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ORIGINAL ARTICLE

Cost-effectiveness and efficacy of fluoride varnish for caries prevention in South African children: A cluster-randomized controlled community trial

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Abstract

Objectives: This cluster-randomized controlled community trial aimed to assess the efficacy and costs of fluoride varnish (FV) application for caries prevention in a high-risk population in South Africa.

Methods: 513 children aged 4–8 years from two schools in a township in South Africa were randomly allocated by class to the FV or Control (CO) groups. In addition to supervised toothbrushing with fluoridated toothpaste in both groups, FV was applied in 3-month intervals by trained local non-professional assistants. Intraoral examinations were conducted at baseline, 12, 21 and 24 months. Primary outcome was the increment of teeth with cavitated lesions (i.e. newly developed or progressed, formerly non-cavitated lesions), requiring restoration or extraction over the study period. Additionally, treatment and re-treatment costs were analyzed.

Results: 513 children ($d_{1\text{-}4}$mft 5.9 ± 4.3 (mean ± SD)) were randomly allocated to FV ($n = 287$) or CO ($n = 226$). 10.2% FV and CO teeth received or required a restoration; 3.9% FV and 4.1% CO teeth were extracted, without significant differences between groups. While FV generated high initial costs, follow-up costs were comparable in both groups, resulting in FV being significantly more expensive than CO (1667 ± 1055 ZAR vs. 950 ± 943 ZAR, $p < .001$).

Conclusions: Regular FV application, in addition to daily supervised toothbrushing, had no significant caries-preventive effect and was not cost-effective in a primary school setting within a peri-urban, high-risk community in South Africa. Alternative interventions on community or public health level should be considered to reduce the caries burden in high-risk communities.

KEYWORDS
caries, cost-effectiveness, fluoride varnish, oral health, prevention

1 | INTRODUCTION

Dental caries is a chronic and multifactorial disease that affects most adults and children worldwide and is a significant public health challenge. According to the 2017 Global Burden of Diseases, Injuries and Risk Factors Study, untreated caries in permanent (29.4%) and deciduous (7.8%) teeth is the most prevalent of all assessed conditions, with improvements in childrens' oral health in high-income countries being compensated by an increasing burden in low- and middle-income countries, especially in disadvantaged communities.[1,2] This is most apparent in Africa, where limited accessibility to oral healthcare services also means that symptomatic caries can only be insufficiently addressed.[3] For example, the latest South African national oral health survey, conducted between 1999 and 2002, reports a mean caries prevalence in 6-years-olds of 60.3%,[4] and a more recent study from the Western Cape Region from 2011 to 2015 reports this prevalence to be even higher at 84% for 6-year-olds.[5]

Oral health programs tackling the caries burden in these countries and communities are required,[3,6,7] with school-based programs having been suggested to be cost-effective while reducing inequalities in accessibility.[8] One such program is the LiveSmart program, organized by the Dental Wellness Trust Charity and running in Khayelitsha and Mfuleni, two townships of Cape Town, South Africa, which aims to teach children the importance of brushing their teeth and washing their hands as well as eating and drinking healthily. The program is run by teachers during school term and by trained local non-professional assistants ('Toothbrush Mamas') afterwards. Approximately 12,000 children across 369 schools participate.[9]

One component of the LiveSmart program is the application of a fluoride varnish (FV). The latest Cochrane Review (2013) on the effectiveness of FV for caries prevention in children and adolescents found a pooled preventive fraction of 43% (95% (CI): 30%–57%) and 37% (95% (CI): 24%–51%) in permanent and primary teeth, respectively. Other systematic reviews confirmed these results.[10,11] However, the observed efficacy of FV was found to be associated with the year of study publication; newer studies found limited or no beneficial effects at all, possibly as the caries increment in both the FV and the control group was extremely low in these recent trials.[12] Such low efficacy was subsequently found to negatively affect the cost-effectiveness of FV application.[13] This may be grounded partially in the fact that these studies stemmed from high-income countries, in which the caries increment is low in most age groups due to wide access to fluoride, mainly via toothpaste.

This study aimed to assess the efficacy and cost-effectiveness of FV application within the LiveSmart program (that is, in a high-risk population in South Africa) in a cluster-randomized controlled community trial.

2 | METHODS

2.1 | Study design

This study is a multi-centre, two-arm, parallel-group, single-blinded, cluster-randomized controlled superiority trial, conducted at two schools in the township Khayelitsha, South Africa, from 12 February 2018 to 18 February 2020. The clusters were school classes (see below). The study flow is summarized in Figure 1.

Approval has been obtained by the Biomedical Science Research Ethics Committee of the University of the Western Cape (BM18/1/3), and the study was registered at ClinicalTrials.gov (NCT03429829). The study was originally planned with a three-year follow-up, but was discontinued after 24 months due to the COVID-19 pandemic. In addition, the planned primary outcome 'caries increment on patient level' (measured by the change in the DMFS/dmfs index) has been changed to 'caries increment on tooth level' (increment of teeth with cavitated lesions (ie newly developed ones or progressed, formerly non-cavitated lesions), requiring restorations or extraction) in order to mitigate various influences. Most notably is the change in dentition over the study period for this cohort, which strongly affects the DMFS/dmfs index due to exfoliation and newly erupting permanent teeth.

2.2 | Setting and participants

This study was conducted under the umbrella of the LiveSmart tooth brushing program that is organized by the Dental Wellness Trust Charity.[9] Recruitment was conducted at the Itsitsa and Nyameko Primary Schools between 5 February 2018 and 15 February 2018, with a second recruitment wave between 21 May 2018 and 31 May 2018 for late responders. Children attending the reception grade and grade 1, aged 4–8 years, were included. Parental consent as well as childrens' assent and cooperation for treatment was required.

Recruitment was realized by giving study information and letters seeking consent to all eligible children to take home. All children with a signed consent form and who participated in the baseline examination were included in the study. Children with chronic stomatitis or ulcerated gums, a history of asthma or known allergies to the used materials were excluded. To account for logistic difficulties, all non-responders in February 2018 received a second letter and were recruited three months later, provided their parents had consented and the children participated in a baseline examination.

2.3 | Sample size

Sample size calculation was based on an assumed reduction in caries incidence during the 3 years study period by FV from 50% (CO) to

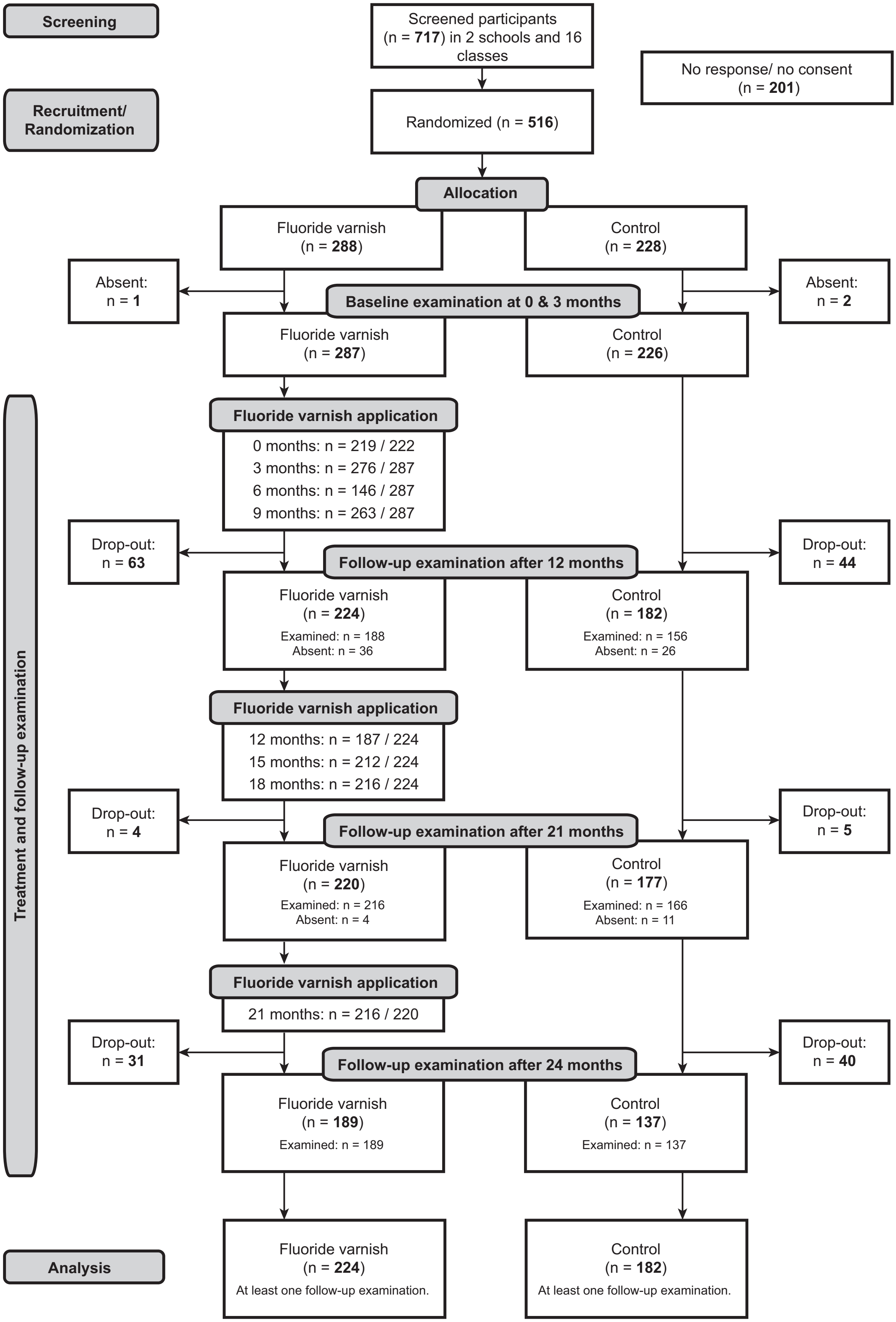

FIGURE 1 Flowchart of the study

35% (FV). This was grounded in the high chance of developing caries over this period according to the last South African national oral health survey[4] and a preventive fraction of 30%,[14] as outlined. With $\alpha = 0.05$, 1-$\beta = 0.9$ and factoring-in a drop-out rate of 30%, we aimed to include 600 children in total. Out of 717 children screened, 513 could be included. While a higher sample size was not achievable, our findings (see below) suggest that statistically significant differences in caries increment between groups are unlikely to be found, even with a higher sample size.

2.4 | Allocation and blinding

Children were randomly allocated to either FV or the CO. Cluster randomization of classes was performed using toss of coin before baseline examination was conducted, ensuring an even distribution of classes per school and grade as well as an unbiased allocation. The examiners who evaluated the outcome were unaware which group the children belonged to, whether FV or CO. Neither the children nor the trained local non-professional assistants applying the FV were blinded.

2.5 | Interventions and follow-up

Inclusion and exclusion criteria were confirmed for all children that provided their parents' consent in February 2018, or in case of initial non-responders three months later. At the same visit, they received an intraoral examination, recording the dental caries status for each tooth surface. Examinations were conducted according to WHO basic oral examination recommendations, with children being seated upright in a regular chair and the examiner using a headlamp, intraoral mirror and probe for examination. Follow-up intraoral examinations were planned at the 12-month, 24-month and 36-month visits. At the 12-month follow-up, it was observed that at the end of the school year, a substantial proportion of the children had changed school and were lost to follow-up. To address the subsequent expected drop-out before the 24-month follow-up, a 21-month examination (before the end of the second school year) was added in deviation from the protocol. As discussed, any subsequent visits in or after the third year were not feasible given the COVID-19 pandemic, which is why we eventually terminated the study after the 24-month visit.

FV (22,600 ppm, DMG) was applied in 3-months intervals by the local non-professional assistants who had been trained beforehand and supervised at the first application. Children sat upright during the application; their teeth were first cleaned and dried with cotton wool rolls. After mixing the FV, it was applied as a thin layer to all surfaces of the lower and upper dentition, including proximal surfaces (using floss in case of tight contact points) as well as pits and fissures (using a small brush that was provided together with the varnish by the manufacturer). Children were advised not to drink or eat directly after the application, while this could not be controlled.

Children in the CO group did not receive FV. As children in both groups were part of the LiveSmart tooth brushing program, they all received a new toothbrush at baseline and at every follow-up visit as well as fluoride toothpaste (1,450 ppm, Colgate Maximum Cavity Protection). Their daily toothbrushing was supervised by the local trained non-professional assistants.

For each appointment (examinations and intervention), a 1 week time interval was scheduled. If children were absent, their teachers were contacted for clarification. Whenever feasible, the child was treated/examined in the following days.

2.6 | Data collection and outcomes

Basic demographic data (age and sex) were recorded. During examinations, active and inactive non-cavitated caries lesions, active and arrested cavitated caries lesions, sealants and fillings as well as missing teeth due to caries or any other reason were recorded. To evaluate lesion activity, Nyvad criteria were employed.[15,16] Dentists performing the examination were trained and calibrated on the first children examined at each time point. A core team of three dentists conducted the examinations at all time points and supervised additional dentists that assisted with the examinations at various follow-ups. Additional dentists were employed for logistic reasons as children could only be examined during school hours, providing a limited time frame. To assess potential adverse reactions (ie contact irritation or allergic reaction involving the oral mucosa) to the FV application, children were monitored as part of the daily supervised toothbrushing by the local trained non-professional assistants.

Our primary outcome was the increment of teeth with cavitated lesions (ie newly developed ones or progressed, formerly non-cavitated lesions), requiring restorations or extraction. Secondary outcomes included (1) the increment of teeth with cavitated caries lesions, receiving or requiring a restoration; (2) the increment of teeth which were extracted; (3) costs. For the latter, a payer's perspective was used, with direct medical costs being considered based on the GEMS (Government Employees Medical Scheme) tariff fee item catalogue.[17] For cost estimation, we applied fees for amalgam restorations, fluoride varnish application and extractions. Costs for the toothbrushing program itself and follow-up examinations were not considered as these were identical in both groups. The horizon of our analysis was 24 months; to account for time preference and opportunity cost of capital, a 4.5% annual discount was applied.[18] Cost estimation and reporting followed the CHEERS guidelines.[19]

2.7 | Statistical analysis

Statistical evaluation was performed using SPSS 20.0 according to the intention-to-treat principle. The level of significance was set at $p < .05$. Three individuals in the CO group accidentally received FV during one follow-up; otherwise, treatment followed allocation.

To examine baseline characteristics, means and standard deviations were calculated for continuous variables, with pairwise comparison between both groups having been conducted using two-sided independent t tests (continuous variables) and chi-square tests (binary variables).

Proportions as well as odds ratios and 95% confidence intervals were computed for the primary outcome as well as the secondary outcomes increment of teeth with cavitated caries lesions, receiving or requiring a restoration and increment of teeth which were extracted. Proportions were compared pairwise using chi-square tests. In consideration of the clustered structure, hierarchical (multi-level) logistic or linear modelling was employed to assess the primary and secondary outcomes, with the class and the individual as clusters.

For the secondary outcome costs, means and standard deviations were calculated using two-sided independent t tests for comparison.

3 | RESULTS

Figure 1 depicts the study flow. 513 children were randomly allocated to FV or CO without significant differences in age, gender or caries experience between groups ($p > .05$) (Table 1). 11% and 16% of the children did not have any caries lesions or cavitated caries lesions at baseline, respectively.

Over the study period, children in the FV group received a mean (SD) of 6.1 (1.8) FV applications, with no observed adverse reactions. Table S1 presents the collective results of the examinations at all follow-ups. Notably, nearly no cavitated surface received a filling over the study period, highlighting a general lack of access to dental services for this study group.

Assessing the increment of teeth with cavitated caries lesions (new cavitated lesions or existing non-cavitated ones progressed to cavitation, which received or required a restoration), the increment of teeth which were extracted, or both (increment of failed teeth), no significant differences were observed between both groups ($p > .05$). While FV generated high initial costs, follow-up costs were similar in FV and CO, resulting in FV being significantly more expensive than CO (Table 2).

In the multivariable analysis, neither group allocation nor age or sex were significantly associated with outcomes ($p > .05$) (Table 3).

TABLE 1 Characteristics of the participants at baseline

Item	FV	CO
N children (boys/girls)	287 (146/141)	226 (119/107)
Mean (SD) age		
Age (years)	6.1 (0.8)	6.1 (0.8)
Mean (SD) number of teeth		
Prim	15.5 (3.0)	15.9 (3.0)
Perm	**6.3 (3.8)**	**5.6 (4.0)**
Total	21.8 (2.2)	21.5 (2.5)
Mean (SD) number of cavitated carious surfaces		
Prim	8.2 (10.5)	8.5 (10.4)
Perm	0.2 (0.7)	0.1 (0.6)
Total	8.3 (10.6)	8.6 (10.6)
Mean (SD) number of filled surfaces		
Prim	0.0 (0.3)	0.1 (0.7)
Perm	0.0 (0.0)	0.0 (0.0)
Total	0.0 (0.3)	0.1 (0.7)
Mean (SD) number of non-cavitated carious surfaces		
Prim	1.3 (2.2)	1.2 (1.6)
Perm	0.5 (1.0)	0.5 (1.0)
Total	1.9 (2.3)	1.7 (1.9)
Mean (SD) dmfs/DMFS indices		
d1-4mfs	13.3 (13.3)	13.6 (13.7)
d3-4mfs	12.0 (13.0)	12.4 (13.7)
D1-4MFS	0.7 (1.2)	0.6 (1.2)
D3-4MFS	0.2 (0.7)	0.1 (0.6)
Mean (SD) dmft/DMFT indices		
d1-4mft	5.9 (4.2)	6.0 (4.4)
d3-4mft	4.8 (4.0)	4.9 (4.2)
D1-4MFT	0.7 (1.1)	0.6 (1.1)
D3-4MFT	0.1 (0.5)	0.1 (0.4)

Note: Bold estimates indicate significant differences ($p < .05$) calculated using two-sided independent t tests for continuous measures and chi-squared tests for binary measures.

4 | DISCUSSION

This study failed to demonstrate a caries-preventive effect of regular FV application in a primary school setting within a peri-urban, high-risk community in South Africa. While our finding is in line with meta-analyses indicating that many studies failed to confirm the benefits of FV for caries prevention, we had hypothesized that in this low socio-economic, high-caries risk group FV may have substantial caries-preventive benefits.[12,20] We refute our hypothesis for multifaceted reasons.

First, this cohort showed an extremely high-caries prevalence (89%) and experience (mean $d_{1\text{-}4}$mft = 5.9) at baseline. These numbers are in line with a survey in the Western Cape area in 2015, showing a prevalence of 84% and mean caries experience of 6.2 for 6-years-olds.[5] Recent reviews[11,20] reported an inverse relationship between baseline caries experience and the benefits of FV, presumably as there are fewer surfaces on which caries can be prevented.[20] Second, such high-caries prevalence and experience[21,22] have been found to be associated with low oral health awareness in peri-urban communities in South Africa and with adverse oral health-related behaviours.[3,5] Children mainly rely on food available at schools, which is sugary and unhealthy; moreover, teachers usually have only limited knowledge on healthy nutrition.[23,24] It may well be that the additional supply of fluoride was not sufficient to tackle the excessive intake of sugar, a key cause for caries development.[25–27] A recent

TABLE 2 Teeth with new cavitated caries lesions or existing early ones progressing to cavitated lesions, requiring restorations or extractions over the study period as well as costs associated with FV application and re-treatment

Item	FV	CO
Increment of teeth with cavitated lesions	790/7758 (10.2%)	624/6149 (10.2%)
Increment of teeth requiring extraction	303/7758 (3.9%)	250/6149 (4.1%)
Failed (extracted or cavitated/restored)	1035/7758 (13.4%)	821/6149 (13.4%)
Initial costs (ZAR, mean (SD))	**727 (221)**	**2 (14)**
Re-treatment costs during follow-up (ZAR, mean (SD))	939 (932)	948 (943)
Total costs after 24 months (ZAR, mean (SD))	**1667 (1055)**	**950 (943)**

Note: Bold estimates indicate significant differences ($p < .05$) calculated using two-sided independent t tests continuous measures and chi-squared tests for proportions. Initial costs only applied to the FV application (note that as described, three individuals in the control group accidentally received fluoride varnish). Follow-up cost are the combined costs of required restorations or extractions.

TABLE 3 Parameters associated with a tooth's risk of new cavitated caries lesions or existing early ones progressing to cavitated lesions, requiring restorations or extractions

Item	Increment of teeth with cavitated lesions	Increment of teeth requiring extraction	Failed (cavitated lesion, restoration or extraction)
Group (ref: control)	0.98 (0.93–1.04)	0.99 (0.95–1.03)	0.99 (0.92–1.06)
Age (years)	1.00 (0.94–1.06)	1.00 (0.96–1.04)	1.00 (0.93–1.07)
Sex (ref: male)	0.99 (0.95–1.03)	1.00 (0.97–1.02)	0.98 (0.94–1.03)

Note: Test ratios and their 95% CI are shown.

study finding further supported this aspect showing that daily supervised toothbrushing using fluoridated toothpaste coupled with the prohibition of sugary snacking in school is already effective in preventing caries among pre-school children.[28] Another reason for a limited benefit of the FV intervention in this study might be the specific setting, that is FV application under limited moisture control and by trained local non-professional assistants; moreover, eating and drinking following the FV application could not be controlled in this school-based trial but has been discussed to potentially limit the preventive effect of FV.[29]

FV application was not cost-effective in this trial and setting, mainly as there were no cost-savings in restorative or further care avoided by FV, while regular application of FV generated significant costs. An earlier simulation from 2006 outlined that FV, based on an assumed effectiveness of 35.4%, would be cost-saving after 3–4 years given long-term savings.[30] A similar conclusion was drawn by two more recent analyses, outlining that FV might be cost-effective in high-caries risk populations in Germany[13] or non-fluoridated areas in Chile.[31] Notably, cost-effectiveness was only marginal and only occurred long-term or in specific groups or settings.[13] A much higher cost-effectiveness of FV was found in a Canadian study on pre-school children in low-income communities. Over 5 years, an average of 4.38 cavities per child was avoided in the FV group, saving 823 CAD for restorative care per child, compared to the costs of 7.9 CAD per FV application.[32]

Any discussion on how to prevent caries in poor communities with high-caries rates usually involves fluoride.[20,25,26] With limited fluoride concentration in the local drinking water, the FV project was conceived to supplement the fluoride delivery within an existing toothbrushing program, previously shown not to be sufficiently efficacious on its own.[33] A previous initiative to deliver fissure sealants in this community revealed that supplementary preventive effects were possible.[34] However, sealants required professional expertise and costs, reducing the sustainability of the project. The outlined FV program was expected to offer a cost-effective way to reach large numbers of children. Alternative community or public health level strategies may be needed to address the high-caries risk in disadvantaged communities in South Africa; the recent introduction of a national sugar tax is an example of how to tackle caries population wide and equitably,[35–38] particularly if sugar taxation is supported by oral health education and behaviour change strategies.[39,40]

This study comes with a number of strengths and limitations. First, it is a large, randomized community-based trial, with high internal validity. Second, it addresses a high-need population in a low-to middle-income country, where the need for research to address high disease burden is pressing. Third, this study utilized trained local non-professional assistants to apply FV and supervise toothbrushing, which may have negatively impacted the effectiveness of the treatment. Lastly, we did not reach the anticipated sample size and also had to terminate the study earlier due to the COVID-19 pandemic, both of which may have impacted on our statistical power. Given the extremely small or absent differences in our outcomes between groups, though it is unlikely that longer follow-up or a larger sample would have substantially changed our findings.

In conclusion, within this randomized controlled trial regular FV application did not have a significant preventive impact on the increment of teeth with cavitated lesions, requiring or receiving restorations or extractions, in a primary school setting within a peri-urban, high-risk community in South Africa. Given similar follow-up costs in both groups, FV was significantly more expensive than CO due to high initial costs of FV. Alternative interventions at the community or public health level should be considered.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

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CONFLICT OF INTEREST

NM, KS and DS declare that they have no conflict of interest. LG is heading the Dental Wellness Trust Charity. LG, MW and FS are consultants for DMG Dental-Material Gesellschaft mbH, but did not receive any payment or personal benefits for this study. SE and MC are employees of DMG Dental-Material Gesellschaft mbH, but do not receive any personal benefit from the sales of the product used in this study.

AUTHORS' CONTRIBUTIONS

SE, LG, NM and MC conceived and designed the study. SE, FS and MC wrote the manuscript. All authors conducted the study and analysed the data, interpreted the data, and read, revised and agreed to be accountable for the manuscript.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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