes	Comment: single-blind Quote: "dental examinations were conducted under blind conditions but as *off the shelf* toothpaste (without over wrapping or repackaging) was delivered to the participants, subjects and their families were aware of which toothpaste they were using"
Incomplete outcome data addressed?	Yes	Quote: "a further two analyses were performed for the primary outcome dmft to try to estimate the population effect. The first included data from all children who were clinically examined and were originally part of the study population but included those who did not complete the study. The second also included subjects initially randomised but not examined clinically by imputing the means and standard deviations from the control group"
Free of selective reporting?	No	Comment: dmfs not reported
Losses to follow-up less than 20%?	No	Comment: withdrawals in both intervention groups of 32%; children were excluded after randomization. Quote: "children were withdrawn from test and control groups if toothpaste or questionnaires were returned by the post office as undeliverable"; "reply paid cards were returned by the parents of 641 test children, indicating that they did not wish their children to participate and during the five years of the study 1,432 children moved away from the area. Five children withdrew from the 1450 ppm F toothpaste group, one because the dentist advised this, three because of

		concerns about fluorosis and one because of an allergy to the toothpaste"
Diagnosis reliability?	Unclear	Comment: the study does not mention the number of examiners or the intra and inter-examiner reliability Quote: "in each district the clinical examinations were undertaken by trained, standardized and calibrated examiners according to the standards set by BASCD"
Baseline characteristics balanced?	Unclear	Comment: the study does not provide information about baseline socio-demographic characteristics. Also, children were not examined at baseline; it was assumed that all children were caries-free at the beginning of the trial
Free of contamination?	Unclear	Comment: no strategies to avoid contamination between groups were reported; it is not possible to rule out contamination at home or school as the randomization was performed within each district

Gerdin[62]		
Participants	Children aged 3.25-3.74 years old at the beginning of the trial, who were participants in a dental care program for preschool children in Gothenburg, Sweden, and lived in the same part of the city	
Interventions	Test group (115 children allocated): 250ppm toothpaste, non-abrasive polymethyl metacrylate, potassium fluoride and manganese, pH 5.5 Control group (115 children allocated): 1000ppm toothpaste, non-abrasive polymethyl metacrylate, sodium fluoride, pH 6.5 Toothbrushing at home, supervised and aided by parents, twice daily, vertical technique and rubbing with small movements, pea size amount of toothpaste, no rinsing with water after toothbrushing	
Outcomes	caries increment: dft and dfs	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	No	Comment: non-random allocation Quote: "the groups were randomized according to the children's birth-month so that the children born in even months formed one group, and children born in odd months formed the other group"
Allocation concealment?	No	Comment: non-random allocation prevents allocation concealment
Blinding?	Yes	Comment: double-blind Quote: "the toothpastes were coded by means of symbols. Toothpaste (1) was labeled with blue flowers, and toothpaste (2) was labeled with red butterflies. Adhesive labels with the same symbols were handed out for use on the children's special recording cards, on their visiting cards, on their toothbrushes etc. so each should know if he or she was a *flower* or a *butterfly*"; "the recorders were the same during the whole trial, and they had no knowledge of the contents of the trial toothpastes"
Incomplete	No	Comment: the study does not provide information about

outcome data addressed?		incomplete outcome data
Free of selective reporting?	No	Comment: proportion of children developing caries not reported
Losses to follow-up less than 20%?	Yes	Comment: 6% test group and 9% control group Quote: "each group comprised 115 children at the beginning of the trial"; "in the groups remained at the recordings after two years, 105 (boys 54, girls 51) and 108 (boys 56, girls 52) respectively"; "the non-responses from the groups were small and were only caused by the moving of a child from the city"
Diagnosis reliability?	Unclear	Comment: the study does not mention the inter and intra-examiner reliability Quote: "the caries recordings were performed in independent examinations by two dentists"; "the recorders were calibrated with respect to both their clinical and their roentgenological recordings at the beginning of the trial and after two years"
Baseline characteristics balanced?	Unclear	Comment: although it is mentioned that the groups were similar regarding socio-economic status, consumption habits, oral hygiene, individual fluoride prophylaxis etc., only data about caries baseline levels and sex distribution are provided
Free of contamination?	Unclear	Comment: no strategies to avoid contamination between groups were reported; it is not possible to rule out contamination at home or school as children were allocated to the groups according to their birth-month

Sonju-Clasen et al.[58]		
Participants	Children aged 5-6 years old at final examination, from 10 (out of a total of 30) Salzgitter (Germany) kindergartens	
Interventions	Test group (5 kindergartens and 155 children allocated): 250 ppm F, xanthan, carbopol 956, sorbitol, silica as abrasive, sodium fluoride as the active substance, cocamidopropyl-betain-1,5 as detergent, pH 6,5 Control group (5 kindergartens and 164 children allocated): 1450 ppm F, xanthan, carbopol 956, sorbitol, silica as abrasive, sodium fluoride as the active substance, sodium laurylsulphate as detergent, pH 6,8 Daily toothbrushing in the kindergartens with a pea-sized amount of the toothpaste (supervised by the kindergarten staff). All children used a 250 ppm F toothpaste at home	
Outcomes	dmfs, dmft, proportion of caries-free children	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Comment: the method of randomization was not mentioned Quote: "to assure an even distribution of kindergartens from different areas and social groups in each study group, Salzgitter was divided into five geographical areas from which two kindergartens were randomly assigned to one of the two study groups"
Allocation concealment?	Unclear	Comment: as it is not possible to know which method of randomization was used, allocation concealment cannot be

		assessed
Blinding?	Yes	Comment: double-blind Quote: “at the time of the examinations the examiner was not aware if the child belonged to a study group or not”; “neither the kindergarten children nor the kindergarten staff were aware of the purpose of the study, nor were they told that a toothpaste containing a different amount of fluoride was given to other kindergartens”
Incomplete outcome data addressed?	No	Comment: the study does not provide information about incomplete outcome data
Free of selective reporting?	Yes	Comment: dmft, dmfs and proportion of children developing caries reported
Losses to follow-up less than 20%?	No	Quote: “of the 319 children examined at baseline, 172 were available for examination after 22 months (83 in the low-fluoride group and 89 in the high-fluoride group), giving a drop-out rate of 46% (46,5% in the low-fluoride group and 45, 7% in the high-fluoride group)”; “the majority of the subjects who failed to complete the study either went to new kindergartens in the area or, to a lesser extent, changed residence”
Diagnosis reliability?	Yes	Comment: one examiner Quote: “the intra-examiner reliability, calculated as Scott's *pi* (for dmfs*),* was 0·89; this reflects very good intraexaminer reliability”
Baseline characteristics balanced?	Unclear	Comment: although it is mentioned that the groups were similar regarding age, sex and baseline caries levels, the number of boys was greater in the control group. It is assumed that there was an even distribution according to socioeconomic status, although the method of randomization is not clearly stated Quote: “the groups were not significantly different with respect to sex, age or proportion of caries-free children”; “to assure an even distribution of kindergartens from different areas and social groups in each study group, Salzgitter was divided into five geographical areas from which two kindergartens were randomly assigned to one of the two study groups”
Free of contamination?	Yes	Comment: contamination avoided at kindergartens due to the allocation scheme; contamination at home not probable Quote: “the children's toothbrushing routines at home were not interfered with: they all used a 250 ppm fluoride toothpaste at home”

Vilhena et al.[63]	
Participants	4-year-old children that attended all primary schools of São José dos Campos, São Paulo, Brazil (0.6-0.8 ppm F in the drinking water)
Interventions	Test group (59 classrooms and 354 children allocated): liquid toothpaste, 550 ppm F, NaF, pH 4.5 Control group (56 classrooms and 360 children allocated): 1100 ppm F toothpaste, NaF, pH 7.0 (Sorriso Fresh, Colgate Palmolive, São Paulo,

	Brazil) Two more test groups not considered Supervised toothbrushing performed on school days, for one minute Parents were asked to brush their children's teeth for 1 min at least twice a day. The liquid toothpastes were applied to the toothbrushes using the 'drop' technique	
Outcomes	dmfs	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "for the random allocation to the groups, the classrooms were considered as units of draw, in order that only 1 type of toothpaste was distributed in each classroom"; "assignment of the included children to the study groups was done by 1 of the researchers…, using a previously established algorithm…. the software… generated random numbers ranging from 0 to 1"
Allocation concealment?	No	Quote: "open random allocation schedule"
Blinding?	Yes	Comment: single-blind Quote: "the study was blinded only for the examiner, since the commercial toothpaste was maintained in its original package"
Incomplete outcome data addressed?	Yes	Comment: missing data not associated to the outcome
Free of selective reporting?	No	Comment: only dmfs reported
Losses to follow-up less than 20%?	No	Comment: withdrawals of 29% (test group) and 25% (control group) Quote: "the drop-out rate was around 25% which is a little bit higher than expected"
Diagnosis reliability?	Yes	Comment: two examiners; intra-examiner reliability examiner 1 (k= 0.91) and examiner 2 (k= 0.95); inter-examiner reliability first examination (k= 0.85) and second examination (k= 0.87)
Baseline characteristics balanced?	Unclear	Comment: the study shows that the groups were similar regarding baseline dmfs, age and sex. Individual information about socioeconomic status was not assessed, so it s not possible to know whether the method used to balance the groups according to this variable was successful
Free of contamination?	Yes	Quote: "only 1 type of toothpaste was distributed in each classroom"; "family kits containing 5 toothbrushes, 6 toothpaste tubes (120 g each) and 1 leaflet about oral hygiene care and compliance need were distributed for all participants every 4 months. The kits were supplied to be used by the whole family in order to guarantee the use of the respective toothpaste by the children, thus facilitating

	compliance with the study protocol"

Winter et al.[59]		
Participants	Preschool children with a starting age of 2 years resident in the Norwich Health District, England	
Interventions	Test group: 550 ppm toothpaste containing a mixture of 0.209 % sodium monofluorphosphate and 0.060% sodium fluoride, calcium glycerophosphate as abrasive Control group:1055ppm toothpaste containing 0.80% sodium monofluorphosphate, calcium glycerophosphate as abrasive There is no information regarding the number of children allocated to each group Parents were instructed to clean the child's teeth at least twice a day and to use a pea size amount of toothpaste	
Outcomes	dmft, dmfs, ms, fs, proportion of caries-free children	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Comment: the method of randomization is not mentioned Quote: "children included in the study were randomly allocated into test (J) and control (R) groups. However, twins were allocated as pairs"
Allocation concealment?	Unclear	Comment: as it is not possible to know which method of randomization was used, allocation concealment cannot be assessed
Blinding?	Yes	Comment: double-blind Quote: "double-blind clinical trial"; "toothpaste was supplied in 50g tubes bearing the name of the Eastman Dental Hospital, the date of manufacture and the group code"
Incomplete outcome data addressed?	No	Comment: the study does provide mention information about incomplete outcome data
Free of selective reporting?	Yes	Comment: dmft, dmfs and proportion of children developing caries reported
Losses to follow-up less than 20%?	No	Comment: the study does not provide the drop-rates separately Quote: "at the end of the trial, 2177 (72%) children were examined clinically"
Diagnosis reliability?	No	Comment: clinical diagnosis (three examiners): kappa inter 0.65-0.71 and kappa intra 0.90-0.97; radiographic diagnosis (one examiner): kappa intra 0.92
Baseline characteristics balanced?	Unclear	Comment: the groups were similar regarding sex and social class; children were not examined at the baseline; it was assumed most children were caries-free Quote: "group J was made up of 550 boys and 554 girls and group R of 554 boys and 519 girls, the compositions of which were not significantly different; "the social class distributions of children in groups J and R were little different"; "the reason

		for conducting a trial at its inception on 2-year-old-children was based on the expectation that most would be free from caries”
Free of contamination?	Yes	Quote: “sufficient toothpaste was provided for the whole family in 50g tubes bearing the name of the Eastman Dental Hospital, the date of manufacture and the group code”; “collection of used and partially used tubes was made at each of the monthly visits, ensuring that fresh paste was employed throughout the trial and gauging indirectly its utilization”

APÊNDICE E- Estratégia de busca desenvolvida para o MEDLINE via PubMed

#1 DENTAL CARIES [mh]
#2 TOOTH DEMINERALIZATION [mh]
#3 DMF INDEX [mh]
#4 (dmft or dmfs or dft or dfs)
#5 ((tooth or teeth or dent*) and (caries or carious or decay or deminerali* or cavit*))
#6 #1 or #2 or #3 or #4 or #5
#7 FLUORIDES [mh]
#8 FLUORIDES, TOPICAL [mh]
#9 CARIOSTATIC AGENTS [mh]
#10 (fluor* or cariost*)
#11 #7 or #8 or # 9 or #10
#12 TOOTHPASTES [mh]
#13 TOOTHPASTE [mh]
#14 (dentifric* or toothpaste* or tooth paste*)
#15 #12 or #13 or #14
#16 #6 and #11 and #15

APÊNDICE F - Formulário para extração de dados

Identificação do estudo		
Título: Autor(es): Fonte (nome, volume, número, págs., ano de publicação, idioma): Contato autor principal: Informação coletada por: Data:		
Avaliação do risco de viés do estudo		
a. A sequência de alocação foi gerada de forma adequada? Descrição:		( )Sim ( )Não ( )Incerto
b. Houve ocultação da alocação? Descrição:		( )Sim ( )Não ( )Incerto
c. O conhecimento da alocação da intervenção foi adequadamente evitado durante o estudo? Descrição:		( )Sim ( )Não ( )Incerto
d. Houve análise de dados incompletos ou ausentes? Descrição:		( )Sim ( )Não ( )Incerto
e. O estudo apresenta relato seletivo do desfecho? Descrição:		( )Sim ( )Não ( )Incerto
f. O estudo está aparentemente livre de outros problemas que poderiam introduzir viés (comparabilidade no baseline, concordância examinadores, perdas, contaminação entre grupos)? Descrição:		( )Sim ( )Não ( )Incerto
Métodos		
1 Desenho do estudo	Randomizado? Duplo-cego? Cross-over?	( )Sim ( )Não ( ) Incerto ( )Sim ( )Não ( ) Incerto ( )Sim ( )Não ( ) Incerto
2 Critérios de inclusão		
3 Critérios de exclusão		
4 Tipo de população (idade, sexo, nível inicial de cárie, nível sócio-econômico)		
5 Tipo de intervenção grupo teste (concentração, agente, abrasivo, pH, água fluoretada)		
6 Tipo de intervenção grupo controle (concentração, agente, abrasivo, pH, água fluoretada)		
7 Desfecho (incluir informação sobre o exame)		
8 Efeitos adversos (fluorose)		
9 Duração do estudo		
10 Intervalo de acompanhamento		
11Viés de atrição (perdas e exclusões)		
12 Análise estatística		
13 Resultados	N grupo teste: N grupo contr:	N que desenvolveu nova lesão cárie esmalte grupo teste (cavitada_____total_____) N que desenvolveu nova lesão cárie dentina grupo teste (cavitada_____total_____) N total novas lesões grupo teste (_____) µ (_____) dp (_____) N que desenvolveu nova lesão cárie esmalte grupo contr (cavitada_____total_____) N que desenvolveu nova lesão cárie dentina grupo contr (cavitada_____total_____) N total novas lesões grupo contr. (_____) µ (_____) dp (_____)

14 Conclusão do estudo segundo os autores	
15 Observações	

APÊNDICE G - Fórmulas utilizadas na análise estatística

1) Fração prevenida (FP)

$$\frac{I_c - I_t}{I_c} \times 100$$

Ic= incremento de cárie no grupo controle
It= incremento de cárie no grupo teste

2) Intervalo de confiança da FP pelo método de Fieller

$$100 \left\{ 1 - \frac{b}{a\left(\frac{1 - z^2c^2}{a^2}\right)} \right\} \pm 100 \frac{z\left(a^2d^2 + b^2c^2 - z^2c^2d^2\right)^{1/2}}{a^2\left(1 - \frac{z^2c^2}{a^2}\right)}$$

a= incremento de cárie no grupo controle
b= incremento de cárie no grupo teste
c= erro padrão do incremento no grupo controle
d= erro padrão do incremento no grupo teste
z= 1,96 para intervalos de confiança de 95%

3) Número necessário a tratar para causar um desfecho benéfico adicional (NNTB) a partir da fração prevenida

$$\frac{1}{I_p \times FP}$$

Ip= incremento de cárie na população especificada
FP= fração prevenida

4) Número necessário a tratar para causar um desfecho benéfico adicional (NNTB) a partir da diferença de risco

$$\frac{1}{DR} = \frac{1}{Ip - (Ip \times RR_{ma})}$$

DR= diferença de risco
Ip= incidência de cárie na população especificada
RR_{ma}= risco relativo sumário obtido na metánalise

5) Número necessário a tratar para causar um desfecho danoso adicional (NNTH) a partir da diferença de risco

$$\frac{1}{DR} = \frac{1}{(Ip \times RR_{ma}) - Ip}$$

DR= diferença de risco
Ip= incidência de cárie na população especificada
RR_{ma}= risco relativo sumário obtido na metánalise