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Fluoride Varnish in Nursery Schools: A Randomised Controlled Trial – Protecting Teeth @3

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Abstract
Studies suggest that fluoride varnish (FV) application can reduce dental caries in child populations. The multiple-component national child oral health improvement programme in Scotland (Childsmile) includes nursery-based universal supervised toothbrushing and deprivation-targeted FV applications, together with community and dental practice prevention interventions. This trial, a double-blind, two-arm randomised control trial, aimed to assess the effectiveness and cost-effectiveness of the nursery-based FV applications plus treatment-as-usual (TAU) Childsmile programme interventions, compared to TAU Childsmile interventions alone, in children not targeted to receive nursery FV as part of the programme. Participating children in the first year of nursery (aged three), with or without existing caries, were randomised to either FV or TAU and followed up for 24 months until the first year of primary school. Treatments were administered at six-monthly intervals. The primary endpoint was "worsening of d3mft" from baseline to 24 months. Secondary endpoints were worsening of d3mfs, d3t, mt, and ft. Individual record-linkage captured wider programme activities and tertiary endpoints. A total of 1,284 children were randomised, leading to 1,150 evaluable children ($n = 577$ FV, $n = 573$ TAU, 10% dropouts). Mean age was 3.5 years, 50% were female ($n = 576$), 17% had caries at baseline ($n = 195$), all balanced between the groups. Most children received three/four treatments. Overall, 26.9% ($n = 155$) had worsened d3mft in the FV group, and 31.6% ($n = 181$) in the TAU group, with an odds ratio (OR) of 0.80 (0.62–1.03), $p = 0.078$. The results for worsening of the secondary endpoints were: d3mfs 0.79 (0.61–1.01) $p = 0.063$, d3t 0.75 (0.57–0.99) $p = 0.043$, mt 1.34 (0.75–2.39) $p = 0.319$, and ft 0.77 (0.53–1.14) $p = 0.191$. We calculated a number needed to treat of 21 and a cost of GBP 686 to prevent a single worsening of d3mft. There was a modest non-significant reduction in the worsening of d3mft in the nursery FV group compared to TAU, suggesting that this intervention is unlikely to represent an effective or cost-effective addition to the population oral health improvement programme.

Introduction

Oral health is a major public health issue, with dental caries being the most common global disease [Peres et al., 2019]. In response to persistent poor oral health, the Scottish Government set out its policy "An Action Plan for

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Improving Oral Health and Modernising Dental Services in Scotland" [Scottish Government, 2005]. The aim was to shift the balance of care towards a more preventive and anticipatory care approach. A key priority was developing a programme to improve the oral health of young children. The influence of early years on the life course is well documented, with socio-economic background and health-related behaviour patterns in early life influencing health in later years [Peres et al., 2019].

An oral health improvement programme for children in Scotland (Childsmile) was developed, with pilots commencing in 2006. The components of Childsmile included: daily supervised toothbrushing (with 1,000 ppm F toothpaste) in nursery school; free toothpaste and toothbrush packs for home use; toothbrushing in the first 2 years of primary education in the more deprived areas; community-based dental health support workers; and preventive care including fluoride varnish (FV) and oral health advice within primary dental services [Macpherson et al., 2010, 2015, 2019a, b].

One part of the programme that is targeted to those children at an increased risk of dental caries, is a nursery- and school-based FV application scheme. A minimum of 20% of children in the most deprived areas in each health service administrative area (Health Board) are offered twice-yearly application of FV via the education setting. The universal nursery supervised toothbrushing component has been shown to be both effective and cost-effective [Macpherson et al., 2013; Anopa et al., 2015]. To date, there has been no evaluation of the added benefit of the nursery-based twice-yearly FV application component of Childsmile.

A Cochrane systematic review of FV application concluded that it reduced worsening of caries in the primary dentition with a prevention fraction of 37% [Marinho et al., 2013]. Prior to the commencement of this trial, 3 small trials of FV in the nursery/kindergarten setting were identified [Grodzka et al., 1982; Chu et al., 2002; Borutta et al., 2006]. They all showed a marginal caries-preventive effect of FV against different comparison groups; with none being undertaken as part of a wider public health programme.

The objective of this trial was to compare the effectiveness of FV plus treatment as usual (TAU; all other components of Childsmile), with TAU only in preventing any worsening of obvious decay experience, over a two-year period from the first year of nursery education (aged three years old) to the first year at primary school (aged five years old).

Methods

The full Protecting Teeth @3-Years (PT@3) trial protocol has previously been published [Wright et al., 2015], and the methods are reported here in summary.

Participants

The participants were three years old attending their first year of education in nursery schools within the areas of four NHS Health Boards in Scotland (Greater Glasgow and Clyde, Fife, Lothian, and Tayside). The nurseries which were targeted in each Health Board area were those just above the cut-off for inclusion in the FV scheme within the main Childsmile programme, that is, the next most socially disadvantaged areas based on the Scottish Index of Multiple Deprivation (SIMD) of the home postcode of the children [SIMD, 2013].

Consent was obtained from the parents or guardians of the children. The children were included whether or not they had pre-existing dental caries lesions but were excluded if they had: (a) contraindications for the FV, that is, hypersensitivity to colophony and/or any other constituents; (b) a history of bronchial asthma requiring hospitalisation; (c) a history of allergic episodes requiring hospital admission; or (d) showing signs of distress on the day of baseline inspection or showing signs of verbal or non-verbal reluctance. Recruitment was carried out from December 2012 in the three cohorts in the academic years 2012/13, 2013/14, 2014/15.

Sample Size

From a local study of three-year-olds, it was estimated that approximately 41% of 3-year-olds from deprived communities would experience new decay over the course of two years of follow-up [McMahon et al., 2010]. A two-group χ^2 test with a two-sided significance level of 0.05 would have 90% power to detect the difference between a group 1 proportion of 0.41 and a group 2 proportion of 0.31 (an odds ratio of 1.55) when the sample size in each group is 483. We therefore needed a total of 966 evaluable subjects.

Interventions

Treatment consisted of either the active FV treatment (Duraphat 50 mg/mL) or they got a "sham" FV application (with an applicator brushing the teeth with no FV on it). The standard Childsmile programme protocol was used to apply the FV to all tooth surfaces [Childsmile, 2019].

Children attended their usual sources of dental care during the trial and practitioners continued with their normal care. The children also received the other Childsmile interventions, regardless of their treatment allocation.

Study Schedule

The schedule of contacts with the participating children is summarised in Figure 1. At baseline, a dental inspection and randomisation was carried out. Treatment visits were at baseline, 6, 12, and 18 months. Before each treatment, a brief oral check was performed, and if the child had a temporary condition such as cold sores, abrasions, or systemic illnesses, then the treatment was not carried out although they remained in the study. After 24 months of follow-up, the study finished with an endpoint dental inspection in the first year of primary school.

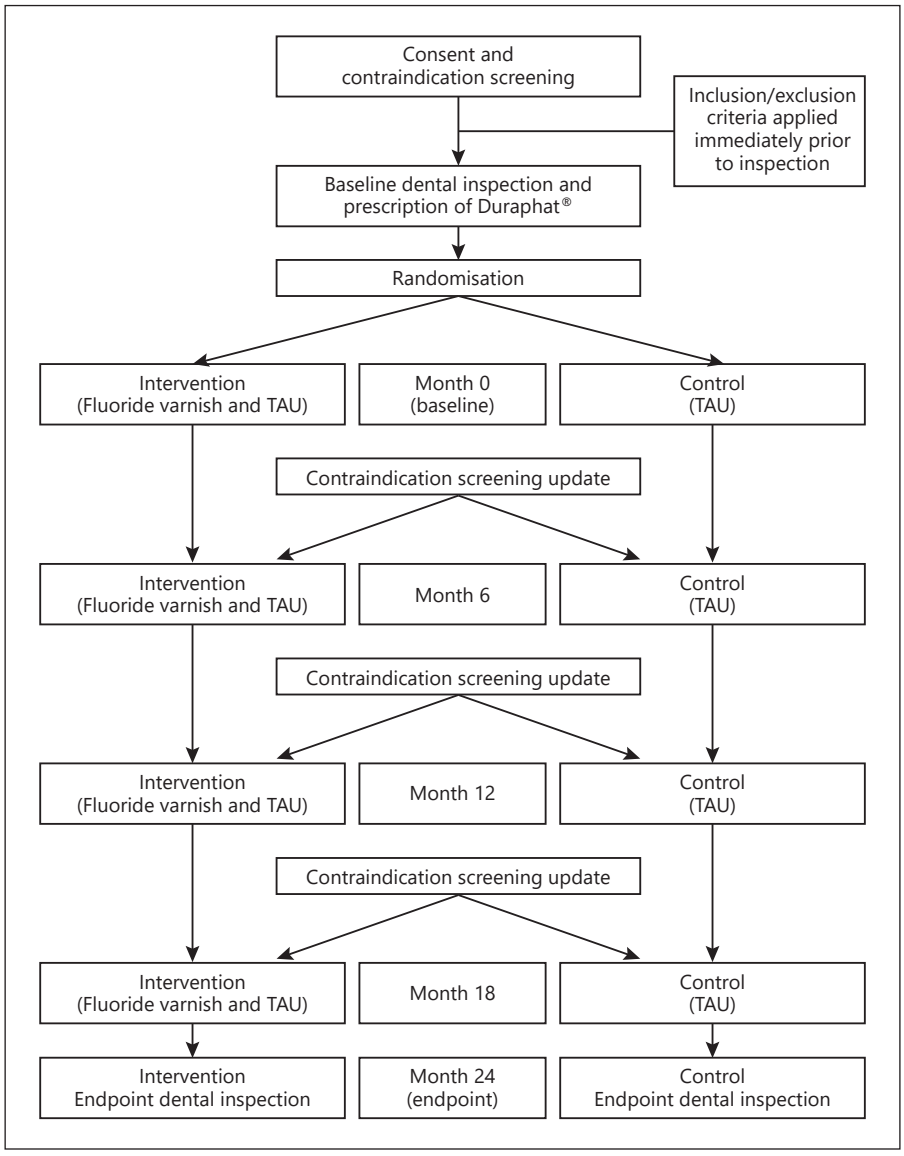

Fig. 1. Trial visit schedule.

Dental Inspections

Dental inspectors undertaking the examinations all had routine training and calibration using the protocols of the Scottish National Dental Inspection Programme (NDIP) [NDIP, 2018]. Following our protocols, calibration was carried out by inter-rater agreement kappa statistics (not intra-rater agreement). Caries was assessed at the dentinal level (d3) following the criteria of the British Association for the Study of Community Dentistry (BASCD) [Pine et al., 1997].

Randomisation

Eligible children were randomised to receive either fluoride FV plus TAU or TAU only in a 1:1 ratio. Randomisation followed the baseline dental inspection and took place via a telephone call to the Interactive Voice Response System (IVRS) at the Robertson Centre for Biostatistics, University of Glasgow, a UKCRC Registered Clinical Trials Unit. Blocks of 2 and 4 were used for each nursery school separately.

Allocation Concealment and Blinding

The treatment allocation was determined for each child by the IVRS and provided to the treatment teams at the time of the first treatment. The blocking was concealed to the treatment teams. The treatments were blind to the child (and therefore the parent or guardian) due to the sham application and were also blind to the baseline and the final inspecting dental professionals.

Outcomes and Endpoints for Analysis

The primary outcome was dental caries as measured by d3mft. The primary endpoint was a worsening (i.e., a change that is >0) in the primary outcome at 24 months. It was anticipated that there would be a small number of cases where subtraction of the baseline

d3mft from the final d3mft would result in a negative change. Where this occurred, such cases were set to zero in the analyses.

Secondary outcomes were d3mfs, a count of affected individual surfaces rather than the whole tooth, and the individual components that contribute to d3mft, namely d3t (decayed teeth), mt (missing teeth), and ft (filled teeth). Secondary endpoints include a worsening of the secondary outcomes in a similar manner to the primary endpoint. Additional secondary endpoints include the absolute changes on a continuous scale, at 24 months of follow-up minus the d3mft at baseline, for all of the above endpoints.

Record-Linkage and Tertiary Endpoints

Personal data from the administrative logs from the study were sent to NHS Scotland's electronic Data Research and Innovation Service (eDRIS) [eDRIS, 2010]. This service was used to link the trial participants to individual health records from various national dental service datasets held by the NHS, including a link to SIMD using the children's home postcode. Using this method, we assessed whether or not the individual trial children had received: Childsmile dietary advice and toothbrushing advice in dental practice (prior to the study and during the study), additional FV applications received in dental practice during the study period, attendance at dental practice, and attendance at hospital dental outpatient clinics. Using record linkage, we also created tertiary endpoints during the study period, namely: hospital admission for dental extractions under general anaesthesia; treatments provided by dental practice including fillings, pulpotomy, preformed metal crowns, and extraction of deciduous teeth with local anaesthetic.

Statistical Analysis

The "worsening" binary endpoints and the tertiary endpoints from record-linkage were analysed by Mantel-Haenszel χ^2 tests and odds ratios, with the attendant 95% CIs. Changes in the endpoints were analysed by Wilcoxon tests. The number of successful treatment visits were compared with a χ^2 test. Pre-determined subgroup analyses (Prior Decay and SIMD) for the primary endpoint were carried out by logistic regression with interaction terms between treatment and each subgroup variable. All statistical tests were 2-tailed tests at the 5% significance level. All analyses followed the intention-to-treat principle [Hollis and Campbell, 1999; McMahon, 2002]. The number needed to treat (NNT) was calculated, together with 95% confidence limits. Analyses were carried out using SAS 9.4 software, Cary, NC, USA.

Intervention Costs

The cost baseline year was 2016/17. Following the UK's National Institute for Health and Care Excellence (NICE) public health economic evaluation guidelines, a discount rate of 1.5% was employed [NICE, 2012]. Labour and staff travel costs that were related to staff delivering the interventions were collected for a subset of the trial participants in the 2014/15 intake. Members of staff were asked to fill in a "labour and staff travel cost" form each time they visited a nursery. A full economic evaluation of the study is currently being carried out and will be reported separately.

Safety

A Pharmacovigilance system was used to track the occurrence of Adverse Events, Adverse Reactions, Serious Adverse Events, Serious Adverse Reactions, Suspected Serious Adverse Reactions, and Suspected Unexpected Serious Adverse Reactions.

Table 1. Baseline characteristics

Variable	FV (n = 577)	TAU (n = 573)	Total (n = 1,150)
Age, mean (SD), years	3.52 (0.24)	3.54 (0.24)	3.53 (0.24)
Sex, *n* (%)			
Female	288 (50)	288 (50)	576 (50)
Male	289 (50)	285 (50)	574 (50)
SIMD, *n* (%)			
1 (most deprived)	124 (22)	111 (20)	235 (21)
2	183 (32)	201 (35)	384 (34)
3	137 (24)	126 (22)	263 (23)
4	77 (13)	74 (13)	151 (13)
5 (most affluent)	52 (9)	57 (10)	109 (10)
Caries at baseline, *n* (%)			
Yes	98 (17)	97 (17)	195 (17)
No	479 (83)	476 (83)	955 (83)

FV, fluoride varnish treatment group; TAU, treatment as usual treatment group; SIMD, Scottish Index of Multiple Deprivation (there is a small amount of missing data, 4 in each group).

Results

The flow of participants through the trial is shown in the CONSORT diagram (Fig. 2). A total of 1,916 children for whom parental/carer consent was obtained were assessed for eligibility. Of these children, 1,284 were randomised from 112 classes in 65 nursery schools, with 643 in the FV (plus TAU) group and 641 in the TAU only arm. Trial monitoring data confirmed that all of the nurseries were participating in the Childsmile supervised toothbrushing programme. At the end of the study 1,150 children (90%) had evaluable endpoints (577 FV, 573 TAU) which exceeds the a-priori sample size requirement of 966 evaluable participants. The most common reason for not completing the trial was moving out of the area.

The baseline characteristics of the children participating in the study are presented in Table 1. The mean age of the children was 3.53 years (standard deviation, SD 0.24) and was balanced between the treatment groups (FV 3.53, TAU 3.54). The proportion of females was the same in the FV and TAU groups, with 288 (50%) in each group. The distribution of the categories of SIMD was similar in both groups, with (for example) the percentage of children in the most deprived category being 22% in the FV group (n = 124) and 20% in the TAU group (n = 111). This study allowed the randomisation of children who had pre-existing obvious decay experience, and the proportions with pre-existing caries were identical in the

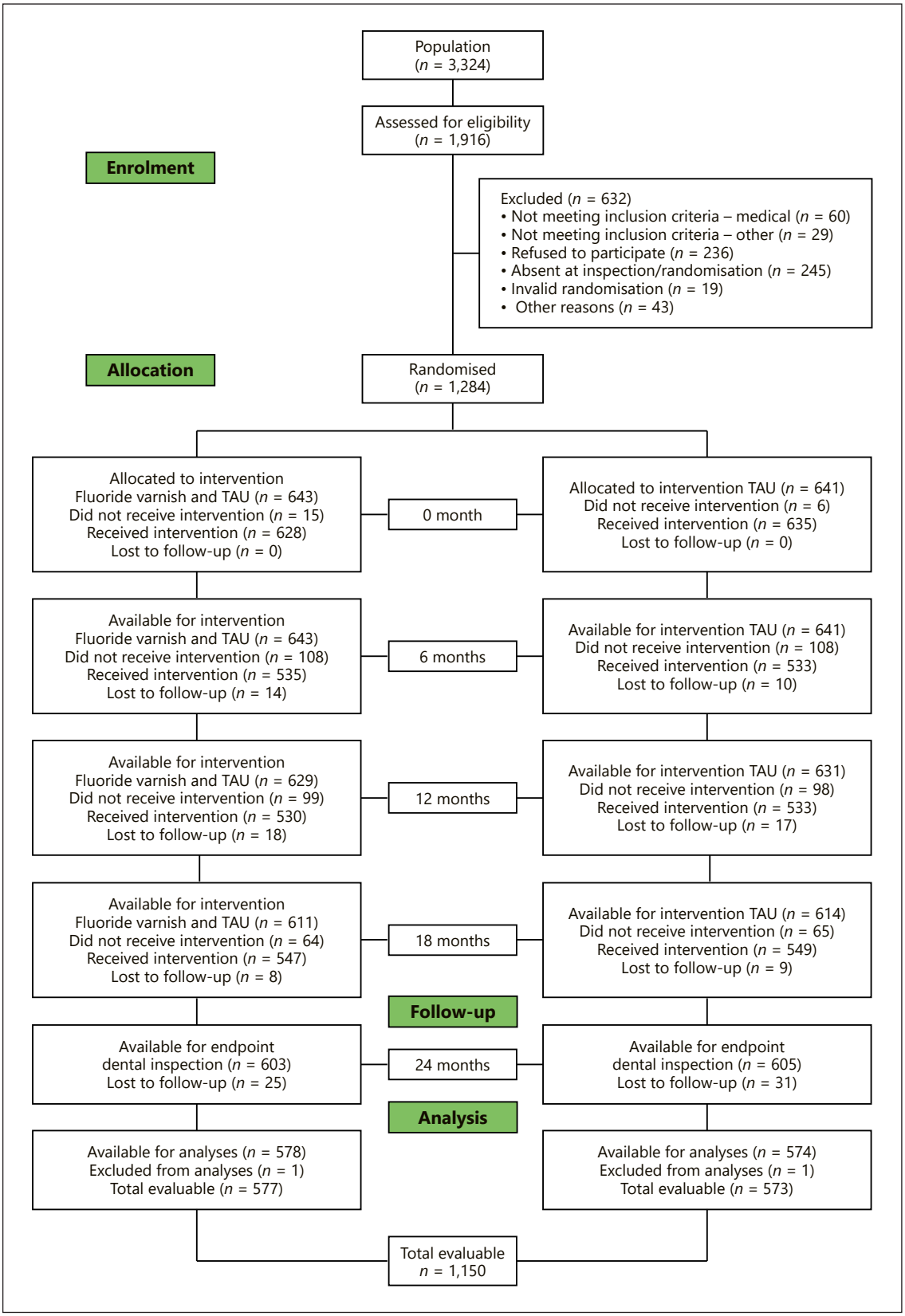

Fig. 2. CONSORT diagram of participant flow.

Table 2. Childsmile programme and dental service activity before and during the trial (data accessed by record linkage)

Endpoint	FV (n = 577)	TAU (n = 573)	p value
Prior to the study period			
Dietary advice 0–2 years old, n (%)	278 (48)	284 (50)	n/a
Toothbrushing advice 0–2 years old, n (%)	275 (48)	283 (49)	n/a
During the trial period			
Additional FV at practice, n (%)			
0	348 (60)	336 (59)	0.578
1	110 (19)	122 (21)	
2	75 (13)	82 (14)	
3	40 (7)	29 (5)	
4	4 (1)	4 (1)	
Dietary advice 3–5 years old, n (%)	265 (46)	246 (43)	0.307
Toothbrushing advice 3–5 years old, n (%)	284 (49)	274 (48)	0.634
Attendance at practice, n (%)	319 (55)	327 (57)	0.543
Hospital Outpatient Dental Clinics[a], n (%)	9 (2)	8 (1)	0.818

FV, fluoride varnish treatment group; TAU, treatment as usual treatment group. [a] Hospital Clinics for oral surgery, community dentistry, restorative dentistry, paediatric dentistry.

FV group (n = 98, 17%) and in the TAU group (n = 97, 17%).

The mean baseline d3mft was 0.6 (SD 1.8) in the FV group and 0.5 in the TAU group (SD 1.6), and the equivalent figures for d3mfs were 1.2 (SD 1.8) and 1.1 (SD 4.7), respectively.

During the study period, 84% (485) of the children in the FV group received three or four treatments, and 86% (493) in the TAU group received three or four sham treatments. No adverse events or reactions were reported in this trial. All of the 15 dentists that undertook the baseline and endpoint inspections were calibrated with inter-observer kappa statistics ranging from 0.77 to 1.00, and a mean of 0.95 (SD 0.09).

For children receiving additional FV in dental practice, there was a mean of 0.7 additional FV applications in each group (SD 1.0 for the FV group and 0.9 for the TAU group). Frequency counts are given in Table 2 with 348 in the FV group (60%) and 336 in the TAU group (59%) not receiving any additional FV. Approximately half of the children received dietary advice and toothbrushing instruction in dental practice, both before and during the study, with no differences between the treatment groups. There were no differences between the study groups in the proportions either attending dental practice or hospital outpatient dental clinics (Table 2).

The results for the primary endpoint are that 155 (27%) of the children in the FV group and 181 children in the TAU group (32%) had a worsening of d3mft, with an odds-ratio (OR) of 0.80 (0.62, 1.03) p = 0.078, which is not statistically significant (Table 3). The secondary endpoints are also shown in Table 3. Worsening of decay at the tooth level (d3t), with 119 (21%) worsening in the FV group and 147 (26%) in the TAU group, just reached statistical significance OR = 0.75 (0.57, 0.99), p = 0.043. There were no differences in hospital admission for dental extractions under general anaesthesia or the other tertiary endpoints. The analyses of the changes from baseline as continuous endpoints were also analysed with an increase in mean d3mft of 0.9 to a value of 1.4 in both treatment groups. Mean d3mfs increased by 2.5 to 3.5 in the FV group and increased by 2.6 to 3.5 in the TAU group. There were no significant differences between the groups when analysed in this way.

The treatment effect was smaller for children with caries at baseline OR 0.85 (0.47–1.53) than those without OR 0.75 (0.55–1.02), but the interaction test was not significant with p = 0.708. There was some variation of the treatment effect in the levels of SIMD1 OR 0.64 (0.38–1.11), SIMD2 OR 0.83 (0.56–1.32), SIMD3 OR 1.08 (0.63–1.87), and OR 0.60 (0.33–1.08) for SIMD4 and 5 combined, but this was not large enough to trigger a significant interaction test with p = 0.421.

Table 3. Endpoint analyses

Endpoint	FV (n = 577)	TAU (n = 573)	OR	95% CI	p value
Primary endpoint, n (%)					
Worse d3mft (teeth)	155 (27)	181 (32)	0.80	0.62–1.03	0.078
Secondary endpoints, n (%)					
Worse d3mfs (surfaces)	165 (29)	193 (34)	0.79	0.61–1.01	0.063
Worse d3t (decayed)	119 (21)	147 (26)	0.75	0.57–0.99	0.043
Worse mt (missing)	28 (5)	21 (4)	1.34	0.75–2.39	0.319
Worse ft (filled)	52 (9)	65 (11)	0.77	0.53–1.14	0.191
Tertiary endpoints, n (%)					
Extraction by GA	11 (2)	8 (1)	1.37	0.55–3.44	0.498
Fillings	55 (10)	61 (11)	0.88	0.60–1.30	0.531
Pulpotomy	4 (1)	3 (1)	1.33	0.30–5.95	0.712
Preformed metal crowns	13 (2)	10 (2)	1.30	0.56–2.98	0.539
Extraction of deciduous teeth	1 (0)	0 (0)	n/a		0.319

FV, fluoride varnish treatment group; TAU, treatment as usual treatment group; GA, general anaesthetic. Tertiary endpoints were accessed by record-linkage to non-trial data during the study.

The NNT to prevent one child from having a worsening of d3mft was 21. The mean cost per child in the FV group was GBP 32.66 (SD GBP 13.21). Thus, it would cost GBP 685.86, which is GBP 32.66 multiplied by 21, to prevent one child from having a worsening of d3mft.

Discussion

Our findings show that FV provides a modest and non-significant reduction in dental caries experience (d3mft) at a relatively high cost when delivered in a nursery setting twice a year from 3 years of age, over and above the multiple-component treatment as usual prevention interventions delivered in the Childsmile Programme.

This study is the largest ever randomised controlled trial assessing the effectiveness and cost-effectiveness of FV application for young children in a pre-school nursery (kindergarten) setting. The trial was conducted to a high standard with robust governance and scrutiny processes as it was defined as a Clinical Trial of an Investigational Medicinal Product (CTIMP) and came under UK and EU Clinical Trial Regulations. Uniquely, we were able to harness the NHS Scotland routine administrative data and data linkage infrastructure to track the primary and secondary dental care provision at the individual child participant level that enabled further within-trial dental service activity and endpoint data to be captured. Fidelity to the trial protocol was excellent with a high level of follow-up for the primary endpoint (90%), thus providing power to detect clinically significant differences, and there were high levels of treatment delivery (85% receiving three or four applications).

The challenges of recruiting young children from nursery schools brought with it some study limitations. Unlike in schools, attendance in nurseries is not compulsory and combined with the nursery school year (and holiday) timetable, it was difficult to ensure that the children had all of the intervention visits completed. However, only 15% of the children did not receive three or four interventions in the study period. While this is a limitation, it is also the reality of delivering interventions to children in the nursery school environment, which was the primary aim of the study. Additionally, due to the setting, caries was assessed at the dentinal level (non-cavitated and cavitated lesions). While this is the usual endpoint measure for fluoride studies, it is acknowledged that enamel caries was not included and that the potential benefits of the prevention and reversal of early lesions were therefore not investigated.

Our main findings are similar to the recent systematic review of the effect of FV application on dental caries among pre-schoolers published since the end of our trial [de Sousa et al., 2019]. This review included clinical trials of FV either alone or as part of a combined intervention and compared FV application with placebo, usual care or no intervention. The review included 20 trials, with 17

included in a meta-analysis. It reported a relative risk at the individual level of 0.88 (95% CI 0.81–0.95), and estimated that in a population of pre-school children with 50% caries incidence, FV would need to be applied to 17 children to avoid new caries in one child. The authors questioned the caries-protective effectiveness of FV in young children. However, to enable policy makers to make informed decisions about whether to commence or stop FV as part of public health programmes or dental service provision, the authors of the systematic review called for further evidence on the cost-effectiveness of FV, further studies evaluating FV in the real-world context of other usual care oral health improvement activities (rather than vs. placebo or head-to-head against other interventions), and further studies assessing significant endpoints such as dental caries-related hospitalisations. Our trial contributes to each of these evidence gaps.

Since the commencement of our study, there have been no substantial trials investigating the added benefit of FV over and above wider public health activities, including supervised toothbrushing programmes. However, there have been 2 relatively small and underpowered trials by Agouropoulos et al. [2014] ($n = 328$) and Muñoz-Millán et al. [2018] ($n = 189$) that assessed FV intervention versus placebo in populations that were already receiving supervised toothbrushing, and neither found a significant difference in caries increment.

It is worth re-iterating that the context of the FV nursery intervention is within the considerable multiple activities of the Childsmile programme including supervised nursery toothbrushing (with home distribution of toothbrush/toothpaste packs), home visits from dental health support workers in the early years, and preventive activities delivered through dental practice. Thus, the Childsmile Programme can include FV in both the nursery setting and in dental practice. This trial was aimed at assessing the effect of the additional varnishes in the nursery setting.

Finally, the systematic review of de Sousa et al. [2019] found no studies reporting on caries-related hospitalisations. We were able to assess this through record-linkage and found no impact on hospitalisations including on elective hospital admissions for dental extractions under general anaesthesia, and on outpatient attendance at dental hospitals.

The initial cost analysis results do not show particularly good value for money – with an NNT of 21 in a population of preschool children with caries incidence of approximately 30% and a cost of GBP 686 to avoid new caries in one child. Our findings amplify the doubt that was cast upon the cost-effectiveness of FV by another recent UK-based (Northern Ireland) large trial that was undertaken in the clinical dental practice setting – where the costs of FV were found to outweigh the savings in treatment [O'Neill et al., 2017].

Conclusions

This study, which investigated the effect of FV applications in the nursery setting in addition to the other components of a national programme, showed a modest and non-significant anti-caries effect. This is perhaps to be expected given the access to fluoride on a regular basis via the other parts of the Childsmile programme, particularly the daily supervised toothbrushing scheme which includes home packs of toothpaste and toothbrushes that are delivered via the nursery setting. We had previously shown the effectiveness and cost-effectiveness of supervised early years toothbrushing programmes, and these have begun to be adopted around the world. FV applications in nursery school are unlikely to be an effective or cost-effective addition to the Childsmile population programme.

These results suggest that there is a need for an appraisal of the application of FV to pre-school children at an increased risk via nursery settings as part of population oral health improvement policies and programmes.

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Statement of Ethics

Duraphat FV was considered to be an Investigational Medicinal Product (IMP) by the Medicines and Health Care Regulatory Authority (MHRA) (EUDRACT number: 2012-002287-26). This trial was registered at ClinicalTrials.gov (NCT01674933). Ethical approval was obtained from the NHS West of Scotland Research Ethics Committee (12/WS/0136). Information governance approval for data linkage was obtained via Public Benefit Privacy Panel (PBPP 1617-0125.McMahon).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

L.M.D.M. conceived the study and was the Chief Investigator. W.W., S.T., and D.I.C. were responsible for the coordination of the study, and A.D.M. was the study statistician. Y.A. and E.M. designed the economic evaluation. A.D.M. analysed the clinical data, and Y.A. analysed the economic data. A.D.M. wrote the first draft of the protocol and the first draft of the manuscript. All authors contributed to the development of the protocol and contributed to the writing of the manuscript and read and approved the final version of the manuscript.

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