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., Crede, 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.
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 Tenvuo, 1990), metabolic activity of dental plaque (Oppermann and Johansen, 1980; Oppermann and Rolla, 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 + SnF₂ + stomahesive (Craig et al., 1981, using AgF + SnF₂ + stomahesive), and 95% of caries progression (McDonald and Shelham, 1994, using AgF + SnF₂). Finally, in vivo studies in permanent teeth indicated that silver fluoride arrests approximal caries progression (Hyde, 1973, using AgNO₃) and the initiation of caries lesions (Green, 1989, using AgF + SnF₂). 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.

Table 1. Fluoride Efficacy in Preventing Caries

<table>
<thead>
<tr>
<th>Fluoride Delivery System</th>
<th>Estimated Caries Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk</td>
<td>?</td>
</tr>
<tr>
<td>Salt</td>
<td>15%</td>
</tr>
<tr>
<td>Toothpaste</td>
<td>24%</td>
</tr>
<tr>
<td>Mouthwash</td>
<td>26%</td>
</tr>
<tr>
<td>Water (adults)</td>
<td>27%</td>
</tr>
<tr>
<td>Gel (children)</td>
<td>28%</td>
</tr>
<tr>
<td>Water (children)</td>
<td>34%</td>
</tr>
<tr>
<td>Varnish</td>
<td>46%</td>
</tr>
<tr>
<td>SDF permanent teeth</td>
<td>&gt; 60%</td>
</tr>
<tr>
<td>SDF deciduous teeth</td>
<td>&gt; 70%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Year after Treatment</th>
<th># Teeth</th>
<th>Success*</th>
<th>Partial Success</th>
<th>Unsuccessful</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64</td>
<td>37 (58%)</td>
<td>17 (27%)</td>
<td>13 (20%)</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>10 (37%)</td>
<td>5 (19%)</td>
<td>12 (44%)</td>
</tr>
<tr>
<td>3</td>
<td>142</td>
<td>87 (61%)</td>
<td>33 (23%)</td>
<td>22 (15%)</td>
</tr>
</tbody>
</table>

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

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 sulphydryl 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):

\[
\text{A/N — SH + AgX} \rightarrow \text{A/N- S- AgX + HX}
\]
The initial reaction of silver nitrate is the formation of calcium sodium hydroxide (and a basic environment) (reaction 1). The less sodium fluoride with calcium phosphate to form fluorapatite (reaction 2). The net result of these interactions is depicted in Fig. 2.

<table>
<thead>
<tr>
<th>Target Effect</th>
<th>Interaction</th>
<th>Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arylinase</td>
<td>Inhibition</td>
<td>Arylinase is inhibited by Ag</td>
<td>Takahashi et al. (1985)</td>
</tr>
<tr>
<td>Azu</td>
<td>Binding</td>
<td>Cu replaced by Ag in azurin</td>
<td>Tordi et al. (1990)</td>
</tr>
<tr>
<td>β-galactosidase</td>
<td>Inhibition</td>
<td>Beta-galactosidase is inhibited by Ag</td>
<td>Wutor et al. (2007)</td>
</tr>
<tr>
<td>Chitosanase</td>
<td>Inhibition</td>
<td>Chitosanase is inhibited by Ag</td>
<td>Park et al. (1999)</td>
</tr>
<tr>
<td>→ CopA</td>
<td>Induction</td>
<td>CopA induced by Ag</td>
<td>Stoyanov et al. (2001)</td>
</tr>
<tr>
<td>→ CopA, CopB</td>
<td>Induction</td>
<td>CopA and CopB induced by Ag</td>
<td>Odermatt et al. (1994)</td>
</tr>
<tr>
<td>→ CopB</td>
<td>Transport</td>
<td>CopB extrudes Ag from cells</td>
<td>Rensing et al. (2000)</td>
</tr>
<tr>
<td>→ Crd1p</td>
<td>Resistant</td>
<td>Cu pump effects Ag resistance</td>
<td>Riggile and Kumamoto (2000)</td>
</tr>
<tr>
<td>→ GNPTA</td>
<td>Inhibition</td>
<td>GNPTA is inhibited by Ag</td>
<td>Goil (1978)</td>
</tr>
<tr>
<td>→ GOT and GPT</td>
<td>Inhibition</td>
<td>GOT and GPT are inhibited by Ag</td>
<td>Costello et al. (2000)</td>
</tr>
<tr>
<td>→ Mono-oxygenase</td>
<td>Inhibition</td>
<td>Mono-oxygenase is inhibited by Ag</td>
<td>Green et al. (1985)</td>
</tr>
<tr>
<td>→ PacS</td>
<td>Induction</td>
<td>PacS is induced by Ag</td>
<td>Rensing et al. (1999)</td>
</tr>
<tr>
<td>→ pH</td>
<td>Collapse</td>
<td>Trans-membrane pH collapse by Ag</td>
<td>Dibrov et al. (2002)</td>
</tr>
<tr>
<td>→ YlC6D-YbdE</td>
<td>Induction</td>
<td>YlC6D-YbdE effects Ag resistance</td>
<td>Franke et al. (2001)</td>
</tr>
</tbody>
</table>

* → indicates induction; —→ 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 progression 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 Yokonimo, 1969; Yamaga et al., 1972) (Table 4). The most commonly recognized interaction is sodium fluoride with calcium phosphate to form fluorapatite (reaction 1). The less commonly recognized interaction is the formation of calcium fluoride and silver phosphate in a basic environment (reaction 2). The initial reaction of silver nitrate is the formation of calcium nitrate, silver phosphate, and silver oxide (reaction 3).

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 fluoride 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 3. Relationship of Silver to Effector Genes and Enzymes

<table>
<thead>
<tr>
<th>Target Effect</th>
<th>Interaction</th>
<th>Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>→ Arabinase</td>
<td>Inhibition</td>
<td>Arabinase is inhibited by Ag</td>
<td>Takahashi et al. (1985)</td>
</tr>
<tr>
<td>→ Azu</td>
<td>Binding</td>
<td>Cu replaced by Ag in azurin</td>
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</tr>
</tbody>
</table>

* → indicates induction; —→ indicates inhibition; →→ indicates induction.

### Table 4. NaF and Ag(NO₃) Reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Reactants</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ca₁₀(PO₄)₆(OH)₂ + NaF</td>
<td>→ Ca₁₀(PO₄)₆F₂ + NaOH</td>
</tr>
<tr>
<td>2</td>
<td>Ca₁₀(PO₄)₆(OH)₂ + NaF</td>
<td>→ CaF₂ + 4NaO + NaOH</td>
</tr>
<tr>
<td>3</td>
<td>Ca₁₀(PO₄)₆(OH)₂ + Ag(NO₃)</td>
<td>→ Ca(NO₃)₂ + Ag₃PO₄ + Ag₂O + H₂O</td>
</tr>
</tbody>
</table>

**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–PO₄, NaF, or SnF₂ (Suzuki et al., 1974). This suggests that the effect of SDF will be greater than that of NaF or SnF₂.

### 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® Coviden, 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
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Manufacturer/Supplier</th>
<th>SDF Conc.</th>
<th>Registration #</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cariostatic®</td>
<td>Inodon Labratorio</td>
<td>10%</td>
<td>80151700912</td>
<td>Brazil</td>
</tr>
<tr>
<td>Cariestop®</td>
<td>Biodinâmica Química e Farmaceutica Ltda</td>
<td>12%</td>
<td>10298550010</td>
<td>Brazil</td>
</tr>
<tr>
<td>Cariestop®</td>
<td>Biodinâmica Química e Farmaceutica Ltda</td>
<td>38%</td>
<td>10298550048</td>
<td>Brazil</td>
</tr>
<tr>
<td>Bioride®</td>
<td>Dentsply Industria e Comercio Ltda</td>
<td>30%</td>
<td>10186370153</td>
<td>Brazil</td>
</tr>
<tr>
<td>Saforide®</td>
<td>J.Morita; Toyo Seiyaku Kasei Ltd.</td>
<td>38%</td>
<td></td>
<td>Japan</td>
</tr>
<tr>
<td>Fluoroplat®</td>
<td>Laboratorios Naf</td>
<td>38%</td>
<td>M.S.yA.S. 5010</td>
<td>Argentina</td>
</tr>
</tbody>
</table>
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):

\[
\text{Prevented Fraction: } PF = \frac{Ic - Ie}{Ic}
\]

\[
\text{Number Needed to Treat: } NNT = \frac{1}{Ic \times PF}
\]

The 95% Confidence Interval:

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

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 met 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).
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 = 0.4-1.3) 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
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):

\[
NNT_{\text{individual}} = \frac{NNT_{\text{population}}}{f},
\]

where \( f \) is the clinician’s estimate of the individual’s risk, compared with the experimental group; and

\[
NNT_{\text{individual}} = \frac{1}{(\text{PEER} \times PF)},
\]

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 \( NNT_{\text{individual}} \) for this person would be: \( 1/0.5 = 2 \). In other words, two people with caries would need to be treated with SDF for one to benefit. A similar analysis can be used to compare SDF with fluoride varnish (\( NNT = 1.4; f = \text{DMFS} = 1.6/\text{yr}; \) Marinho et al., 2002). In this example, if \( f \) for new caries was 0.5x that of Marinho et al. (e.g., \( f = 0.8 \)), \( NNT_{\text{individual}} \) 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 was 0.5x that of Chu et al. (2002) in primary teeth, the NNT would be: \( 1/(0.5 \times 70.3\%) = 2.8 \) 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., Silvéstrey-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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