Silver Diamine Fluoride: A Caries "Silver-Fluoride Bullet"

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CRITICAL REVIEWS IN ORAL BIOLOGY & MEDICINE

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ABSTRACT

The antimicrobial use of silver compounds pivots on the 100-year-old application of silver nitrate, silver foil, and silver sutures for the prevention and treatment of ocular, surgical, and dental infections. Ag^+ kills pathogenic organisms at concentrations of < 50 ppm, and current/potential anti-infective applications include: acute burn coverings, catheter linings, water purification systems, hospital gowns, and caries prevention. To distill the current best evidence relative to caries, this systematic review asked: Will silver diamine fluoride (SDF) more effectively prevent caries than fluoride varnish? A five-database search, reference review, and hand search identified 99 human clinical trials in three languages published between 1966 and 2006. Dual review for controlled clinical trials with the patient as the unit of observation, and excluding cross-sectional, animal, *in vitro* studies, and opinions, identified 2 studies meeting the inclusion criteria. The trials indicated that SDF's lowest prevented fractions for caries arrest and caries prevention were 96.1% and 70.3%, respectively. In contrast, fluoride varnish's highest prevented fractions for caries arrest and caries prevention were 21.3% and 55.7%, respectively. Similarly, SDF's highest numbers needed to treat for caries arrest and caries prevention were 0.8 (95% CI = 0.5-1.0) and 0.9 (95% CI = 0.4-1.1), respectively. For fluoride varnish, the lowest numbers needed to treat for caries arrest and prevention were 3.7 (95% CI = 3.4-3.9) and 1.1 (95% CI = 0.7-1.4), respectively. Adverse events were monitored, with no significant differences between control and experimental groups. These promising results suggest that SDF is more effective than fluoride varnish, and may be a valuable caries-preventive intervention. As well, the availability of a safe, effective, efficient, and equitable caries-preventive agent appears to meet the criteria of both the WHO Millennium Goals and the US Institute of Medicine's criteria for 21st century medical care.

KEY WORDS: systematic review, caries, prevention, fluoride, silver.

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INTRODUCTION

With a wealth of fluoride-based caries-preventive agents (Table 1), why might one be interested in yet another fluoride delivery system? The answer lies in silver diamine fluoride's (SDF) hypothesized ability to halt the caries process and simultaneously prevent the formation of new caries. This hypothesized ability is thought to derive from the combined effects of: silver-salt-stimulated sclerotic or calcified dentin formation (*e.g.*, Stebbins, 1891), silver nitrate's potent germicidal effect (*e.g.,* Miller, 1905; Howe, 1917; Klein and Knutson, 1942), and fluoride's ability to reduce decay (*e.g.*, Marinho *et al*., 2002, 2004a,b). [Dentists termed silver nitrate "Howe's solution" after Percy Howe, who reported on its use for caries prevention. Howe was The Forsyth Institute's first research director, and the Forsyth library is named after him.] The specific interest in SDF centers around its 5 presumed attributes (Bedi and Sardo-Infirri, 1999): control of pain and infection, ease and simplicity of use (paint on), affordability of material (pennies *per* application), minimal requirement for personnel time and training (one minute, once *per* year), and the fact that it is non-invasive. In this sense, SDF has the potentially unique ability to be a "silver-fluoride bullet," simultaneously halting the cariogenic process and preventing caries.

The need for agents like SDF is perhaps best understood in terms of the World Health Organization (WHO) Millennium Development Goals for Health (Wagstaff and Claeson, 2004), and in particular the oral health goals (Hobdell *et al.,* 2003). The proposed path to achieving these goals is the provision of a basic oral health package, consisting of: emergency care, prevention, and cost-effective interventions, in that order (Frencken *et al*., 2008). To achieve these goals, the use of simple technologies will be required for 'scale up' to improve access to oral health care at a much lower cost. At the same time, all of these preventive interventions will need to be built upon a firm evidence base.

With the continuing population expansion, and the decreasing availability of dentists to provide emergency care and restorative treatment, the likeliest path to oral health will be an intense focus on prevention. Silver fluoride compounds may partially fill this need.

Brief History

The first medicinal use for silver appears to have been around 1000 BC for the storing of potable water (see Russell and Hugo, 1994). Current uses of silver compounds in medicine revolve around the application of silver nitrate, silver foil, and silver sutures for the prevention of ocular and surgical infections (*e.g.*, Credé, 1881; Halsted, 1895). Von Naegeli (1893) demonstrated that silver can kill spirogyra, and found that various forms of silver have different effects, with silver nitrate being a very effective antimicrobial agent.

Table 1. Fluoride Efficacy in Preventing Caries

Fluoride Delivery System	Estimated Caries Reduction	Reference
Milk	?	Yeung *et al.* (2005)
Salt	15%	Marthaler and Petersen (2005)
Toothpaste	24%	Marinho *et al.* (2004a)
Mouthwash	26%	Marinho *et al.* (2004b)
Water (adults)	27%	Griffin *et al.* (2007)
Gel (children)	28%	Marinho *et al.* (2002)
Water (children)	34%	Do and Spencer (2007)
Varnish	46%	Marinho *et al.* (2002)
SDF permanent teeth	> 60%	Current review
SDF deciduous teeth	> 70%	Current review

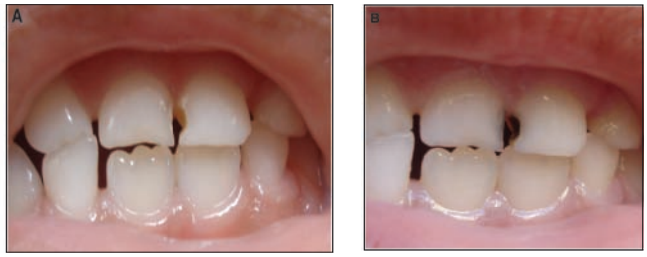

Figure 1. Clinical photographs prior to and following application of silver diamine fluoride. **(A)** Clinical photographs of interproximal caries lesions in maxillary incisors of a 5-year-old girl. **(B)** Clinical photograph of brown staining following a 60-second application of Cariestop® 12% silver diamine fluoride. Note that only the caries lesion, not the tooth, is stained.

Table 2. Effects of Silver Nitrate and Silver Scraps on Decay Prevention (Stebbins, 1891)

Year after Treatment	# Teeth	Success*	Partial Success	Unsuccessful
1	64	37 (58%)	17 (27%)	13 (20%)
2	27	10 (37%)	5 (19%)	12 (44%)
3	142	87 (61%)	33 (23%)	22 (15%)

* Success = no further decay; Partial success = expansion of decay; Unsuccessful = no silver discoloration.

From a dental perspective, Stebbins (1891) reported that teeth restored with amalgam displayed black surfaces where the progress of decay had ceased. Then, reasoning from the current use of silver nitrate treatment for sensitive teeth, and the resulting tooth coloration, he mixed nitric acid with amalgam scraps and applied them to caries lesions in 35 children. Stebbins' results suggest that this treatment successfully inhibited decay in 61% of cases at 3 yrs (Table 2). Stebbins hypothesized that caries inhibition was the result of bacterial killing and the deposition of a "black crust," generating a sclerotic protective coating of secondary dentin. Subsequently, Howe (1917) directly applied silver nitrate to caries lesions with similar results. "Howe's solution" was used for this purpose for the next 50 yrs.

Over the last 40 yrs, numerous preliminary *in vitro* and *in vivo* trials examined the potential efficacy of silver-fluoride regimens in caries prevention. *In vitro* studies suggested that silver-fluoride regimens inhibit *S. mutans* growth (Thibodeau *et al*., 1978; Ostela and Tenovuo, 1990), metabolic activity of dental plaque (Oppermann and Johansen, 1980; Oppermann and Rölla, 1980), and caries lesion depth progression (Klein *et al.,* 1999). Similarly, *in vivo* studies in primary teeth indicated that silver-fluoride application inhibits the lateral spread of caries (Nishino *et al*., 1969, using AgF), occlusal and approximal caries by AgF + SnF_2 + stomahesive (Craig *et al*., 1981, using AgF + SnF_2 + stomahesive), and 95% of caries progression (McDonald and Sheiham, 1994, using AgF + SnF_2). Finally, *in vivo* studies in permanent teeth indicated that silver fluoride arrests approximal caries progression (Hyde, 1973, using $AgNO_3$) and the initiation of caries lesions (Green, 1989, using AgF + SnF_2). These early studies led to the use of silver diamine fluoride in Australia (Gotjamanos, 1997), Japan (Yamaga and Yokomizo, 1969), and Mexico (Aron, 1995).

While the preliminary studies of silver fluoride demonstrated an anti-caries effect, they also recognized that silver fluoride can blacken caries lesions (but not sound tooth surfaces) (Fig. 1). Therefore, newer *in vitro* experiments are examining silver fluoride followed by potassium iodide (Knight *et al*., 2006), which produces a white silver iodide reaction product. However, the ability of this product to prevent caries *in vivo* has not yet been demonstrated.

Mechanisms of Action

Soft Lewis acids, like the transition metal silver, have high polarizing power (a large ratio of ionic charge to the radius of the ion) and typically form strong bonds with soft Lewis bases. These include sulfur and nitrogen ligands such as cysteine and histidine residues in proteins. As indicated below, these interactions may account for the effects of silver on bacteria and teeth.

Bacteria

Multiple modes of action have been proposed for silver (*e.g*., Lansdown, 2002a, 2006; Wu *et al*., 2007). This may, in part, be explained by the multiple biological organisms (*e.g*., bacterial, protozoan, fungal, and viral), subcellular targets (*e.g*., cell membranes, organelles, nuclei), and mechanisms (*e.g*., metabolism, replication) that have been examined. Studies have indicated that silver interacts with sulfhydryl groups of proteins and with DNA, altering hydrogen bonding and inhibiting respiratory processes, DNA unwinding, cell-wall synthesis, and cell division (*e.g*., Oppermann *et al.,* 1980; Lansdown, 2002a, 2006). At the macro level, these interactions effect bacterial killing and inhibit biofilm formation (*e.g*., Wu *et al*., 2007). The central mechanism for these diverse effects is proposed to be the interaction of silver with thiol goups by the following mechanism (Russell and Hugo, 1994):

$$A/N — SH + AgX \rightarrow A/N\text{-}\ S\text{-}\ AgX + HX$$

Table 3. Relationship of Silver to Effector Genes and Enzymes

Target Effect*	Interaction	Description	Reference
---| Arabinase	Inhibition	Arabinase is inhibited by Ag	Takahashi *et al.* (1985)
--- Azu	Binding	Cu replaced by Ag in azurin	Tordi *et al.* (1990)
---| β-galactosidase	Inhibition	Beta-galactosidase is inhibited by Ag	Wutor *et al.* (2007)
---| Chitosanase	Inhibition	Chitosanase is inhibited by Ag	Park *et al.* (1999)
--+> CopA	Induction	CopA induced by Ag	Stoyanov *et al.* (2001)
--+> CopA, CopB	Induction	CopA and CopB induced by Ag	Odermatt *et al.* (1994)
--- CopB	Transport	CopB extrudes Ag from cells	Rensing *et al.* (2000)
--- Crd1p	Resistant	Cu pump effects Ag resistance	Riggle and Kumamoto (2000)
---| GNPTA	Inhibition	GPT is inhibited by Ag	Goil (1978)
---| GOT and GPT	Inhibition	GOT and GPT are inhibited by Ag	Goil (1978)
---| Keto-reductase	Inhibition	Ketoreductase is inhibited by Ag	Costello *et al.* (2000)
---| Mono-oxygenase	Inhibition	Monooxygenase is inhibited by Ag	Green *et al.* (1985)
--+> PacS	Induction	PacS is induced by Ag	Rensing *et al.* (1999)
--+> pH	Collapse	Trans-membrane pH collapse by Ag	Dibrov *et al.* (2002)
--+> YlcBCD–YbdE	Induction	YlcBCD–YbdE effects Ag resistance	Franke *et al.* (2001)

* --- indicates interaction; ---| indicates inhibition; --+> indicates induction.

where A/N represents amino (A) or nucleic (N) acids (respectively), SH represents a thiol group, Ag represents silver, and X represents an anion (in the current example, diamine fluoride). This interaction indicates how silver diamine fluoride, when applied to caries lesions, might interact with bacteria and mediate caries arrest through bacterial killing and inhibit caries progress through the inhibition of biofilm formation.

To identify the potential molecular interactions, we searched the Ariadne Genomics ResNet bacterial cartridge for silver-bacterial relationships and used Ariadne Genomics Pathway Studio to map these relationships (http://www.ariadnegenomics.com/). The results identified a specific set of silver targets that affect the inhibition or induction of genes and transporter systems (Table 3).

Teeth

In examining the modes of action of sodium fluoride and silver nitrate on teeth, investigators found that the 2 compounds have complex mechanisms (Yamaga and Yokomizo, 1969; Yamaga *et al*., 1972) (Table 4). The most commonly recognized interaction is sodium fluoride with calcium phosphate to form fluorapatite and sodium hydroxide (and a basic environment) (reaction 1). The less commonly recognized interaction is the combination of tooth calcium to form calcium fluoride and a basic environment (reaction 2). The initial reaction of silver nitrate is the formation of calcium nitrate, silver phosphate, and silver oxide (reaction 3).

Table 4. NaF and $Ag(NO_3)$ Reactions

Reaction	Reactants	Products
1	$Ca_{10}(PO_4)_6(OH)_2 + NaF$	$\rightarrow Ca_{10}(PO_4)_6F_2 + NaOH$
2	$Ca_{10}(PO_4)_6(OH)_2 + NaF$	$\rightarrow CaF_2 + Na_3O_4 + NaOH$
3	$Ca_{10}(PO_4)_6(OH)_2 + Ag(NO_3)$	$\rightarrow Ca(NO_3)_2 + Ag_3PO_4 + Ag_2O + H_2O$

Knowledge of these reactions led to the development of silver diamine fluoride. In this context, fluoride and silver interact synergistically to form fluorapatite (Table 5). The first step is the formation of calcium flouride and silver phosphate in a basic environment (reaction 4). The second reaction is the subsequent dissociation of calcium and fluoride (reaction 5). The last step is the formation of fluorapatite (reaction 6). The net result of these interactions is depicted in Fig. 2.

Table 5. $Ag(NH_3)_2$ F Reactions

Reaction	Reactants	Products
4	$Ca_{10}(PO_4)_6(OH)_2 + Ag(NH_3)_2F$	$\rightarrow CaF_2 + Ag_3PO_4 + NH_4OH$
5	CaF_2	$\rightarrow Ca^{++} + 2F^-$
6	$Ca_{10}(PO_4)_6(OH)_2 + 2F^-$	$\rightarrow Ca_{10}(PO_4)_6F_2 + 2OH^-$

In vitro studies have indicated that SDF penetrates enamel to a depth of 25 microns, and approximately 2-3 times more fluoride is retained than that delivered by NaF-PO_4, NaF, or SnF_2 (Suzuki *et al.,* 1974). This suggests that the effect of SDF will be greater than that of NaF or SnF_2.

Current Medical Uses of Silver

Applications for silver in health care are now highly evolved. Silver-containing topical ointments have been approved by the US Food and Drug Administration and marketed globally to prevent bacterial infections in burn victims (*e.g*., silver sulfadiazide, Silvazine® and Flamazine®, Smith & Nephew, London, UK). A range of wound dressings with slow-release Ag compounds has been introduced, including, *e.g*., Acticoat® (Smith & Nephew), Actisorb Silver® (Johnson & Johnson, Piscataway, NJ,USA), Silverlon® (Argentum Medical, Willowbrook, IL, USA), and others. Silver-containing catheters for urinary infection prevention are available (*e.g.,* DOVER® Covidien, Norfolk, NE, USA), and hospitals use colloidal silver to purify the water supply and reduce the spread of infectious diseases (*e.g*., Modol *et al*., 2007). As well, silver fabrics are used for surgical gowns and draperies to prevent microbial transmission (*e.g*., X-Static®, Noble BioMaterials, Scranton, PA, USA). Newer dental applications for

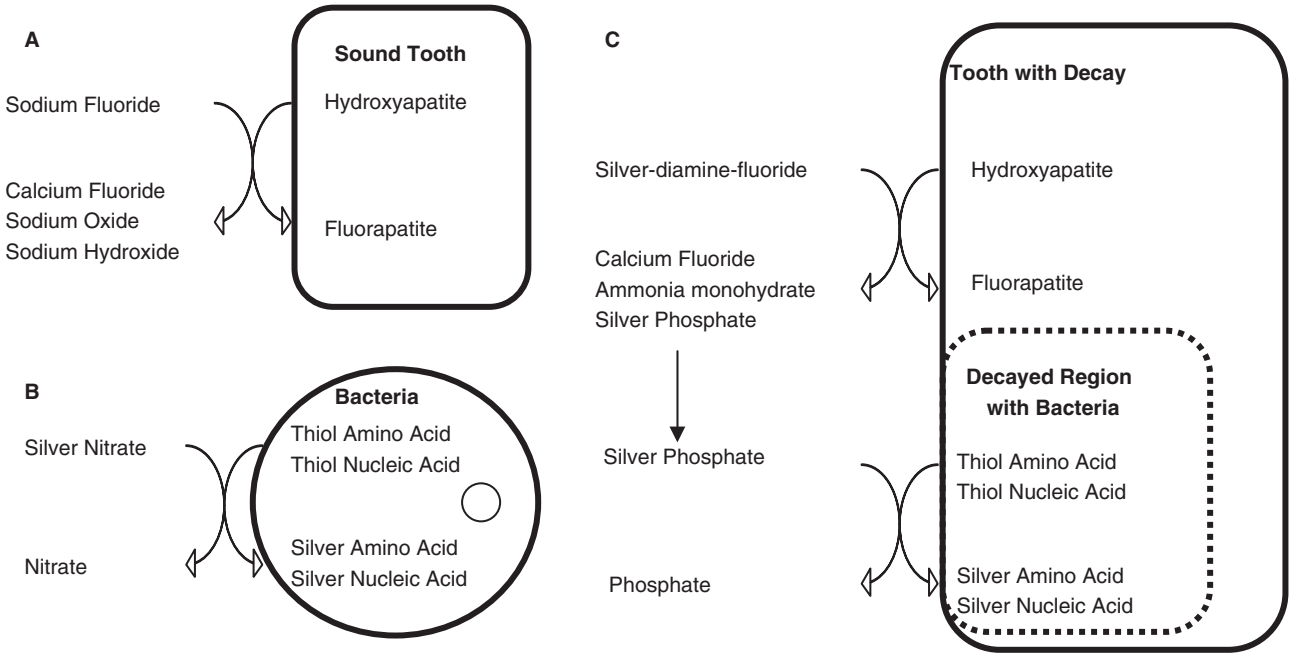

Figure 2. Diagrams representing effects of fluoride, silver nitrate, and silver diamine fluoride on teeth and bacteria. **(A)** In sound teeth, fluoride reacts with hydroxyapatite to form fluorapatite. Fluorapatite is less acid-soluble than hydroxyapatite, inhibiting the decay process. **(B)** In bacteria, silver reacts with thiol groups of amino and nucleic acids. Silver amino and nucleic acids are unable to carry out metolic and reproductive functions, leading to bacterial killing. **(C)** In teeth with decay, silver diamine fluoride reacts with hydroxyapatite to form fluorapatite, and the by-product silver phosphate. Silver phosphate subsequently reacts with bacterial amino and nucleic acid thiol groups to form silver amino and nucleic acids.

silver—beyond amalgam—are also extant for caries prevention or are being tested for composite filling materials (*e.g.*, Kawashita *et al*., 2000) and the reduction of periodontal pathogens (*e.g.*, Spacciapoli *et al.,* 2001).

Caries Treatment with SDF

For over 100 years, dentists surgically and successfully treated caries and periodontal disease with three metals: silver, gold, and stainless steel. But based on research over the last 30 years, we know that caries and periodontal disease are infections (*e.g.*, Gibbons and van Houte, 1975). For caries, the mechanism of pathogenic bacterial action is tooth decalcification. Perhaps, consequently, the current primary preventive agent for inhibiting caries is fluoride, which decreases acid solubility. Conversely, relatively little attention has been paid to controlling the infection. Given the apparent advantages (and potential disadvantages) of SDF for infection control, preventing caries, and its clinical availability in Brazil, Argentina, and Japan (Table 6), this systematic review was undertaken. We addressed the following question: Will silver diamine fluoride, when compared with a control, arrest or prevent caries? Initial reports suggested that SDF may be effective in controlling caries *in vitro* (*e.g.*, Yamaga *et al.*, 1972; Gotjamanos and Orton, 1998; Klein *et al.*, 1999) and *in vivo* (McDonald and Sheiham, 1994). Further, clinical trials have suggested SDF's efficacy in preventing caries in both the primary and permanent dentition (*e.g.*, Nishino *et al*., 1969; Almeida, 1994; Lo *et al*., 2001; Chu *et al*., 2002; Llodra *et al*., 2005; Wong *et al.,* 2005). If SDF use proves to be safe, effective, patient-centered, timely, efficient, and equitable (Institute of Medicine, 2001), and widely implemented, SDF could become a key element for comprehensive and effective preventive programs that meet the WHO Millennium Goals. SDF could potentially increase access to care, improve oral health, and ultimately reduce the need for emergency care and treatment.

Table 6. Commercially Available and Approved Silver Diamine Fluoride Solutions

Product Name	Manufacturer/Supplier	SDF Conc.	Registration #	Country
Cariostatic®	Inodon Labratorio	10%	80151700032	Brazil
Cariestop®	Biodinâmica Quimica e Farmaceutica Ltda	12%	10298550010	Brazil
Cariestop®	Biodinâmica Quimica e Farmaceutica Ltda	38%	10298550048	Brazil
Bioride®	Dentsply Industria e Comercio Ltda	30%	10186370153	Brazil
Saforide®	J.Morita; Toyo Seiyaku Kasei Ltd.	38%		Japan
FluoroplatV	Laboratorios Naf	38%	M.S.yA.S. 5010	Argentina

Table 7. Search and Evaluation Results

Evaluation		Results
Database	MEDLINE	66
	LILACS	29
	EMBASE	13
	Cochrane	7
	BBO	35
	Potential Unique	149
Title & Abstract	Actual Unique	110
	Exclude	98
	Include	12
Hand Search	Identify	3
	Exclude	3
Evaluation	Exclude	10
	Include	2

Table 8. Excluded Articles

	Reference	Reason for Exclusion
1	Almeida *et al.* (1994)	No control group
2	Gotjamanos (1996)	SDF used beneath filling material
3	Gotjamanos and Orton (1998)	*In vitro* study
4	Klein *et al.* (1999)	*In vitro* study
5	Lo *et al.* (2001)	Early report of Chu *et al.* (2002)
6	McDonald and Sheiham, 1994	SDF not used alone.
7	Nishino *et al.* (1974)	*In vitro* study
8	Nishino *et al.* (1969)	Cohort trial with tooth as unit of observation
9	Yamaga *et al.* (1972)	Commentary
10	Wong *et al.* (2005)	Bayesian analysis of Chu *et al.* (2002)

SYSTEMATIC REVIEW

Search Strategy

A search strategy was developed for articles indexed in MEDLINE, LILACS, EMBASE, the Cochrane Library, and the Brazilian Dental Library databases that were written in English, Spanish, or Portuguese between the years 1966 and December 31, 2006. The following inclusion criteria were used to identify potentially relevant reports: addressed use of silver diamine fluoride and caries; study carried out in humans; clinical trial of a randomized controlled, cohort, or case-control type; patient is the unit of observation; and includes variance assessment. Exclusion criteria were: early reports of longer studies; *in vitro* or animal studies; narrative reviews or editorials; and articles published in languages other than English, Spanish, or Portuguese. The search concept for MEDLINE was:

("Silver Nitrate"[MeSH] OR "Silver Proteins"[MeSH] OR "silver diamine"[Substance Name]

OR "silver diamine fluoride"[Substance Name] OR "silver fluoride"[Substance Name]) AND

("Dental Caries"[MeSH] OR "Tooth Demineralization"[MeSH])

Critical Appraisal

Two investigators independently read all the titles and abstracts from the multiple search results to identify articles for potential inclusion. The same two investigators obtained and reviewed complete articles that appeared to meet inclusion criteria. These investigators appraised the complete articles for inclusion, reviewed reference lists for additional articles, critically appraised the articles for quality (Jadad, 1998), and created evidence tables. A third investigator resolved disagreements.

Quantitative Assessments

Prevented fraction (PF; also termed 'relative risk reduction') (Kleinbaum *et al*., 1982) and number needed to treat (NNT) (Laupacis *et al*., 1988; Guyatt *et al*., 1998) were calculated from the original data according to the following formulas for populations (van Rijkom *et al*., 1998):

$$\text{Prevented Fraction: } PF = (Ic—Ie) / Ic$$

where Ic = control group increment, Ie = experimental group increment, and Increment = (starting active carious surfaces *per* person - ending active carious surfaces *per* person), or (ending new carious surfaces *per* person):

$$\text{Number Needed to Treat: } NNT = 1 / (Ic * PF)$$

The 95% Confidence Interval:

$$CI = 1.96 \sqrt{[(Ic * (1\text{-}Ic)/\#\text{ control patients}) + Ie * ((1\text{-}Ie)/\#\text{ experimental patients})]}$$

Findings and Data Distillation

The MEDLINE, LILACS, EMBASE, Cochrane Library, and the Brazilian Dental Library (BBO) database searches identified, respectively, 66, 29, 13, 7, and 35 reports that appeared to relate to silver diamine fluoride and caries (Table 7). Examination of the references identified 110 unique reports. Inspection of the titles and abstracts by two investigators (AR and TS) excluded 98 reports (Appendix), leaving 12 reports that appeared to be relevant. These reports were obtained and their reference lists examined for additional relevant articles, which identified 3 additional potential reports. None of these 3 reports met inclusion criteria. Twelve articles were reviewed for inclusion, 10 were excluded (Table 8), and 2 m*et all* inclusion criteria (Tables 9, 10). Both reports were critically appraised for internal validity, and subsequently used for data extraction.

Both included studies examined the clinical effect of silver diamine fluoride on caries arrest and prevention, and compared the results with a control of either fluoride varnish (Chu *et al*., 2002) or water (Chu *et al*., 2002; Llodra *et al*., 2005) (Table 9). Llodra *et al.* (2005) used a blinded randomization and blinded examination protocol, while Chu *et al.* (2002) used a cohort design. Based on the absence of either reported randomization or blinding, Llodra *et al*. (2005), and Chu *et al.* (2002) scored 4 and 2 (out of 5), respectively, on the Jadad scale (Jadad, 1998).

Table 9. Included Articles

Reference	Study Design	Problem	Experimental	Comparison	Outcome
Chu *et al.* (2002)		Carious primary maxillary anterior teeth	SDF (38%) 44.8 ppm F 1x/yr	(1) FV* (5%) 22.6 ppm F 4x/yr (2) Water 4x/yr	(1) Caries arrest (2) New caries at 2.5 yrs
Llodra *et al.* (2005)		Carious primary teeth Carious permanent first molars	SDF (38%) 2x/yr	Water 4x/yr	(1) Caries arrest (2) New caries at 3 yrs

* FV = fluoride varnish.

These studies examined the effect of SDF following application to primary teeth (Chu *et al*., 2002) or both primary and permanent teeth (Llodra *et al*., 2005). The frequency of SDF application was either biannual (Llodra *et al*., 2005) or annual (Chu *et al.,* 2002), and trial duration ranged from 2.5 yrs (Chu *et al*., 2002) to 3 yrs (Llodra *et al*., 2005). The SDF concentration for both studies was 38%. The results from both studies indicated that SDF was effective in arresting and preventing caries (Table 7).

Chu *et al.* (2002) selected children with carious maxillary anterior teeth, and with or without carious excavation, and compared 1x *per* yr SDF application with 4x *per* yr fluoride varnish or 4x *per* yr water application. The results (Table 8) indicate that SDF was substantially more effective than fluoride varnish or water in both arresting and preventing caries. For example, the lowest SDF-prevented fractions were 96.1% and 70.3% for caries arrest and prevention, respectively. In contrast, for fluoride varnish, the highest prevented fractions were 21.3% and 55.7% for caries arrest and prevention, respectively. (The original report did not provide data for a determination of confidence intervals. The original article did, however, analyze and demonstrate significant differences between SDF and fluoride varnish.) The NNT also demonstrated the substantial benefit of SDF when compared with fluoride varnish. The highest SDF NNTs were 0.8 (95% CI = 0.5-1.0) and 0.9 (95% CI = 0.4-1.1) for caries arrest and prevention, respectively. In contrast, the lowest fluoride varnish NNTs were 3.7 (95% CI = 3.4-3.9) and 1.1 (95% CI = 0.7-1.4) for caries arrest and prevention, respectively.

Llodra *et al.* (2005) selected children with carious primary teeth and/or carious permanent molars, and compared 2x *per* yr SDF application with 2x *per* yr examination. The results (Table 8) indicate that for both primary teeth and permanent molars, SDF was beneficial. In primary teeth, the prevented fractions for SDF were 55.6% and 78.6% for caries arrest and prevention, respectively. In permanent teeth, the prevented fractions for SDF were 100% and 63.6% for caries arrest and prevention, respectively. (The original report did not provide data for a determination of confidence intervals. The original article did, however, analyze and demonstrate significant differences between SDF and examination.) The NNT also indicated a substantial benefit of SDF. In primary teeth, the NNTs for caries arrest and prevention were 1.0 (95% CI = 0.4-1.3) and 0.9 (95% CI = 0.4-1.3), respectively. In permanent teeth, the NNTs for caries arrest and prevention were 10 (95% CI = 8.4-11.2) and 1.4 (95% CI = 0.3—1.9), respectively.

Regarding adverse events, both trials indicated that there was no significant difference between the control and experimental groups in pulpal incident (both < 1%). Staining was similar in both control and experimental groups, and troubled 7% of participants (Chu *et al.,* 2002). Finally, SDF did cause 24-hour tissue sensitivity in three of the 153 participants (Chu *et al*., 2002).

DISCUSSION

Analysis of the data from this narrative and systematic review suggests that the application of SDF, applied 1x or 2x *per* yr, can significantly arrest active caries, significantly reduce the incidence of new caries, and not substantially increase the risk of adverse events. The two controlled trials reported differences in pre- and post-measures of analysis. This review extrapolated from the original data to report the prevented fraction (also termed relative risk reduction) and number needed to treat (NNT), generating complementary assessments that can be applied to individuals, and could ultimately be applied to economic analysis.

Quantitative Assessments

Prevented fraction in this context indicates the caries arrest or prevention in the experimental group relative to the control group (higher is better). Overall, SDF's prevented fractions for caries arrest and prevention in both primary and permanent teeth consistently exceed the 46% found for fluoride varnish (*e.g*., Marinho *et al*., 2002). From Chu *et al.* (2002), SDF's prevented fractions for caries arrest and prevention in primary teeth were > 96% and > 70%, respectively. From Llodra *et al.* (2005), SDF's prevented fractions for caries arrest and prevention in primary teeth were > 55% and > 75%, respectively. Llodra *et al.* (2005) found similar results for permanent teeth, with SDF's prevented fractions for caries arrest and prevention equal to 100% and 64%, respectively. Thus, while both studies used different designs and different application intervals, both demonstrated a substantial beneficial effect.

The NNT indicates the number of children who would need to be treated to prevent the development of 1 additional decayed surface (lower is better). For a given PF, it is dependent on the population incidence and study duration. NNT therefore provides a measure of the efficiency of the treatment in a given population. The NNT can also be used to extrapolate effects to individuals. Similar to prevented fraction, the NNTs for SDF were substantially lower than the 1.4 found for fluoride varnish (Marinho *et al.,* 2002). From Chu *et al*. (2002), the highest NNTs for SDF caries arrest and prevention in primary teeth were both < 1. From Llodra *et al.* (2005), the NNTs for SDF caries arrest and prevention in primary teeth were both ≤ 1. In

Table 10. Evidence Table

Reference	Trial Type	N	Experimental + Comparison	Trial Length	Outcome*						Outcome			
Chu *et al.* (2002)	Prospective controlled		Carious maxillary anterior primary teeth	30 months	Active caries Surf./Subj. Start	End	Inc	PF	NNT	95% CI	New caries Surf./Subj. End	PF	NNT	95% CI
		76	Excavation + 38% SDF 1x/yr		4.13	1.64	2.49	96.1	0.8	0.5-1.0	0.26	83.5	0.8	0.2-1.0
		77	38% SDF 1x/yr		4.26	1.44	2.82	122	0.6	0.3-0.8	0.47	70.3	0.9	0.4-1.1
		76	Excavation + 5% FV 4x/yr		3.92	2.47	1.45	14.2	5.6	5.3-5.8	0.89	43.7	1.5	1.1-1.7
		73	5% FV 4x/yr		3.82	2.28	1.54	21.3	3.7	3.4-3.9	0.70	55.7	1.1	0.7-1.4
		73	Water 4x/year		3.75	2.48	1.27				1.58			
Llodra *et al.* (2005)	Prospective controlled randomized		Decayed primary teeth and occlusal of permanent 1st molars	36 months	Active caries Surf./Subj.		Inc	PF	NNT		New caries Surf./ Subj.	PF	NNT	95% CI
			Primary:		Start	End					End			
		225	38% SDF 2x/year		3.0	0.2	2.8	55.6	1	0.4-1.3	0.3	78.6	0.9	0.4-1.3
		227	Examination 2x/year		2.9	1.1	1.8				1.4			
			Permanent:		Start	End					End			
		225	38% SDF 2x/year		0.3	0.1	0.2	100	10	8.4-11.2	0.4	63.6	1.4	0.3-1.9
		227	Examination 2x/year		0.3	0.2	0.1				1.1			

* Inc = increment, PF = prevented fraction, NNT = number needed to treat.

other words, from the work of both Chu *et al*. (2002) and Llodra *et al*. (2005), every person with caries in primary teeth would benefit from SDF application. In contrast, for fluoride varnish, two people would need to be treated for one to benefit.

For permanent teeth, however, analysis of the data from Llodra *et al.* (2005) indicated that the NNT for caries arrest was 10, while caries prevention was 1.4. Thus, in permanent teeth, 10 people with caries would need to be treated with SDF for one to benefit in arrested caries. Similarly, two people with caries would need to be treated with SDF for one to benefit in caries prevention.

Application to Individuals

While the foregoing was based on clinical trials, the NNT can be useful for extrapolating from clinical trials to make predictions for individuals and ultimately communities. For example, for individuals, NNT is calculated in two ways (Sackett *et al.,* 2000):

$$NNT_{individual} = NNT_{population} / f, \quad (1)$$

where f is the clinician's estimate of the individual's risk, compared with the experimental group; and

$$NNT_{individual} = 1/ (PEER * PF), \quad (2)$$

where PEER is the clinician's estimate of the individual's expected event rate without treatment.

In Eq. 1, for example, if the clinician estimated that an individual's risk of new caries in primary teeth was 0.5x that of Chu *et al*. (2002) [*e.g.*, ~ 0.75 new carious surfaces/person over 2.5 yrs *vs*. 1.58 new carious surfaces/person in Chu *et al*. (2002)], the $NNT_{individual}$ for this person would be: 1/0.5 = 2. In other words, two people would need to be treated with SDF for one person to benefit. A similar analysis can be used to compare SDF with fluoride varnish (NNT = 1.4; f = DMFS = 1.6/yr; Marinho *et al*., 2002). In this example, if f for new caries was 0.5x that of Marinho *et al*. (e.g., f = 0.8), $NNT_{individual}$ for this individual would be: 1.4/0.8 = 1.75. In other words, 1.75 patients would need to be treated with SDF for one person to benefit. (Note: NNT is normally rounded up, so the actual assessment would be that two people would be treated for one to benefit.)

In Eq. 2, if the clinician estimated that a person's expected event rate for new caries is 0.5 new carious surfaces in 2.5 yrs, the NNT would be: 1/ (0.5 * 70.3%) = 2.8 for primary teeth. In other words, 2.8 persons would need to be treated with SDF for one to benefit.

The foregoing suggests that SDF may offer substantial caries-preventive benefits over fluoride varnish. However, there are numerous caveats: safety, adverse events, study design, and effect in permanent teeth.

Safety

Safety is a critical issue in the clinical application of SDF. The long-standing use of silver is both an asset and a concern. The historical efficacy data are plentiful and compelling (*e.g.,* Lansdown, 2002a, 2006), and toxicity and adverse events are rare (*e.g.,* Lansdown, 2002b, 2006; Lansdown and Williams, 2004). However, many long-standing agents were "grandfathered" by government agencies (*e.g.,* in the US, by the Food and Drug Administration), allowing for their continued use with minimal safety testing as compared with new agents. Thus, while many potential adverse effects could occur, we could not identify published trials addressing this, other than the adverse events identified in this review. There are two major perspectives here: a person's and a practice's.

Practice Perspective

There are several hypothesized adverse effects of SDF: pulpal irritation, caries staining, tissue irritation, and fluorosis. Three of these adverse events were examined in the reported studies: generation of non-vital teeth, staining of caries lesions, and tissue irritation. The hypothetical risks attributed to SDF and its possible toxicity to the pulp were not supported. On the contrary, there was a similar incidence of pulpal lesions in both the control and experimental groups, and in both the primary and permanent teeth. Reports of staining were also similar, and it did trouble 7% of participants. Reversible lesions in oral mucosa through inadvertent contact with SDF solution occurred in three reported individuals, with the appearance of a small, mildly painful white lesion in the mucosa, which disappeared within 48 hrs without treatment. The possibility of acute toxicity or the induction of fluorosis through the use of SDF has been debated (*e.g.,* Gotjamanos, 1997; Neesham, 1997). The nexus of this concern emanated from fluorosis in rats, where SDF was used at several-fold the concentration used in the studies reported here. However, without data, one cannot exclude (or support) this possibility.

From a practical standpoint, one can consider personal and general safety. Silver nitrate, when spilled on the skin, clothes, or countertops, causes dark staining—a well-recognized phenomenon for anyone working with radiographs. This staining on the skin is relatively short-term (wks), while the staining of clothing and counters is long-lasting. Thus, caution in the use of silver nitrate in a busy clinical setting is required. From a general safety perspective, the European Union classifies silver nitrate as both corrosive (C) and dangerous for the environment (N). The US National Fire Protection Association classifies silver nitrate as: 'An oxidizer (Ox); Can cause temporary incapacitation or possible residual injury (Blue 2); Will not burn (Red 0); At elevated temperatures and pressures may form explosive mixtures with water (Yellow 2)'.

Individual's Perspective

From the individual's safety standpoint, there are 3 components of SDF: silver, amine, and fluoride. Silver alone has been used for millennia as an antimicrobial agent, and has found a multitude of clinical and industrial disinfectant applications (*e.g.,* Silvestry-Rodriguez *et al*., 2007) , including water purification and the control of dental unit waterline biofilms (*e.g*., O'Donnell *et al.,* 2007). The more complex silver nitrate has been used for over 100 years for medical applications. Among the more common uses are eye drops for newborns to prevent infections, and cauterizing of oral aphthous ulcers. Finally, fluoride, identified some 50 years ago as an anti-caries agent, is used routinely in a multitude of applications for caries prevention, in a variety of delivery systems, including varnish, gel, salt, toothpaste, water, rinse, and milk (*e.g*., Marinho *et al*., 2004a,b).

For dose-related safety specifically associated with caries prevention, the delivered dose of SDF is approximately a drop for each quadrant, delivered with a brush, and rinsed off afterward. Thus, from both the historical and quantitative perspectives, while it is possible that SDF can generate adverse events, the likelihood seems low. That said, demonstrating safety still needs attention. A cautionary tale in this regard is the finding of fluorosis in ~ 10% of people associated with water fluoridation (McDonagh *et al*., 2000).

Study Design, Populations, and Optimization

In terms of study design, the implemented literature search identified only one cohort and one randomized controlled trial. Neither study provided a power calculation. This, therefore, is a limited dataset upon which to build a new preventive strategy. At the same time, the study sizes, study lengths, substantial differences between the experimental and control groups, and similar results between the studies suggest that the results are reasonable outcome estimates for caries control by SDF. Given the risk profiles of the persons in the two included studies, subsequent studies might consider a stratified random assignment to provide a better assessment of the potential benefits of SDF among people with different levels of risk.

Subsets in the study populations are also a consideration. Only one of the two identified and qualifying studies extended their research to permanent teeth (Llodra *et al.,* 2005). Further, one study (Chu *et al*., 2002) examined only maxillary anterior, and not posterior, teeth. This limits the data upon which one might base clinical application of SDF. In contrast, caries is a bacterial infection leading to enamel and dentin demineralization. Thus, while the quantitative effect may vary between primary and permanent teeth, between anterior and posterior teeth, between populations, and between risk groups, the direction of effect should be similar. This assertion needs further investigation.

Finally, treatment optimization remains, in part, an open question. The two included studies applied SDF either once or twice *per* year, and obtained similar results. This suggests that 1 application *per* year may be sufficient. In contrast, an NNT for permanent teeth of 10 is relatively high, and permanent teeth may benefit from more frequent application.

Conclusions

In sum, while numerous questions remain to be answered, the modest dataset identified here supports the hypothesis that SDF

can have a significant and substantial benefit in arresting and preventing caries. By implication, SDF could provide a new quantitative preventive benefit for individuals and populations. Application is simple, the solution is low-cost, and application does not require complex training of the health professionals. Thus, SDF appears to meet the criteria of both the WHO Millennium Goals, and the Institute of Medicine's criteria for 21st century medicine (Institute of Medicine, 2001). Clearly, however, broader study sets are required to investigate alternative protocols, delivery systems (*e.g.*, Kawasaki *et al*., 2005), and age and risk groups for occlusal, proximal, and root caries. As well, the applications of SDF for treating tooth sensitivity (*e.g.*, Youssef, 1995), periodontal pockets (*e.g.*, Spacciapoli, 2001), and pulpal infections (*e.g.*, Englander *et al.,* 1958) need to be evaluated.

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