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A Cluster-randomized Controlled Trial: Fluoride Varnish in School Children

ABSTRACT

We conducted a school-based parallel cluster randomized controlled trial with 36-month follow-up of children aged 7 to 8 years. Primary schools were randomly assigned to 2 groups: 3 applications of fluoride varnish (22,600 ppm) each year or no intervention. The primary outcome was DFS increment in the first permanent molars, with the hypothesis that 9 applications of varnish over 3 years would result in a lower increment in the test group. Follow-up measurements were recorded by examiners blind to the allocation. Ninety-five schools were randomized to the test and 95 to the reference groups; 1473 (test) and 1494 (reference) children participated in the trial. An intention-to-treat analysis was carried out with random effects models. The DFS increment was 0.65 (SD 2.15) in the test and 0.67 (SD 2.10) in the reference groups, respectively. There was no statistically significant difference between the groups. We were unable to demonstrate an effect for fluoride varnish when it was used as a public health intervention to prevent caries in the first permanent molar teeth (International Standard Randomized Controlled Trial Registration: ISRCTN: #72589426)

KEY WORDS: fluoride varnish, caries, children, school, prevention.

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INTRODUCTION

Although dental caries experience in children living in Western European countries has fallen over the past 30 yrs, the disease remains a significant public health problem (WHO, 2011). Effective public health interventions delivered in the school setting have the potential to reduce caries and the resultant impact of the disease (WHO, 2003). Prevention is particularly important for the permanent dentition, since restorations replacing lost tooth tissue will need ongoing maintenance throughout the lifetime of the individual.

A Cochrane systematic review (Marinho *et al*., 2002) suggested that fluoride varnish substantially reduces tooth decay in both primary and permanent teeth of children and adolescents. The meta-analysis of 7 trials produced a D(M)FS pooled prevented fraction estimate of 46% (95%CI, 30% to 63%; $p < 0.0001$). These findings suggest that this simple method of fluoride delivery could be effective when used as a public health intervention in the school setting. The objective of this trial was to measure the effectiveness of fluoride varnish as a public health intervention to prevent caries in the first permanent molars of 7- and 8-year-old children when delivered in the school setting.

METHODS

A cluster-randomized, two-arm, parallel trial with an allocation ratio of 1:1 was undertaken in state-funded schools located in East Lancashire, England. The area was chosen because of the relatively high caries prevalence in 12-year-old children (Dental Observatory, 2001) and the absence of a fluoridated water supply. The trial population was children aged 7 to 8 yrs attending schools in the area.

Approval for the trial was secured from the Preston Research Ethics Committee and a Certificate of Trials Authorization from the Medical and Healthcare Products Regulatory Agency. Approval was also obtained from Research Governance Committees of the relevant local National Health Service organizations and school administrators (Trial Registration: ISRCTN # 72589426).

The inclusion criterion for schools was all (n = 207) state-maintained Primary Schools in East Lancashire that formally agreed to take part in the study. Schools that agreed to participate were randomized into test and reference groups by the study statistician, using computer-generated random numbers, stratified by the locality of the school and the size of the school. Data from local epidemiological surveys (Dental Observatory, 2004) demonstrate that children attending large schools have significantly higher caries experience than those attending small schools (see online Appendix). An ordered list of random group codes for all schools was produced, and only the study

statistician and the trial manager had access to these codes. Parents of children in participating schools were invited by letter to consent to their child's participation in the trial and to complete an eligibility assessment form. Once written parental consent was obtained, eligibility assessment was checked by trained examiners prior to examination. Children who refused to participate in the trial at this point were deemed not to have provided consent for the trial.

Exclusion criteria for the children included:

- a history of asthma or severe allergic reaction that required hospitalization,
- presence of fixed orthodontic appliances involving more than 4 permanent teeth,
- participation in any other clinical study during the 3 mos preceding the initial examination, and
- presence of ulcerative gingivitis/stomatitis.

One drop (0.1 mL) of Duraphat® (Colgate Oral Pharmaceuticals, New York, NY, USA) fluoride varnish *per* arch was applied to the first permanent molars 3 times a yr over a three-year period. This was a public health intervention, supplementary to children's self-care regimes and any advice or treatment provided by their family dentist. The varnish was prescribed and the first application was placed by a dentist; subsequent applications were placed by dental therapists at four-month (± 2 wks) intervals thereafter. All dentists and therapists received the same standardized varnish application training. Participants were advised not to have fluoride treatment administered by their dentist for 2 days after application of the varnish.

The primary outcome measure was DFS increment in the first permanent molars; secondary outcome measures were DFT increment and the presence or absence of caries in any of the first permanent molars. Examination was at the caries-into-dentin level according to a national diagnostic protocol (Mitropoulos *et al.*, 1992). Baseline dental examinations were carried out by eight trained and pre-calibrated dentist examiners supported by a trained dental assistant. Examiners and their assistants were given a sealed envelope containing the allocation code for the school; this was opened after all baseline examinations had been completed and the dentists made another appointment for application of the fluoride varnish in test schools. This system ensured allocation concealment and facilitated efficient delivery of the intervention. The follow-up clinical examinations were conducted at 36 mos (± 2 mos) by five trained and pre-calibrated dentist examiners using the same diagnostic protocol.

From an unpublished study conducted on children 6 to 8 yrs of age in a similar location in the North West of England, the mean three-year DFS increment in first permanent molars was 0.33 (SD 0.48). Based on the findings of the Cochrane systematic review (Marinho *et al.*, 2002), we anticipated that fluoride varnish would reduce caries in permanent teeth (DFS) by at least 25%. This would mean a reduction to 0.25 DFS in the test group (effect size 0.0825). Participating schools had an average of 33 children *per* school in the relevant birth cohort. We assumed that 50% of children would consent to take part in the trial. A sample size of 80 schools in each study group with 13 children *per* cluster (1040 children in each group, 2080 children in total) would have 90% power to detect a 25% difference in the DFS increment over 3 yrs, assuming an intra-school correlation coefficient of 0.03. This sample size allows for a 20% drop-out rate over 3 yrs.

Analyses were were confined to first permanent molar teeth using Stata Statistical Software: Release 11.1 (StataCorp, College Station, TX, USA) and were performed by the study statistician blind to the allocation. An intention-to-treat analysis was undertaken. Children who changed schools during the course of the trial were analyzed according to their randomization at baseline. Statistical methods to account for the clustering of observations within schools were used throughout. For summary statistics, overall summary scores and cluster summary scores are presented for comparison. For unadjusted and adjusted analyses of the effect of intervention, random effects models were used.

RESULTS

The trial CONSORT flow chart is presented in the Fig. Of the 207 schools in the locality, 190 (92%) agreed to participate and were randomized. A total of 6167 children attended these schools, and 3133 (50.8%) parents provided informed consent for their child to participate (a comparison of the characteristics of consenting and non-consenting children appears in the online Appendix). Recruitment took place between 27 February 2006 and 28 April 2006, and follow-up examinations between 12 January 2009 and 3 April 2009. Fifty children were ineligible because of a history of severe allergic reaction, seven children refused an examination, one parent withdrew consent, and 108 were absent from school at baseline examination. 1473 children in the test and 1494 in the reference groups had baseline examinations. Over 3 yrs, 197 (13%) and 166 (11%) children in the test and reference groups, respectively, were lost to follow-up; 1276 children in the test and 1328 in the reference groups had both baseline and follow-up examinations.

Examiners were calibrated to a benchmark examiner. For DMFT, baseline ranges were: sensitivity, 0.98 to 0.89, and specificity, 0.97 to 0.92. At outcome, ranges were: sensitivity, 0.65 to 0.94, and specificity, 1.00 to 0.99 (see online Appendix for full analyses). Table 1 compares the baseline characteristics of test and reference groups. Similar socio-demographic values, for age, gender, ethic grouping, and IMD [Index of Multiple Deprivation (Department of Communities and Local Government, 2007)], were recorded at baseline. The groups had similar caries experience in their primary dentition at baseline [median dmft = 3 (Interquartile Range [IQR] 5.5)] and in test [median dmft = 3 (IQR 6)] reference groups. Median DFS was 0 in each group at baseline, and the number with DFS = 0 was 1187/1473 (80.6%) and 1194/1494 (80%) in test and reference groups, respectively.

The median number of fluoride applications in the intervention group was 9; 902 (60.2%) children received all 9 applications, and 1342 (90%) received 6 or more applications. Table 2

Table 1. Baseline Information for Each Group at Individual and Cluster Level

		Reference				Test		
School factors at baseline								
Number of schools		95				95		
Median (Interquartile Range)		14 (8.5)				14 (10.5)		
Number of children *per* school		Min = 2, Max = 44				Min = 1, Max = 33		
Children factors at baseline								
Number of children		1588				1545		
Not eligible		94				72		
Absent		73 (77.7%)				30 (41.7%)		
Baseline exam		15 (16.0%)				35 (48.6%)		
Left school		3 (3.2%)				2 (2.8%)		
Refused no consent		-				1 (1.4%)		
Refused on day		3 (3.2%)				4 (5.6%)		
Eligible		1494 (94.1%)				1473 (95.3%)		
Mean age in yrs (SD)		8.1 (0.3)				8.0 (0.3)		
N (%) boys		740/1494 (50%)				722/1473 (49%)		
N (%) white British		1180/1494 (79%)				1124/1472 (76%)		
Median (IQR) IMD score		29.4 (31.8) n = 1485				30.7 (35.1) n = 1465		
Median (IQR) dmft		3 (6)				3 (5.5)		
Median DFS		0				0		
N DFS = 0		1194/1494 (80%)				1187/1473 (80.6%)		
Teeth (6s) unerupted or missing other by age	7 yrs	8 yrs	9 yrs	All	7 yrs	8 yrs	9 yrs	All
0	617	804	4	1425	632	776	2	1410
1	19	10	0	29	22	6	0	28
2	13	8	0	21	11	10	0	21
3	9	2	0	11	6	1	0	7
4	5	3	0	8	6	1	0	7
		Total 1494				Total 1473		

presents the summary statistics and simple effects estimates for the outcomes of the trial, and Table 3 summarizes the adjusted effect estimates with random effects models.

DFS/ DFT

Summary statistics of caries increment were similar in each arm (Table 2). Although the number of students *per* school ranged from 2 to 41, effect estimates were similar whether overall mean scores or means of cluster summaries were analyzed. Because of the abundance of zeros in the data and the high variability of outcome compared with the mean, count measures were used to analyze the effect of intervention on caries at follow-up adjusted for caries at baseline (Table 3). Random effects models were used to account for the clustering in the data. The random effects negative binomial models were the best fit to the data. Results showed that the expected incident rate of caries at follow-up was similar for the intervention and control arms. Based on the models evaluated, there was insufficient evidence of an effect of intervention on caries at follow-up for either DFS (Incidence rate ratio [IRR] = 1.07, 95%CI 0.91 to 1.26) or DFT (IRR = 1.01, 95%CI 0.88 to 1.16).

Caries at Follow-up (DMFT > 0)

The proportion of children with caries at follow-up (DMFT > 0) was similar in the intervention and control arms, with overall proportions of 28.9% in test and 27.8% in reference groups, giving a Risk Ratio of 1.04. Again, results were broadly similar when means of cluster summaries were analyzed. With a random effects logistic regression model, the odds of caries at follow-up in the test group as indicated by DMFT > 0 was 1.11 times that of the control group adjusted for baseline DMFT (OR = 1.11, 95%CI 0.89 to 1.38). There was insufficient evidence of an effect of intervention on the presence or absence of caries at follow-up.

A total of 12 children in the intervention group reported adverse reactions over the duration of the trial (see full details in online Appendix). All adverse reactions were self-limiting, and four children were withdrawn from the trial as a precautionary measure because of mild adverse reactions.

DISCUSSION

We conducted this trial to evaluate the effectiveness of fluoride varnish as a public health intervention delivered in schools. The trial participants were recruited from a deprived high-risk caries population in the UK; a local 2001 survey reported a mean DMFT of 1.26 and caries prevalence of 49% in 12-year-olds (Dental Observatory, 2001). More than 60% of the test group received all 9 applications, and over 90% received 6 or more applications. There was a small number of minor, adverse reactions reported; however, we could find no evidence of a caries-preventive effect in the first permanent molars.

Table 2. Outcomes of Fluoride Varnish Trial - Summary Statistics and Simple Effect Estimates

	Reference	Test	Effect Estimates[a]
Number of clusters			
Enrolled and eligible	95	95	
Followed up after 3 yrs	95	94	
Number of children			
Enrolled and eligible	1494	1473	
Followed up after 3 yrs	1328	1276	
Total DFS increment[b]			
Zero increment	963/1320	910/1270	1873/2590
Overall mean score (SD)	0.67 (2.10)	0.65 (2.15)	–0.02
Mean of cluster summaries (SD)	0.63 (0.66)	0.66 (0.73)	0.03 (–0.17 to 0.23)
Total DFT increment[c]			
Zero increment	970/1320	916/1270	
Overall mean score (SD)	0.35 (0.90)	0.36 (0.91)	0.01
Mean of cluster summaries (SD)	0.33 (0.30)	0.36 (0.35)	0.03 (–0.06 to 0.13)
Caries at follow-up (DMFT)[d] (Present/absent)			
DMFT > 0	369/1327	369/1276	
Overall proportion DMFT > 0	27.8%	28.9%	RR = 1.04
Mean of cluster proportions (SD) DMFT > 0	26.6% (16.2)	28.2% (14.4)	RR = 1.06 (0.90 to 1.26)

[a]Mean difference for continuous outcomes, risk ratio for dichotomous outcomes.
[b]Total DFS increment.
2604 children eligible for analysis (A n = 1328, B n = 1276). A (n = 1320): seven children excluded with all 4 teeth missing at baseline, one child excluded crown on all 4 teeth at follow-up. B (n = 1270): six children excluded all 4 teeth missing at baseline. 189 clusters, 2590 children. Min, 14; Max, 20.
[c]Total DFT increment.
2604 children eligible for analysis (A n = 1328, B n = 1276). A (n = 1320): seven children excluded with all 4 teeth missing at baseline, one child excluded crown on all 4 teeth at follow-up. B (n = 1270): six children excluded all 4 teeth missing at baseline. 189 clusters, 2590 children. Min, 3; Max, 4.
[d]DMFT at follow-up.
2604 children eligible for analysis (A n = 1328, B n = 1276). A (n = 1327): one child excluded crown on all 4 teeth at follow-up. B (n = 1276): 189 clusters, 2603 children.

Table 3. Outcomes of Fluoride Varnish Trial: Adjusted Effect Estimates (Incidence rate ratios and Odds ratios) Using Random Effects Models

	Effect Estimates
DFS Follow-up	
Random effects (Beta) negative binomial regression (adjusting for baseline DFS)	IRR 1.07 (0.91 to 1.26)
Random effects (Beta) negative binomial regression (adjusting for baseline DFS and age)	IRR 1.07 (0.91 to 1.26)
DFT Follow-up	
Random effects (Beta) negative binomial regression (adjusting for baseline DFT)	IRR 1.01 (0.88 to 1.16)
Random effects (Beta) negative binomial regression (adjusting for baseline DFT and age)	IRR 1.01 (0.88 to 1.16)
DMFT follow-up (Present/Absent)	
Random effects logistic regression (adjusting for baseline DMFT)	OR = 1.11 (0.89 to 1.38) Rho = 0.03
Random effects logistic regression (adjusting for baseline DMFT and age)	OR = 1.11 (0.89 to 1.39) Rho = 0.03

This pragmatic trial was undertaken according to UK regulations for clinical trials of investigative medicinal products (House of Commons, 2004) and according to Good Clinical Practice guidelines (IHC, 2002). A cluster design was used, which increases the risk of selection bias; if participants have prior knowledge of the allocation, they may decline to participate; however, neither schools nor participants knew about the allocation before recruitment or completion of baseline assessments, and no school withdrew after the allocation. Covariates (baseline DMFT and age) were included in the analyses to increase the precision of the effect estimate through a postulated strong relationship with the outcome. In comparison of the crude (Table 2) with the adjusted models (Table 3), the effect estimate of the intervention was very similar, so there is little evidence of effect modification. A 'no intervention' control was used, and there was adequate blinding of outcome examiners. The expected caries increment used in the power calculation was exceeded. Both school and participant recruitment targets

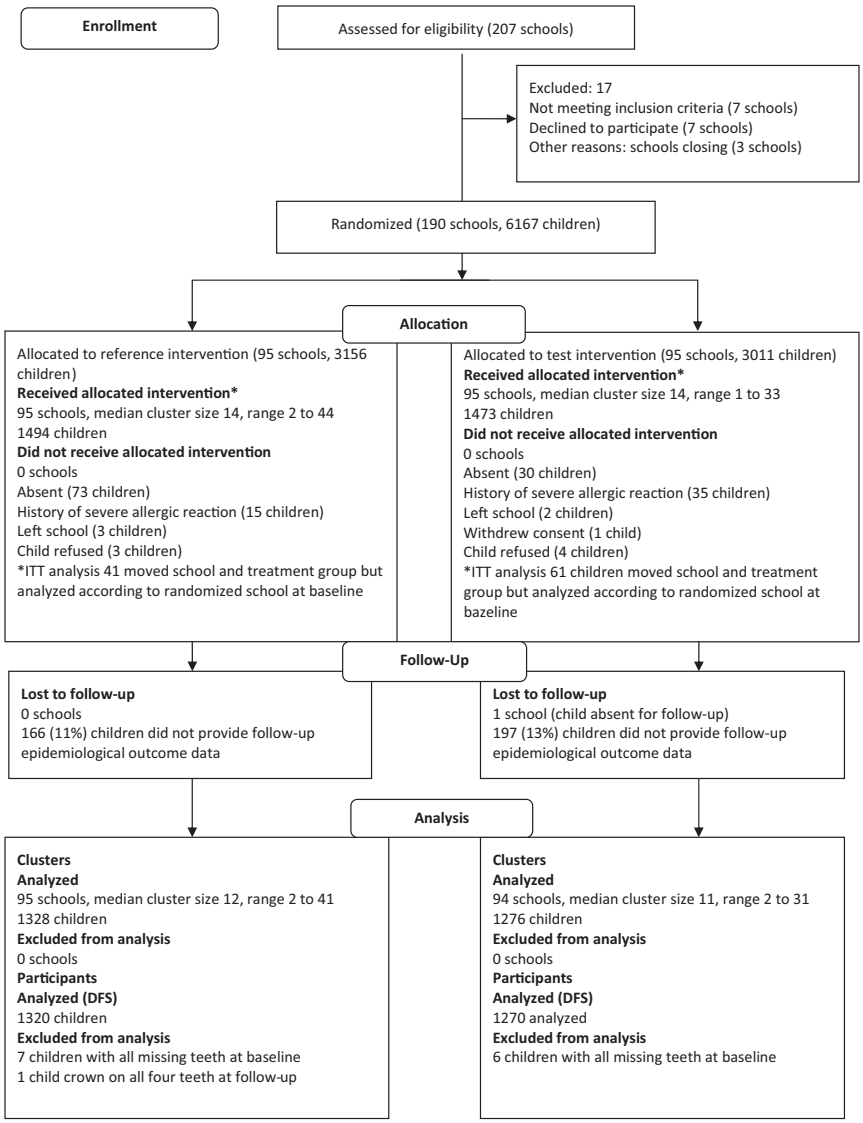

Figure. CONSORT flow diagram.

were hit, and we report a lower-than-anticipated loss to follow-up. Therefore, the trial was adequately powered to detect the effect size estimated by the systematic review (Marinho *et al*., 2002). The trial was not powered to undertake a subgroup analysis of the impact of the intervention on inequalities in dental caries experience, and this was not part of the protocol. However, a descriptive, hypothesis-generating analysis was undertaken to calculate caries scores by quintiles of deprivation, and this is presented in the online Appendix. The potential effect size suggests that very large numbers would be required to investigate the intervention, even in high-risk populations.

The findings of this trial are at odds with the findings of the Cochrane systematic review (Marinho *et al*., 2002). The review includes small, older efficacy studies, all of which had a risk of bias due to questionable allocation concealment. All of the studies were conducted at a time and/or place when and/or where there was less exposure to fluoride through widespread use of dentifrice. Our findings are in agreement with a smaller scale cluster RCT of fluoride varnish conducted in the North West of England (Hardman et al., 2007), which reported no preventive effect in the permanent dentition of children aged 6 to 8 yrs who were followed up for 2 yrs (5 applications). The authors attributed their failure to demonstrate an effect to low consent rates and a lower-than-expected caries increment. We report higher caries increments than the estimate used in our power calculation, and although only 50% of parents provided consent, the socio-economic profiles of consenting and non-consenting children were very similar, suggesting that our findings have good external validity (see online Appendix). This was a pragmatic trial, and although providing consent for a trial is different from providing consent for a public health program, it is obvious that low consent rates reduce the effectiveness of public health interventions (Splieth *et al*., 2005).

This trial has implications for public health planners. Studies have demonstrated statistically significant (but not necessarily clinically significant) reductions in caries in the primary dentition in high-risk populations (Lawrence *et al.*, 2008; Slade *et al*., 2011). However, a recent trial (Tagliaferro *et al*., 2011) was unable to demonstrate an effect in the permanent dentition in high-risk populations. Based on the results of the systematic review (Marinho *et al.*, 2002) alone, school varnish programs are likely to be implemented without rigorous evaluation, but the findings of this trial suggest that programs to prevent caries in the permanent dentition are not an efficient use of resources.

The results highlight the need for careful interpretation of the findings of systematic reviews of fluoride interventions. It is questionable whether the treatment benefits of topical fluoride evidenced in trials undertaken in high-caries populations with relatively low fluoride exposure will be seen in trials with participants with frequent exposure to fluoride. This variation in fluoride exposure is a possible cause of clinical heterogeneity in meta-analyses (Marinho *et al*., 2002), and subgroup analysis according to caries prevalence may be a sensible approach to take in future systematic reviews. Public health planners must therefore look beneath the 'headline effect' size of reviews before deciding to fund public health programs.

In conclusion, we could find no evidence of a caries-preventive benefit of 22,600 ppm fluoride varnish applied to the first permanent molar teeth in the school setting.

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