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# Everyone else is using it, so why isn't the UK? Silver diamine fluoride for children and young people

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***Introduction***: Silver diamine fluoride (SDF) is used to prevent and arrest caries across the globe, particularly in the developing world. Whilst its use in the Western World is increasing, it is not yet routinely used in the United Kingdom, nor is it advocated by our national guidelines. ***Objectives***: To explore the literature surrounding the use of SDF, and consider the reasons why SDF has not yet been widely adopted in the United Kingdom (UK). ***Discussion***: There is a growing evidence base for the use of SDF for the arrest and prevention of dental caries in the primary and permanent dentition. Potential side effects include staining of carious tooth structure, but in some cases this is acceptable to parents. There is no evidence for the cost effectiveness of SDF, although it may be a reasonably cost-effective option. ***Conclusion***: SDF is perhaps not yet widely adopted in the UK due to a perceived parental concern about its staining effect. With a growing evidence base and reportedly higher efficacy than fluoride varnish for caries prevention and arrest, SDF has the potential to play an important role in managing dental disease in children and young people in both primary and secondary care.

**Keywords:** *paediatric dentistry, caries, silver diamine fluoride*

## Introduction

Aqueous silver diamine fluoride (SDF) is a topical solution comprised of silver, ammonia and fluoride ($(Ag(NH_3))_2F$) (Burgess and Vaghela, 2018). Whilst silver-based formulae have been used for centuries in both medicine and dentistry, SDF has recently experienced a surge in popularity across the world. Applied topically, SDF is considered as an alternative to fluoride varnish, acting to both prevent and arrest dental caries, in addition to addressing symptoms arising from dentine hypersensitivity (Burgess and Vaghela, 2018; Chibinski *et al.,* 2017; Patel *et al.,* 2018). Nonetheless, the use of SDF in the United Kingdom (UK) remains limited. This review explores whether the literature supports the use of SDF for children and young people and considers the barriers to its use in the UK.

## History of SDF

There are reports of dental use of silver for its antimicrobial properties as far back as 659AD, though its ability to arrest caries in children was not acknowledged in the literature until 1891 (Rosenblatt *et al.,* 2009; Gao *et al.,* 2018; Stebbins, 1891).

From the 1970's, in-vivo and in-vitro research into SDF resulted in Nishino and Yamaga developing Saforide, the original SDF product (Crystal and Niederman, 2019). Since its development for caries management in Japan, SDF has been used in other countries, including Australia, Brazil, Mexico and China (Burgess and Vaghela, 2018; Peng *et al*., 2012; Gao *et al*., 2016). Despite widespread use in some parts of the world, the role of SDF in many western countries has been limited. Nonetheless, this is beginning to change as regulatory bodies recognise the growing evidence base and facilitate change. SDF has been used increasingly in the USA since 2014, and more recently in Canada. Its use is recommended by the American Academy of Paediatric Dentistry (AAPD) for the arrest of caries in primary teeth, as part of a comprehensive caries management programme (Crystal *et al*., 2017a; Yeung and, Argaez 2017). The World Health Organisation (2017) recommended SDF to arrest early childhood caries. As a result of this growth in use, the evidence base is building in both quantity and quality, as SDF is increasingly viewed as a competitor to fluoride varnish for caries prevention and arrest.

## Properties and mechanisms of action

Each component of the SDF solution has a role: the silver is an antimicrobial agent, the ammonia stabilises the solution, whilst the fluoride aids remineralisation (Burgess and Vaghela, 2018; Rosenblatt *et al.,* 2009; Horst *et al.,* 2016).

The caries preventive effect is thought to stem from the increased mineral content in the enamel and the effect of fluoride in increasing resistance to acid (Rosenblatt *et al.,* 2009; Gao *et al.,* 2016). The increased preventive potential may result from the greater fluoride content in enamel provided by SDF, but confirmatory research is required (Oliveira *et al.,* 2019). The cariostatic action of

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SDF is multifaceted. It acts on proteins and hydroxyapatite in the tooth structure (Lou *et al.,* 2011). The silver components are bactericidal and inhibit development of the cariogenic biofilm (Burgess and Vaghela, 2018; Chibinski *et al.,* 2017; Rosenblatt *et al.,* 2009; Gao *et al.,* 2016). This, in conjunction with the formation of fluorapatite and calcium fluoride, increases resistance to acid dissolution and demineralization. Interestingly, SDF does not appear to to change the microbiome within the caries biofilm (Goodell *et al.,* 2017; Berger *et al.,* 2018).

SDF can penetrate both enamel and dentine, thus fluoride is retained 2-3 times more in the tooth structure than with other agents such as sodium fluoride (Burgess and Vaghela, 2018; Rosenblatt *et al.,* 2009). Furthermore, application of SDF protects collagen from degradation during the demineralisation process (Chibinski *et al.,* 2017; Gao *et al.,* 2016; Mei *et al.,* 2018). In combination, these properties are likely to contribute to the reported increased efficacy of SDF over alternative treatments (Chibinski *et al.,* 2017).

SDF may also reduce dentine hypersensitivity (Craig *et al.,* 2012; Castillo *et al.,* 2011). Silver nitrate may block the dentine tubules, potentially reducing sensitivity by providing a physical barrier to prevent neural stimulation in the dentine-pulp complex (Burgess and Vaghela, 2018; Crystal *et al.,* 2017a; Davari *et al.,* 2013).

SDF may also mineralise the enamel defects of molar-incisor hypomineralisation (Gamboa, 2017). In one case a child's symptoms improved after application of SDF to hypomineralised molars (MacLean, 2018).

SDF is applied topically to teeth with a microbrush, without the need for prior caries removal (Yeung *et al.,* 2017). It is therefore not surprising that SDF may be useful in children with limited co-operation (Crystal and Niederman, 2019). Its relatively low cost supports its use in developing countries (Burgess and Vaghela, 2018; Chibinski *et al.,* 2017). It is available in a range of concentrations (38%, 30% and 12%, with 44800ppm, 35,400ppm and 14200ppm Fluoride, respectively) (Mei *et al.,* 2013; Richards, 2018; Chu and Lo, 2008). The most used preparation is 38% SDF provided under the trade name Advantage Arrest™ (©Elevate Oral Care LLC, USA).

## The evidence base for SDF

There is a wealth of evidence for the use of SDF in dentistry. Most studies investigate its use in the prevention and arrest of caries, with the strongest body of evidence pertaining to the latter. Most studies relate to the primary dentition, though there is a growing body of evidence on its effect in first permanent molars. A further small number of studies relate to its use in dentine hypersensitivity.

For this review, the literature was searched using the electronic database PubMed. Search terms were appropriate to each area explored. Forward citation searches were carried out from included papers. Free hand searches were conducted, particularly where evidence was limited. For each, the evidence was appraised, with the strongest level of evidence available included.

## Primary Teeth

### *Arrest*

Across England, Wales and Northern Ireland, the Child Dental Health Survey of 2013 reported almost a third and a half of 5- and 8-year olds respectively to have obvious caries in their primary teeth (NHS, 2013). More recent statistics highlighted 12% and 14.5% of 3-year-olds having obvious dental caries in England and Wales, respectively (Public Health England, 2013; Morgan and Monaghan, 2015). Untreated dental caries can negatively affect a child's quality of life, causing pain, sepsis, reduced confidence and absence from school (Alsumait *et al.,* 2015; Gilchrist *et al.,* 2015). Dental treatment requiring general anaesthesia, as was the case for 43,700 children in 2015/2016, carries a further risk of morbidity and mortality, as well as substantial cost to the National Health Service (NHS) (NHS Digital, 2016; Knapp *et al.,* 2017). The arrest of caries using a non-invasive and low-cost treatment such as silver diamine fluoride may reduce this impact on children, their families and society.

Evidence of the ability of SDF to arrest dental caries in primary teeth is particularly extensive. A recent systematic review pooled the results of eight studies to find that 81% (95% CI 68%-89%) of carious lesions treated with SDF arrested; a significant result, albeit with wide confidence intervals (Gao *et al.,* 2016). The included studies showed SDF was more effective than glass-ionomer cement or fluoride varnish, and that caries removal before SDF placement was not necessary. The pooled studies had significant heterogeneity, which should be considered when interpretating the results (Gold, 2017). Most included studies were conducted in South America and Asia, with none being in Europe, which may limit generalisability. A further review with meta-analysis based upon four randomised controlled trials, demonstrated SDF to be 89% more effective than a control, and most importantly, 66% more effective than fluoride varnish or Atraumatic Restorative Technique (ART) in arresting caries (Chibinski *et al.,* 2017). Three of the included studies were of low risk of bias, with one (Seberol and Okte, 2013) at unclear risk, perhaps as saline was used as the control (Chibinski *et al.,* 2017). The participants in three trials had a higher dmft than the UK average, which may also limit generalisability (Godson *et al.,* 2018; Chibinski *et al.,* 2017). One study compared SDF and NaF applied to carious lesions in a Hong Kong kindergarten (Duangthip *et al.,* 2016). Another school-based study in China found that annual application of SDF arrested caries more than NaF varnish with or without caries excavation or water placebo. Interestingly results were better for SDF alone, than SDF with caries excavation (Lo *et al.,* 2001). The dmft for both studies, again, was higher than those seen in most deprived communitites in the UK, and fewer participants used fluoridated toothpaste than in the UK. (Public Health England, 2017b). Despite this, results are promising for the potential of SDF to be used as part of a school based programme.

Studies investigating SDF may be susceptible to detection and performance bias as it is not possible to blind assessors or participants to intervention allocation due its key side effect, namely black staining (Richards,

2017; Gold, 2017). This is discussed later in this paper. Nonetheless, numerous other reviews and clinical studies have found results in the same direction, finding SDF to be effective in arresting caries, including a recent umbrella review, which combined the findings of multiple systematic reviews (Rosenblatt, 2009; Richards, 2017; Contreras *et al.,* 2017; Seifo *et al.,* 2019).

Further to the reported success in arresting caries, a number of interesting findings have also been reported regarding the pattern of arrest produced by SDF. Higher arrest rates were noted for anterior than posterior teeth at both 6 months and 18 months (Fung *et al.,* 2016). Lower anteriors had the highest arrest rates, followed by upper anteriors, lower posteriors and upper posteriors. The same study also found lesions with better plaque control to be more likely to arrest with SDF.

*Prevention*

There is also evidence that SDF can prevent caries. A systematic review by Oliviera and co-workers (2019) found a 54% decrease in new carious lesions with annual SDF application when compared with quarterly fluoride varnish. Further research has echoed these results, finding SDF to not only be effective in preventing caries in the primary dentition, but to be more effective than fluoride varnish (Rosenblatt *et al.,* 2009; Oliviera *et al.,* 2019; Llodra *et al.,* 2005). While these are positive results, caries prevention was not the primary outcome measured in most of these studies, and the four included studies had at least one domain at high or unclear risk of bias. Further research to assess the caries preventive ability of SDF is required (Oliviera *et al.,* 2019). Again, studies have a higher than average caries experience than the UK population (Oliviera *et al.,* 2019)

## Permanent dentition

The evidence for SDF in first permanent molars is not as strong as that for the primary dentition. Trials have found that while SDF is effective at preventing and arresting caries in these teeth, resin sealants may be more so (Llodra *et al.,* 2005; Monse *et al.,* 2012, Liu *et al.,* 2012). Braga and colleagues RCT (2009) found SDF to be more effective than either tooth brushing or the application of a GIC fissure sealant arm at 3- and 6-month follow up, but at 18- and 30-months there was no significant difference. However, this study was of a split mouth design, which cannot ensure intervention fidelity for these types of interventions, which must be considered when interpreting the results. Similarly, Llodra et al. (2005) found SDF to be more effective than a fluoride mouthrinse programme, although the quality of evidence was again limited. This research was conducted in a school, in an area with limited access to fluoridated toothpaste and low water fluoride concentration. SDF may be useful for both the arrest and prevention of caries where isolation is not possible, for example in erupting first permanent molars or where patient co-operation is a limiting factor.

## Dentine Hypersensitivity

Reducing the permeability of dentine by creating a barrier to stimulation of the neural pulpal tissue is a recognised approach to reduce dentine sensitivity, with several topical agents used in this way. Trials have demonstrated the ability of SDF to block dentinal tubules and create this barrier (Craig *et al.,* 2012, Castillo *et al.,* 2011). SDF had greater efficacy than either placebo or an oxalic acid-based preparation in reducing short-term sensitivity, but larger and longer studies are required (Craig *et al.,* 2012, Castillo *et al.,* 2011). Staining may have restricted blinding and might also limit demand for this treatment. Nevertheless, SDF is approved in several countries as a desensitising agent. The reduction in sensitivity may further aid caries prevention by reducing the symptoms arising from early to moderate carious lesions, allowing patients to improve their oral hygiene. Furthermore, there may be a role for SDF in managing the symptoms arising from hypomineralised molars (primary or permanent) in children, though further research is needed in this area as the current evidence base comprises case reports and studies of extracted teeth (Gamboa, 2017; MacLean, 2018).

## Frequency of Application

The evidence to inform the optimal frequency of application of SDF is less clear. Chu and co-workers (2002) found that annual application of 38% SDF was more effective than quarterly application of 5% sodium fluoride varnish in arresting caries. Three monthly application of 12% SDF has been found to be more effective than once yearly application, but the difference between biannual and quarterly application was not significant (Llodra *et al.,* 2005). SDF has been found to be most effective at higher concentration (Duangthip *et al.,* 2018).

Adverse effects relating to frequency of application were investigated by Duangthip and colleagues (2018). They compared 12% and 38% SDF in both annual and biannual applications and found no significant differences in the prevalence of adverse events between groups.

Overall, there is insufficient evidence to compare treatment regimens to enable recommendation of a protocol for SDF application (Oliviera *et al.,* 2019; Richards, 2017; Gold, 2017). Nonetheless, this might not preclude the adoption of SDF in national guidance for prevention. There is limited evidence on the optimal frequency for topical fluoride application varnish, which is the mainstay of prevention in the UK. National guidelines recommend Fluoride varnish to be applied twice per year or more, dependant on caries risk status, despite a lack of evidence to suggest that the effect is frequency dependent, as reported in the same Cochrane review that the guidelines were based on (Marinho *et al.,* 2013; Public Health England, 2017a). Taking into account the available evidence for SDF, alongside the AAPD guidelines for caries arrest, it would seem prudent to apply 38% SDF at least once per year, to be increased in accordance with the patients caries risk status and activity of existing carious lesions (Crystal *et al.,* 2017a). The AAPD guidelines recommend application, followed by a review after 2-4 weeks and reapplication to ensure coverage of all active lesions (Crystal *et al.,* 2017a).

## Acceptability of SDF and considerations for use

An important side effect of SDF is the long-term black staining to caries affected tooth structure; a consequence

of silver chloride deposition (Chu and Lo, 2008; Llodra *et al.,* 2005). The staining does not affect sound enamel or dentine, but can easily stain clothing, work surfaces and instruments. This could be considered a barrier to use in the UK, as was the case with concerns about the aesthetic acceptability of preformed metal crowns. A UK study found these to be acceptable to most parents (Bell *et al.,* 2010).

A study in New York reviewed parents' acceptability of the black staining after SDF application (Crystal *et al.,* 2017b). As might be expected, more parents found the staining to be acceptable on posterior teeth (67.5%), whereas less than a third (29.7%) found it so on anterior teeth. Parents of children from lower socio-economic backgrounds were more accepting of the staining. Whilst staining on posterior teeth appears to be more acceptable than on anterior teeth, it appears that the latter would still be preferable to most parents than for their child to undergo treatment with sedation or a general anaesthetic. Importantly, the acceptability of SDF to children has not yet been investigated.

Duangthip and colleagues (2018) also researched this side effect of SDF application, comparing four different treatment regimens that varied in frequency of application (annual or biannual) and concentration (12% or 38%). Blackening of lesions was observed in all groups, with the risk increasing with higher concentration and frequency of application. Most parents found this to be satisfactory. Again socio-economic status and the visibility of the stained teeth influenced satisfaction.

Another potential implication of SDF is its impact on placing future restorations. It may negatively affect the bonding potential of resins, though other evidence has reported no difference in bond strength to dentine after application of SDF with one study even reporting greater bond strength (Rosenblatt *et al.,* 2009; Selvaraj *et al.,* 2016; Quock *et al.,* 2012; Wu *et al.,* 2016). This does not seem to be an issue with glass-ionomer cements although the evidence base is not strong for either material (Crystal and Niederman, 2019).

Very few studies have reported any other safety concerns for SDF. Duangthip and colleagues (2017) study of 799 children found no report of acute illness or systemic toxicity after 38% SDF application. The authors considered SDF to be safe in regards to fluoride toxicity, calculating that a three-year-old child weighing 10kg would require eight times the amount required to treat their entire dentition before experiencing serious toxicity that would need immediate therapeutic intervention. More minor side effects such as discomfort, gingival swelling or short term-bleaching (chemical burn) were uncommon, and SDF has been reported to be innocuous to the pulp (Rosenblatt *et al.,* 2009; Oliveira *et al.,* 2019; Duangthip *et al.,* 2017). Overall, SDF has been found to be both a safe and effective treatment.

## Future developments

To increase the acceptability of SDF, methods have been proposed to address the issue of black staining. Incorporation of nanosilver particles into the SDF formula may reduce its severity, yet the impact of this addition on the efficacy of the solution has not been determined (Rosenblatt *et al.,* 2009). Further, the nanoparticles can enter the bacterial matrix, which is thought to contribute towards the antimicrobial effect.

In the same vein, the application of potassium iodide (KI) after application of SDF has been suggested to reduce aesthetic concerns. An in vitro study found that KI application immediately after SDF prevented the formation of black staining (Patel *et al.,* 2018). Other studies have found that black staining developed despite application of KI. An example of the authors' experience of using this technique for a young patient with caries is shown in Figure 1.

*Figure 1. Carious lesion lower right primary second molar immediately and 12 weeks after application of Riva Star © to LRE*

## Regulatory Issues

At present, SDF is only commercially available in the UK as Riva Star©. This is a two-component system of 38% SDF solution with potassium iodide. It has been 'CE marked' in Germany as a medical device, allowing it to be marketed and sold within the European Economic Area (EEA) for use as indicated (EU, 2017; Great Britain, 2002).

A medical device is "any instrument, apparatus, appliance, material or other article used alone or in combination…, in humans to diagnose, prevent, monitor, treat or alleviate disease or compensate for an injury", that does not achieve its main intended action by pharmacological means (EU, 2017). This is different to a medicinal product; "any substance or combination of substances presented as having properties for treating or preventing disease in human beings" (EU, 2001). The processes and intricacies of certification are different for each classification and are outwith the scope of this paper. As Riva Star© has been 'CE marked' in Germany, it has not been reviewed in the UK by the Medicines and Healthcare Regulatory Authority. It is unclear what the impact of Brexit may be on these regulations. Riva Star© is indicated for use within the EEA as a de-sensitising agent, and is marketed

in the product literature and online as such. Interestingly, the product information lists the desensitisation of carious lesions as a contraindication to the use of this product (SDI, 2015).

Any use of SDF for caries prevention or arrest in the UK is therefore 'off-label', in the same way that some other fluoride-containing desensitising varnishes are used. Off-label use describes any intentional use other than that described by the manufacturer in the instructions, and such use is at the operator's judgement and risk. The risks and benefits to the patient must be taken into account, along with any ethical and legal implications. The liability for any adverse effects lies with the operator/employer and not the manufacturer (Medicines & Healthcare products Regulatory Agency, 2014).

General Medical Council (2013) guidance states that off-label prescribing is acceptable when there is no suitable alternative that will meet the patient's need, and that, if prescribing in this way clinicians must be satisfied that there is sufficient evidence to demonstrate safety and efficacy. Both of these conditions appear to be met for the use of SDF, as demonstrated in this paper. Nonetheless, patients (and parents) must be aware of the 'off label' use to ensure informed decision-making. As the product is CE marked, similar regulatory implications that affect the UK pertain to the rest of Europe.

In the USA, Advantage Arrest™, a 38% SDF solution, was approved in 2014, and Riva Star© in 2018, by the Food & Drug Administration (FDA) as de-sensitising agents, for use in adults over the age of 21 years (US FDA, 2014; US FDA, 2018). In 2016 a new billing code for "interim caries arresting medicament application" using SDF was approved (American Dental Association, 2019). The AAPD guidance recommends the use of 38% SDF for arresting cavitated caries in primary teeth, which is an off-label use (Crystal *et al.,* 2017). Interestingly, both Advantage Arrest™ and Riva Star© are licensed in Canada for caries prevention and arrest, in children over three years old, although a recent guideline did not provide recommendations for use (Yeung *et al.,* 2017; Government of Canada, 2017; Government of Canada, 2018).

Use of SDF across the UK is currently limited, though this looks set to change. Riva Star© has been recently introduced into at least one paediatric dental department within a UK dental hospital, and a number of other institutions are looking to follow suit. Nonetheless, Advantage Arrest™, the formulation used within the main body of evidence, is not commercially available in the UK and Europe.

Importantly, SDF products are more expensive than Fluoride varnishes, which may preclude their widespread use. The SDF preparation available in the UK costs approximately ten times more per patient than the standard Fluoride varnish (£6.30 : £0.625) (Dental Sky, 2019a; 2019b). The commonly used preparation in the USA has a similar cost per patient as Fluoride varnish ($0.57 : $0.625) (Elevate Oral Care, 2019; Dental Sky, 2019b).

More competitive pricing, and the availability of Advantage Arrest™ in the UK could stimulate further interest. Of course, cost minimisation such as this, is too simplistic and given the potential difference in the effectiveness between products, a full health economic analysis is required to reach a valid decision. Unfortunately, this is not present in the current evidence base, however an American simulation estimated there would be cost savings following use of SDF by avoiding restorative treatment (Johnson *et al.,* 2019).

It is unclear how acceptable the dark staining will be to UK patients and parents, which is a potential barrier to wider use. Seifo and co-workers (2019) found this not to be an issue in their umbrella review with international participants and SDF has clearly proved popular in the USA, despite the aesthetic implications. The addition of potassium iodide to reduce staining, as in the Riva Star© formulation, could increase patient acceptance, but further research is needed on the ability of KI to reduce staining, and whether its inclusion reduces product efficacy. Qualitative studies are also indicated, to investigate whether UK children and parents are concerned about staining.

The need to use the products off-label may also dissuade practitioners, although some topical fluoride-containing desensitisers are currently used off-label for caries prevention without excessive concern. Uptake by practitioners may improve if SDF products became explicitly licensed for caries prevention and arrest. The United States and Canadian authorities have set a clear precedent in this respect, and hence dental practitioners in the UK, particularly those who regularly treat children, will be keen to see whether our own authorities will follow this lead.

## Opportunities for use in the UK

As previously highlighted, many UK children undergo GA for dental extractions, with waiting lists for treatment up to eight months (Knapp *et al.,* 2017). SDF could have an application in the interim in primary care to arrest caries until the appointment, or to arrest the caries until exfoliation.

In terms of prevention, with appropriate training it may be possible for SDF to be applied by dental nurses with extended duties, as is currently the case with Sodium fluoride varnish. This presents opportunity for cost effective community-based programmes along with application in primary and secondary care for prevention, arrest and sensitivity.

Certainly, endorsement from prominent organisations such as the British Society of Paediatric Dentistry, or the Royal Colleges would be particularly influential in increasing the acceptability of SDF amongst UK practitioners. Furthermore, the inclusion of SDF in national guidelines would clearly acknowledge the increasing evidence base for this product.

## Conclusion

In conclusion, there is a strong evidence base for SDF as a safe and effective intervention for arresting caries in the primary dentition. It has the potential to be useful in the UK in the community and primary and secondary care to arrest and prevent caries, reducing the burden of the disease in children. SDF may hold particular use in addressing the number of pre-school children presenting with caries, many of whom need general anaesthetics to receive care. Whilst there are side effects and regulatory issues that pose barriers to its widespread adoption into

the preventive armamentarium in the UK, there is every possibility that these could be overcome, particularly given the success of SDF in other countries.

*Declaration of interests*

The authors state no declarations of interest.

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