Community Dent Oral Epidemiol 2008; 36: 503–516

Community Dentistry and Oral Epidemiology

A 2-year community-randomized controlled trial of fluoride varnish to prevent early childhood caries in Aboriginal children

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Lawrence HP, Binguis D, Douglas J, McKeown L, Switzer B, Figueiredo R, Laporte A. A 2-year community-randomized controlled trial of fluoride varnish to prevent early childhood caries in Aboriginal children. Community Dent Oral Epidemiol 2008; 36: 503–516. © 2008 The Authors. Journal compilation © 2008 Blackwell Munksgaard

Abstract – *Objective:* To measure the effectiveness of fluoride varnish (FV) (Duraflor®, 5% sodium fluoride, Pharmascience Inc., Montréal, QC, Canada) and caregiver counseling in preventing early childhood caries (ECC) in Aboriginal children in a 2-year community-randomized controlled trial. *Methods:* Twenty First Nations communities in the Sioux Lookout Zone (SLZ), Northwest Ontario, Canada were randomized to two study groups. All caregivers received oral health counseling, while children in one group received FV twice per year and the controls received no varnish. A total of 1275, 6 months to 5-year-old children from the SLZ communities were enrolled. In addition, a convenience sample of 150 primarily non-Aboriginal children of the same age were recruited from the neighboring community of Thunder Bay and used as comparisons. Longitudinal examinations for the dmft/s indices were conducted by calibrated hygienists in 2003, 2004 and 2005. *Results:* Aboriginal children living in the SLZ or in Thunder Bay had significantly higher caries prevalence and severity than non-Aboriginal children in Thunder Bay. FV treatment conferred an 18% reduction in the 2-year mean 'net' dmfs increment for Aboriginal children and a 25% reduction for all children, using cluster analysis to adjust for the intra-cluster correlation among children in the same community. Adjusted odds ratio for caries incidence was 1.96 times higher in the controls than in the FV group (95% CI = 1.08–3.56; $P = 0.027$). For those caries-free at baseline, the number (of children) needed to treat (NNT) equaled 7.4. *Conclusions:* Findings support the use of FV at least twice per year, in conjunction with caregiver counseling, to prevent ECC, reduce caries increment and oral health inequalities between young Aboriginal and non-Aboriginal children.

Key words: cluster analysis; dental caries; First Nations (Ojibwa); preschool child; randomized controlled trials; topical fluorides

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Submitted 1 August 2007;
accepted 12 October 2007

It is now widely recognized that oral health is an important part of overall health and well-being and we, as dental professionals, can be proud of how far we have come in enhancing the oral health of both adults and children. Yet in Canada, a segment of our society has been left behind. Canadian Aboriginal children experience far greater prevalence and severity of oral diseases than young non-Aboriginal Canadians. Recently conducted oral health surveys have found that the dental caries burden experienced by preschool aged Aboriginals ranged from 51% to 98%, with a mean d(e/m)ft of 3.1 to 13.7, depending on the communities studied (1–4). Whereas national data gathered via proxy interviews with parents or guardians, as part of the 2002–03 First Nations Regional Longitudinal Health Survey, showed that 29% of 3–5-year-olds were affected by early childhood caries (ECC) and 67% of those were treated for the disease (5). At present, ECC is a public health problem reaching endemic proportions in Canada, sometimes affecting Aboriginal children as young as 6–12 months of age. As these children gain their full complement of primary teeth, their dental problems can become so severe that full mouth rehabilitation, including stainless steel crown restorations and extractions, must be performed under general anesthesia (GA) at hospitals, often a flight away from their communities, where access to operating room services can require long wait times (2), and result in heavy costs to the Federal government's health care budget (6, 7).

Since the mid-1990s, a strategic preventive effort has been underway in the 28 First Nations communities of the Sioux Lookout Zone (SLZ), located in Northwest Ontario, to reduce the number of young children receiving GA dental treatment for ECC. This community-based oral health promotion program operates in conjunction with the Woman and Child Community Nutrition Program and is delivered to prenatal women and new mothers by community-based nutrition educators (2). The program underwent an evaluation in 2001–02 and while it was found to improve caregivers' knowledge of ECC and children's oral hygiene and body mass index, the program did not eliminate the demand for dental services under GA, but simply delayed rehabilitative dental surgery (2). The program evaluation called for a combination of preventive and health promotion strategies to be implemented to assist in reducing ECC and the backlog for pediatric dental surgery.

One of the most promising preventive strategies recommended for children younger than 6 years of age is the periodic application of fluoride varnish (FV). Interest in the use of FV for inhibiting caries in primary teeth has increased in recent years because of the attractive safety properties of varnishes as compared with gels, foams and solutions (8, 9). Of all the professionally applied topical fluoride methods, FV is the most practical for this age cohort; the varnish applications take less time (oral prophylaxis prior to application is not required), create less patient discomfort and achieve greater patient acceptability than fluoride gels (10), foams and rinses. The varnish costs are minimal with the major expense being for the personnel needed to apply it. When dental services utilization rates are high, cost savings can be achieved if the varnish programs are carried out by dental hygienists and dental therapists together with primary health care providers, such as public health nurses, physicians' assistants, community health promoters who are trained to administer the varnish (11, 12).

While the evidence for the benefit of applying FV to permanent teeth is generally very positive, the caries-inhibiting effect of FVs on primary teeth is still being studied. Pooling the results from three trials of the effectiveness of FV on primary teeth (13–15), Marinho et al.'s meta-analysis yielded a d(e/m)fs prevented fraction (PF) of 0.33 (33%) of semiannual applications of different FVs versus placebo/no-treatment (16). On the other hand, two systematic reviews of clinical trials conducted in the primary dentition suggested inconclusive evidence for an anti-caries effect of FV in the primary dentition (17, 18). However, the methodological quality of the studies included in these two reviews varied significantly and most were not randomized controlled trials (19–22). Other studies have looked at caries progression and caries incidence rather than caries increment. Peyron et al. examined the progression of approximal caries over a 2-year period in primary molars of preschool children participating in the City of Malmö Study (1977–85) who were treated semiannually with a 5% sodium fluoride (NaF) varnish – Duraphat (Colgate Oral Pharmaceuticals Inc., a subsidiary of Colgate-Palmolive Co., Canton, MA, USA) (23). After 2 years, 66.7% of the caries lesions in the Duraphat group and 91.2% in the control group showed progression using a radiographic scoring system (27% reduction). A study in Head Start schools in Florida evaluated the effect of Duraphat applied twice in 9 months and found statistically significant reductions in the rate of new lesions and the reversal of enamel lesions (24). A 30-month caries trial found that an annual application of a 38% silver diamine fluoride solution was more effective in arresting dentin caries in the anterior upper teeth of high-caries-risk Chinese preschoolers than the application of a 5% NaF varnish at 3-month intervals or placebo (25).

Two randomized clinical trials of FVs in young children have just been published in the last year. One trial assessed the efficacy of Duraphat added to caregiver counseling to prevent the incidence of ECC in caries-free children from low-income Chinese and Hispanic families living in San Francisco and found a dose–response effect regarding caries incidence odds ratios (OR) (26). The second trial, carried out by a German group, involved high-caries-risk preschool children and sought to determine the caries inhibition effect of semiannual applications of two FVs versus no treatment (27). Caries reductions were in the mid-50% range and both varnishes were deemed suitable for intensive group prevention programs for preschool children.

Our study was designed to measure the effectiveness, safety, practicality and cost of a FV preventive intervention in a high-caries-risk population. Primary health care initiatives are desperately needed to respond to the critical disparities in children's oral health in Canada and evidence of the effectiveness of particular fluoride interventions will assist decision makers in developing programs that address the problem of ECC in Aboriginal populations.

Materials and methods

Trial design and participants

The trial used a cluster randomization design for comparing the effectiveness of FV in conjunction with caregiver counseling and counseling alone to prevent and reduce ECC in Aboriginal children. The trial took place in the SLZ, an area one-third the size of the province (1.5 times the size of the United Kingdom or approximately the same size as Germany) and home to 28 Ojibway-Cree First Nations communities/reserves with a population of ~25 000 people (Fig. 1). Seventy percent of the communities are only accessible by air and none of the communities have fluoridated water supplies.

All of the SLZ communities were eligible to participate in the study, and from the 28, 20 were randomly selected to take part in the study. The researcher sought community involvement in the study by making presentations to the Nishnawbe Aski Nation Health Planning Group and to the SLZ Health Program Managers, physicians and public health nurses. Community leaders were then consulted and all agreed to participate, but each requested that the results not be presented by community in any reports or publications that grew out of the study. All publications, including this paper, followed the CONSORT statement relating to improving the quality of reports of cluster-randomized trials (28, 29).

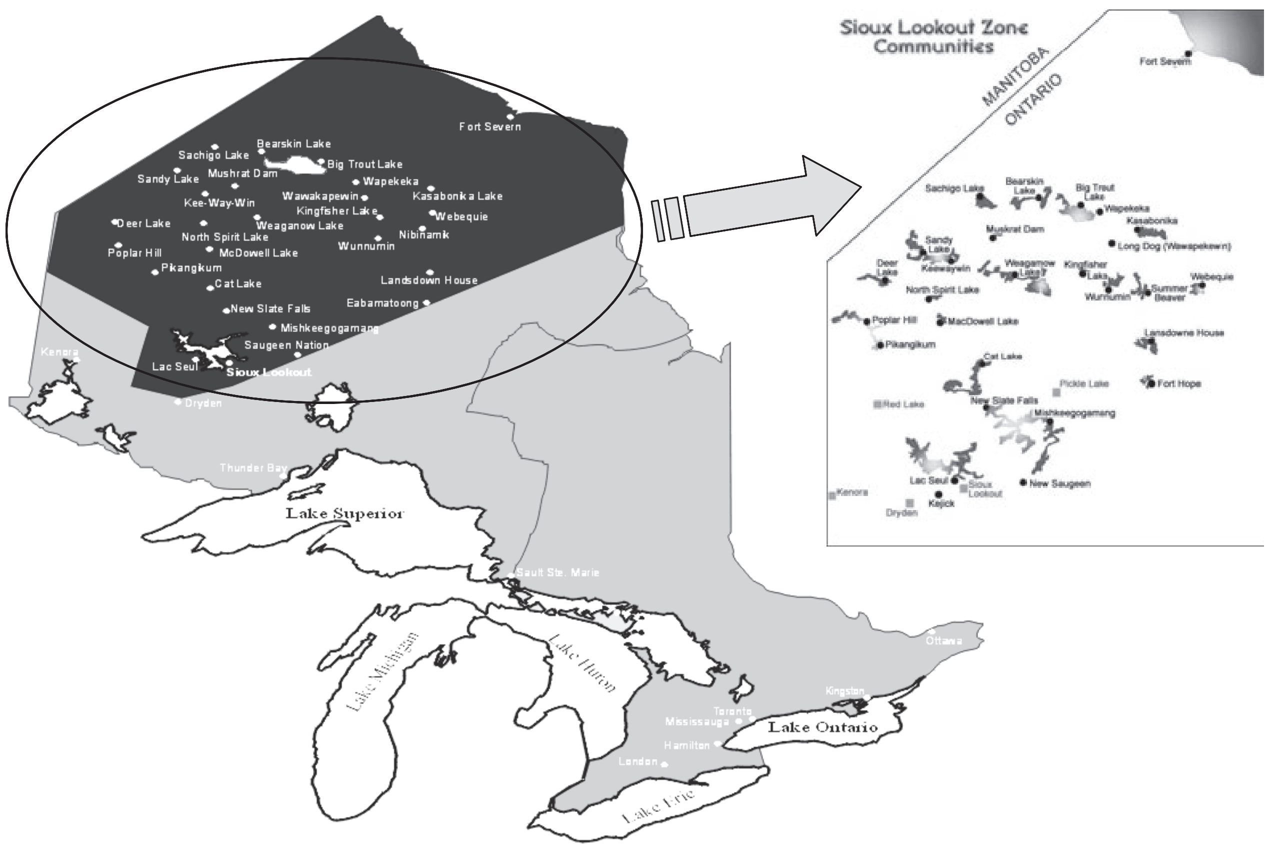

Fig. 1. Map of the Sioux Lookout Zone (SLZ), Ontario.

Inclusion criteria for children were: aged 6 months to 5 years; with at least one primary tooth present; residing in one of the First Nations communities in the SLZ; and a parent, legal guardian or family member who was the primary caregiver providing signed informed consent. Children were excluded if they had no teeth present, stainless steel crowns only, ulcerative gingivitis, stomatitis or allergy to the varnish's colophony component (30–32).

Because of our interest in comparing the oral health of young Aboriginals with a population of non-Aboriginal children, a convenience sample of non-Aboriginal children ($n = 150$) was recruited from eight childcare centers in the Thunder Bay District and its neighboring regions in Northwest Ontario, as well as through 'request for volunteers' advertisements in the local newspapers. This group of children received the FV applications at the same frequency as those in the SLZ.

Interventions

Fluoride varnish

The preventive treatment was Duraflor® (Pharmascience Inc., Montréal, QC, Canada), a 5% w/v sodium FV, i.e. 1 ml of the varnish contains 50 mg NaF, equivalent to 22.6 mg fluoride ion in an alcohol-based suspension of colophonium resin, of which between 0.3 and 0.5 ml (2–5 drops) is applied to the full primary dentition. The product is dispensed in 10 ml tubes. Dental hygienists applied the varnish using a standard method of application as per the policy and procedure manual specifically created for this trial. Teeth were not dried and plastic disposable microbrushes were used to apply varnish to all surfaces of fully erupted or partially erupted teeth, whether they were carious or not. The parents/caregivers received a pamphlet with post fluoride application instructions as well as a 'frequently asked questions' sheet about FV treatments. The frequency of applications was at baseline and at 6-month intervals over a 24-month timeframe (altogether there were four applications with the fifth application at the 24-month assessment not included in the effectiveness analyses). Given the isolation of the First Nations communities, it was decided at the outset of the study to increase the frequency of study visits to every 4 months/year to each community to ensure that participants would receive at least two varnish applications per year.

Caregiver counseling

The primary caregivers of the children in both groups were counseled individually by the dental hygienist examiners (community dental assistants served as translators when necessary) during the baseline, 12- and 24-month follow-up visits on dental habits that help to prevent tooth decay and promote good oral health in children. The oral health education messages followed those found in the Ontario Ministry of Health and Long-Term Care, Early Years Program's recommendations contained in the fact sheet entitled 'Are baby teeth important?' for children from birth to age 5 (33). Children also received toothbrushes for the duration of the study.

Recruitment and randomization

The interventions were targeted at the cluster level, i.e. the study used both cluster sampling and cluster randomization. Specifically, the clusters were the 20 randomly selected SLZ communities and the unit of randomization was the community itself with all eligible participants in each community receiving the same intervention.

Once the 20 communities confirmed their participation, band lists were obtained from the health authorities and were used to identify children eligible for the study. The parents or primary caregivers of all eligible children were contacted by staff not directly involved in the research and those who agreed to participate were asked to sign a consent form, which was explained to the caregiver by research interviewers proficient in both Ojibway and English. After consent was obtained, a study examiner conducted an oral examination on each child and confirmed that the potential participant met the entry criteria.

A randomization master list, based on computer-generated random numbers, assigned each community to a group (i.e. 'treatment' or 'no-treatment' control). The 'treatment' consisted of FV two times per year with caregiver counseling while the 'no-treatment' controls received counseling alone. The designation 'no treatment' was used only with respect to the varnish and not to other dental procedures that the children received as part of their standard care, such as dental treatment under GA.

Ethics

The study protocol was approved by the University of Toronto Health Sciences I Research Ethics Board (REB) and Health Canada's REB. Annual progress reports were submitted and reviewed by the REBs and annual renewals of Ethics approval were granted.

Oral examinations and interviews

The baseline and follow-up study visits at 12 and 24 months involved a full-mouth oral examination of all tooth surfaces and soft tissues using the National Institute of Dental and Craniofacial Research's caries scoring system and diagnostic criteria for ECC (34). Examiner calibration sessions were performed on 8–10 volunteers over a 1.5-day period in the SLZ Dental Department (Sioux Lookout, ON, Canada) for the SLZ sites and in the dental office of Dr M. Bloom for the Thunder Bay sites immediately before the three waves of data collection began. Dental hygienists were calibrated against a gold standard dentist examiner in the use of the dmft/s indices using plane mouth mirrors and explorers. The explorer served to remove plaque and debris and check the surface characteristics of suspected carious lesions. Carious lesions were recorded either at the precavitated (d_1) or the cavitated (d_3) visual level of dentinal involvement and abscessed teeth were referred for treatment. Radiographs were not used. Kappa values for inter-examiner agreement ranged from 0.61 to 0.8 in all survey years, indicating substantial or good agreement (35).

In addition, data on child's demographics and dental history, oral hygiene and use of other modes of fluoride delivery, oral signs and symptoms of dental problems, oral-health-related impacts on the child's and family's quality of life, general health status and adverse events, as well as caregiver's socio-demographics were collected using structured, interviewed questionnaires with the caregiver.

Six teams of dental hygienists and recorders were flown into the participating communities for an average stay of 10 days (range 3–14 days) to carry out the oral examinations and interviews. Different examiners were sent to different communities each year to keep them masked to the community's treatment assignment. Most examinations and interviews were conducted at Health Canada's nursing stations in fully equipped dental clinics and the teams were assisted by local dental assistants. The examinations were carried out with the child in a supine position or on the lap of the caregiver, knee-to-knee with the dental examiner, if the child was too young to sit on the dental chair. In the last study visit, a few children were examined in their schools and caregiver interviews were conducted at the child's home or over the telephone. Local radio broadcasts were used to remind caregivers of their children's appointments. Posters, pamphlets and displays at health fairs were created to promote the project and were used along with media promotions to raise the level of awareness about ECC and the means to prevent it. The project has a logo and a slogan 'Baby teeth – Keep them beautiful with fluoride varnish.

The participating study sites in the Thunder Bay area were visited by two teams of calibrated dental hygienists and recorders who examined the children in a dentist's office. Occasionally, children were examined and received their FV applications in childcare centers.

Outcomes

The primary outcome was the 2-year caries increment, as measured by change from baseline in the decayed, missing and filled surface (dmfs) index, in all primary teeth erupted at start and erupting over the course of the study. The caries increment at the tooth level (dmft) and the caries incidence (new dmfs ≥1) over 24 months were also computed. Caries increment was counted if the surface status changed from 'sound, white spots or filled at baseline' to 'clinical caries', 'missing due to carious extraction' or stainless steel crown at the follow-up examination. Caries reversals ('white spots'/early demineralization to sound) were subtracted from the caries increment, creating a 'net' caries increment. Anterior or posterior teeth missing due to carious extractions were counted as five surfaces missing in the dmfs index. If the reason for missing teeth could not be established, the teeth were considered as missing due to caries. Similarly, primary teeth with stainless steel crowns were counted as five surfaces affected, whether they could or could not be confirmed as being placed to restore caries. The focus of this trial was on primary teeth, so in instances of erupted permanent teeth, these were scored separately from the caries measures.

Treatment effect was measured using the PF, or percent reduction in caries increment resulting from the intervention, and the number (of children) needed to treat (NNT) to prevent one child from developing caries (net dmfs ≥1). The caries incidence (proportion of children developing new caries) in the FV group and the incidence in the control group were compared using the OR, adjusted for the intra-cluster (community) correlation.

The secondary outcomes were the need for GA dental treatment, the oral-health-related quality of life score (includes dental pain/discomfort), the cost of FV treatment, the acceptability of the preventive treatment and any side effects. These data were collected via the structured, interviewed questionnaires with the caregivers (and from reviews of administrative data of records of GA dental procedures) and the results for these outcomes will be reported in future publications.

Sample size

The calculation of the sample size was based on a mean dmft increment in the children in the SLZ receiving standard care plus caregiver counseling of 3.5 (2), a common SD of 2 and a hypothesized minimum 20% treatment effect (0.7 difference). Assuming approximately (mean cluster size) 40 eligible children per community, the sample size was increased by a factor of 2 to adjust for the clustering effect (1 + #children in community or average size of each cluster of 40 − 1 × small intra-cluster correlation coefficient (ICC) of 0.025) (36). Thus, the number of communities required for randomization to obtain 80% power at $\alpha = 0.05$ (two-sample *t*-test, two-sided) for detecting a mean difference in dmft of 0.7 was 6.4 (or 256 subjects per group). In practice, at least eight communities were randomly assigned per intervention group to adjust for the anticipated 30–35% attrition in 2 years (2). As a result of an increase in funding, we were able to further increase the number of communities to be enrolled in the FV group using the formula $k_2 = 1/2k(1 + Q)$, where $k = 8$ clusters per group under equal allocation ($Q = 1$) and we selected an allocation ratio of 2 ($Q = 2$) which yielded 12 communities in the experimental group and eight communities in the control group (36).

Statistical methods

For the primary outcome analysis, the net dmfs increment in the FV and control communities were analysed in the 'intent-to-treat' (ITT) population at the last postrandomization visit (24 months) using cluster-specific methods (37). Initially planned subgroup analyses were performed for age and Aboriginal status and for children with different levels of caries experience at baseline.

Adjustment for confounders were achieved with the generalized estimating equation (GEE) marginal regression modeling approach (37), assuming exchangeable correlation structure (i.e. responses of cluster members are equally correlated), and using logit link for binomial data to construct an extension of standard logistic regression which adjusted for the effect of community clustering. For continuous data outcomes, GEE was used with identity link to build extensions of multiple linear regressions, without and with adjustment for covariates, which included child's age, total dmft and number of precavitated decayed surfaces at baseline, and length of follow-up. Potential confounders controlled for in the model evaluating caries incidence over 2 years included: socio-demographic variables (e.g. caregiver's education, child's age and sex, number of children living in the home), background exposure to other fluoride sources, if any, number of erupted teeth and caries experience at baseline. The main explanatory variable was the intervention group (FV plus counseling group or counseling only group).

The statistical analyses of treatment effectiveness identified above were also performed in the 'per-protocol' population, i.e. children who received the assigned treatment throughout the study and did not deviate from the protocol in any significant way that could have affected the results.

All statistical hypothesis tests were performed with two-sided, type I error level of $\alpha = 0.05$. Data analyses were carried out using SPSS (Version 14.0, SPSS Inc., Chicago, IL, USA) and Stata (Release 9, StataCorp, College Station, TX, USA).

Results

Enrollment and retention

The study enrolled 1275 children from the 20 SLZ communities between August 2003 and February 2004 (Fig. 2). The first follow-up examinations occurred 12 months from baseline. The 24-month follow-up examinations were completed in December 2005. At the final, 24-month follow-up, 952 children were seen, representing a 75% retention rate (no community dropped out of the study). The drop-out rates of study participants did not differ between groups. ITT analysis was carried out for 1146 children who completed either the 12- or 24-month follow-up visits. However, only a small percentage of children (194/1146) had just 1-year of follow-up.

Baseline data

The groups in the SLZ were comparable with respect to child's age and sex distributions, and caregiver's age and educational level (Table 1).

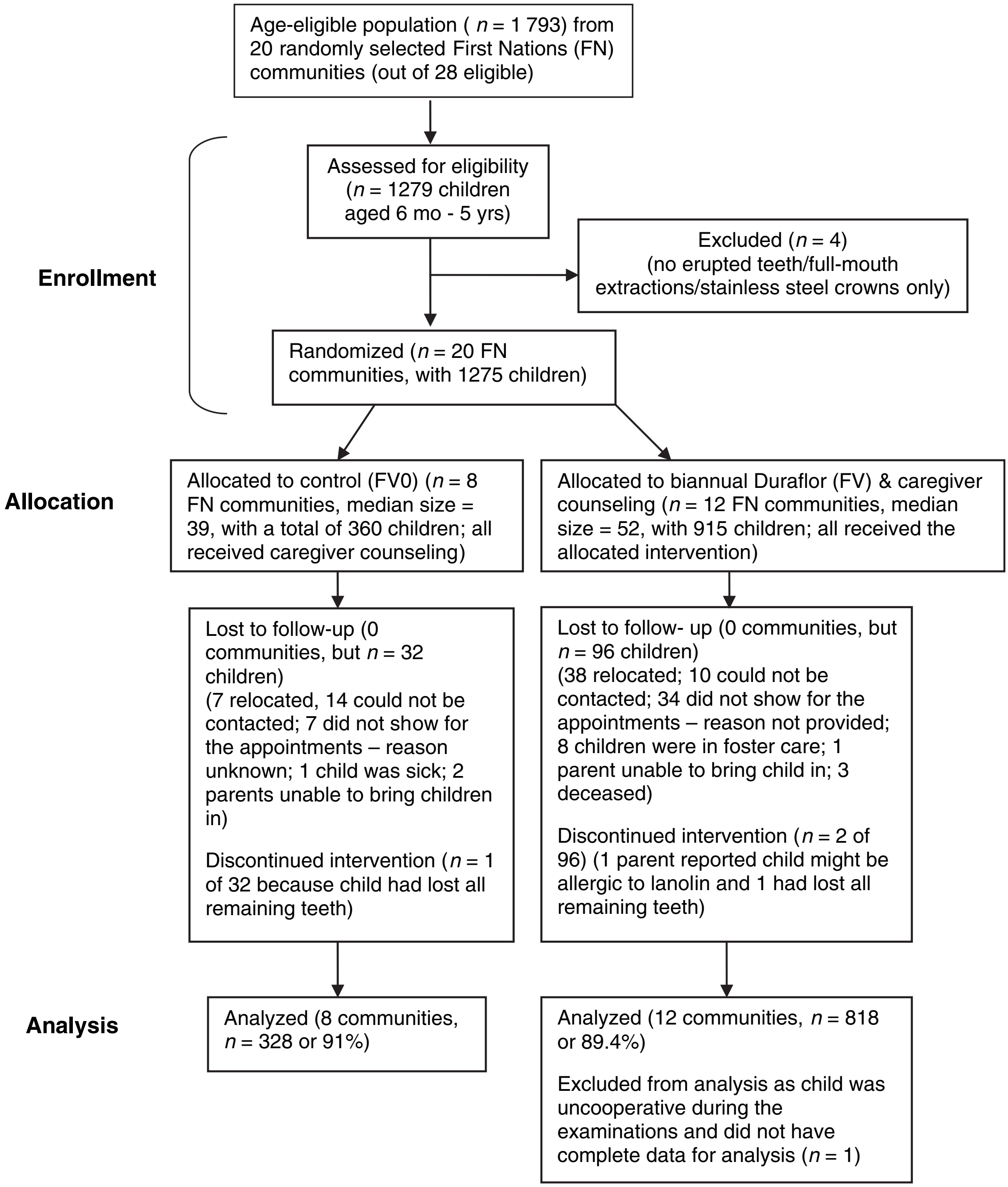

Fig. 2. Flow diagram of the progress of First Nations communities and participants in the Sioux Lookout Zone (SLZ) through the phases of the randomized controlled trial.

Despite the randomization process, some of the larger communities were assigned to the FV intervention group, but chi-square analysis revealed no significant difference between the two groups in the distribution of communities by size. No other randomization imbalances were apparent.

As noted above, a sample of primarily non-Aboriginal children of the same age and gender distributions as those in the SLZ was recruited from Thunder Bay. A total of 102 of 150 children enrolled received periodic FV applications and were seen at the last follow-up (Table 1). Overall, caregivers in Thunder Bay were older, had a higher level of education and fewer off-spring than those in the neighboring Aboriginal communities. The majority of children in this Thunder Bay sample were caries-free at baseline (84%) with mean dmft of one, whereas the mean dmft at baseline in the SLZ was as high as 7, with ~71% caries prevalence (Tables 1 and 2).

Table 1. Baseline demographic and clinical characteristics of participants by group

Characteristic	Sioux Lookout Zone (SLZ) control	SLZ fluoride varnish (FV)	Thunder Bay FV[a]
No. of participating communities/sites	8	12	8
Community size[b], *n*			
Small (<500)	2	5	N/A
Medium (500–1000)	5	3	N/A
Large (>1000)	1	4	N/A
No. of children at follow-up	328/360	818/915	102/150
% Aboriginal	100%	100%	13.7%[a]
Age (years), mean ± SD[c]	2.51 ± 1.18	2.54 ± 1.23	2.62 ± 1.26
<1, *n* (%)	42 (12.8)	107 (13.1)	11 (10.8)
1	79 (24.1)	197 (24.1)	27 (26.5)
2	86 (26.2)	211 (25.8)	23 (22.5)
3	75 (22.9)	185 (22.6)	26 (25.5)
4–5	46 (14.0)	118 (14.4)	15 (14.7)
Sex, *n* (%)			
Female	172 (52.4)	408 (49.9)	49 (48.0)
Male	156 (47.6)	410 (50.1)	53 (52.0)
Caries-free (dmft[d] = 0), *n* (%)	102 (31.1)	223 (27.3)	86 (84.3)
dmft, mean ± SE[e]	6.52 ± 0.34	7.19 ± 0.22	1.07 ± 0.31
Ratio of dt/dmft (%)	4.78/6.52 (73.3)	5.31/7.19 (73.9)	0.71/1.07 (66.4)
Caregiver's age[f] (years)			
Mean ± sd[c]	28.96 ± 7.89	28.71 ± 7.94	32.58 ± 6.38
Caregiver's education level[f]			
High school or higher, *n* (%)	63/242 (26%)	106/607 (17.5%)	88/99 (88.9%)
Up to three off-spring[f], *n* (%)	184/242 (76%)	403/609 (66.2%)	91/100 (91%)

[a]Comparison sample of primarily non-Aboriginal children recruited from childcare centers in the neighboring city of Thunder Bay (n = 14 First Nations children of 102 followed for 24 months).
[b]Chi-squared statistic = 2.90, d.f. = 2, P = 0.234.
[c]SD = standard deviation.
[d]dmft = number of cavitated decayed, missing or filled primary teeth (including stainless steel crowns).
[e]SE = standard error.
[f]Limited to the caregivers who completed the questionnaire.

Table 2. Comparison of baseline oral health status measures of study groups in the Sioux Lookout Zone First Nations communities

Oral health measure	Sioux Lookout Zone (SLZ) control, *n* = 328	SLZ fluoride varnish (FV), *n* = 818	*P*-value[a]
Mean ± SE			
dt	4.78 ± 0.29	5.31 ± 0.18	0.636
mt	1.13 ± 0.15	1.33 ± 0.11	0.465
ft	0.04 ± 0.01	0.04 ± 0.02	0.779
Stainless steel crown (SSC)	0.56 ± 0.11	0.51 ± 0.06	0.684
dmft[b] (including SSC)	6.52 ± 0.34	7.19 ± 0.22	0.817
dfs[c]	11.80 ± 0.90	12.89 ± 0.56	0.486
Cavitated ds	11.73 ± 0.90	12.82 ± 0.56	0.462
Precavitated ds	3.21 ± 0.38	1.33 ± 0.09	0.041
fs	0.06 ± 0.02	0.07 ± 0.03	0.782
No. (%)			
With caries experience (dmft[b] > 0)	226 (68.9)	595 (72.7)	0.510
With 3 + dmft	202 (61.6)	539 (65.9)	0.752
With dental abscess	20 (6.1)	54 (6.6)	0.955
With dental trauma	4 (1.2)	9 (1.1)	0.946

[a]Adjusted for the intra-cluster (community) correlation using the generalized estimating equations (GEE) marginal regression modeling approach.
[b]dmft = number of cavitated decayed, missing or filled primary teeth.
[c]dfs = number of cavitated decayed or filled surfaces on primary teeth.

Table 3. Mean 'net' dmfs increment over 2 years and the caries preventive effect of fluoride varnish in primary teeth by aboriginal status, age and caries risk

	Caregiver counseling (FV0)		Fluoride varnish (FV) and counseling		Adjusted difference[a]		Prevented fraction (PF)
	n	Mean	n	Mean	Mean ± SE[a]	P-value[a]	%
Intent-to-treat (ITT) population							
Aboriginal only	328	13.47 ± 0.90	832	11.00 ± 0.50	−2.80 ± 2.11	0.184	18.3
Age group (year)							
0–1	121	11.18 ± 1.28	342	8.09 ± 0.57	−3.91 ± 2.39	0.101	27.6
2–3	161	16.60 ± 1.38	445	13.55 ± 0.76	−3.73 ± 3.01	0.215	18.4
4–5	46	8.52 ± 2.24	133	4.22 ± 1.02	−4.37 ± 1.78	0.014	50.5
Caries risk (dfs[b])							
0	126	6.08 ± 0.84	354	4.30 ± 0.45	−1.69 ± 1.26	0.180	29.3
1–4	48	11.67 ± 1.85	119	10.28 ± 1.29	−1.33 ± 3.11	0.669	11.9
5+	154	20.08 ± 1.51	447	14.79 ± 0.74	−5.15 ± 3.76	0.171	26.3
All children	328	13.47 ± 0.90	920	10.17 ± 0.46	−4.04 ± 2.23	0.070	24.5
Adjusted means[c]							
Aboriginal only	328	13.48 ± 0.83	832	11.00 ± 0.52	−2.39 ± 2.04	0.241	18.4
All children	328	13.31 ± 0.81	920	10.23 ± 0.48	−3.68 ± 2.35	0.116	23.1
As per protocol (1)[d]							
All children	328	13.47 ± 0.90	801	10.08 ± 0.50	−4.11 ± 2.26	0.069	25.2
As per protocol (2)[e]							
All children	299	13.96 ± 0.95	740	10.42 ± 0.52	−4.35 ± 2.40	0.070	25.4

[a]Adjusted for the intra-cluster (community) correlation using the generalized estimating equations (GEE) marginal regression modeling approach.
[b]Number of cavitated decayed or filled surfaces at baseline.
[c]Adjusted for the covariates: child's age (years), total dmft and number of precavitated decayed surfaces at baseline, and length of follow-up (months).
[d](1) Participants who received four or more FV applications.
[e](2) Participants who were followed for 24 months and received four or more FV applications.

Table 4. Caries incidence and number of children needed to treat (NNT) by age, caries risk and aboriginal status

Intent-to-treat (ITT) population	Caregiver counseling (FV0)		Fluoride varnish (FV) and counseling		Adjusted odds ratio[a]		
	N	n (%)	N	n (%)	(95% CI)[a]	P-value[a]	NNT
All children	328	247 (75.3)	920	617 (67.1)	1.95 (1.07–3.57)	0.030	12.2
Age group (year)							
0–1	121	84 (69.4)	342	209 (61.1)	1.91 (0.84–4.36)	0.123	12.0
2–3	161	132 (82.0)	445	336 (75.5)	1.93 (0.91–4.10)	0.089	15.4
4–5	46	31 (67.4)	133	72 (54.1)	1.75 (1.06–2.88)	0.028	7.5
Caries risk (dfs[b])							
0	126	73 (57.9)	354	157 (44.4)	1.60 (0.86–2.98)	0.138	7.4
1–4	48	41 (85.4)	119	87 (73.1)	2.45 (0.79–7.60)	0.121	8.1
5+	154	133 (86.4)	447	373 (83.4)	1.34 (0.47–3.89)	0.567	33.3
Aboriginal only	328	247 (75.3)	832	595 (71.5)	1.38 (0.80–2.36)	0.244	26.3

[a]Adjusted for the intra-cluster (community) correlation using the generalized estimating equations (GEE) marginal regression modeling approach.
[b]Number of cavitated decayed or filled surfaces at baseline.

At the outset of the study, children in the control communities in the SLZ had, on average, two more surfaces with precavitated carious lesions ('white spots') than those in the FV communities in the SLZ (Table 2). No other significant differences were found in the baseline oral health status measures between these two groups. Similarly, comparisons of respondents to nonrespondents for baseline demographics and clinical parameters did not reveal any statistically significant differences (data not shown).

Fluoride varnish applications: compliance and safety

During the study period, the median number of FV applications per child was six and the mean was

Table 5. Logistic regression model of caries incidence over 2 years, fitted with GEE and adjusting for the cluster trial design (n = 948)

	Adjusted odds ratio	95% Confidence interval	P-value
Control versus fluoride varnish (FV)	1.96	1.08–3.56	0.027
Baseline dfs ≥5 versus 0–4	4.88	3.26–7.30	<0.001
Age group 0–2 years versus 3–5 years	1.94	1.11–3.40	0.020
Female versus male	1.14	0.89–1.46	0.307
18–24 months follow-up versus 12–18 months	1.33	0.87–2.05	0.187
Less than high school versus HS+	1.27	0.92–1.76	0.138
4 or more children versus ≤3	1.28	0.99–1.65	0.057

5.59 (95% CI: 5.48–5.70), which represents an average of three applications per year. Of the 818 children in the SLZ and 102 in Thunder Bay for whom caries increment data were analysed, only 33/920 (3.6%) received two FV applications and 86/920 (9.3%) received three applications during the 24-month trial period, while the remaining 801/920 (87.1%) received at least four or more applications over 2 years.

With one exception, that being a child who was allergic to lanolin, caregivers reported no adverse events during the study (Fig. 2).

Clinical outcomes

For the primary effectiveness variable, i.e. 'net' dmfs increment, the study found an 18.3% reduction (or PF) in the levels of ECC among First Nations children (Table 3). This percentage increased to 24.5% when non-Aboriginal children were also included in the ITT population. Adjustment for covariates did not substantially alter these PFs. There was a slight increase to 25.2% if the few participants who did not receive at least two varnish applications per year (or a total of four fluoride treatments) were removed from the 'per protocol' analysis. Furthermore, to assess the robustness of the primary outcome, 'as per protocol' analysis revealed that if those subjects who were not followed for the entire 2-year intervention period were removed from the calculations, there was only a negligible increase in the PF from 25.2% to 25.4%, thereby confirming the robustness of the estimate. The coefficient of intra-cluster correlation for primary outcome was 0.0455.

The mean net dmft increment in children assigned to the semiannual FV applications and caregiver counseling was 2.88 (±0.13 SE) and 3.49 (±0.23 SE) in the 'counseling only' group (P = 0.160). The P-values for all surface- and tooth-level estimates of treatment effect were adjusted for clustering on community or enrollment site using GEE models and both the original scale and rank-transformed data were fitted to these models; however, the primary inference was taken from the analyses of the original scale data, as the conclusions did not differ using either scale.

Significant OR (P = 0.030) were obtained when the caries incidence in the 'counseling only' group was compared with that of the FV group (Table 4). For illustrative purposes, the results were also presented as the NNT with FV to prevent one child from developing caries. These results indicated an NNT of 12 when all children were accounted for in the analysis and an NNT of 26 when only Aboriginal children were considered.

Prespecified subgroup analyses showed that the caries preventive effect of the FV treatments in primary teeth varied by child's age and caries risk at baseline (Tables 3 and 4). Noteworthy was the caries-inhibiting effect of the varnish on caries increment (PF = 29.3%) and incidence (NNT = 7.4) for children who were caries-free at baseline (Tables 3 and 4, respectively).

Logistic regression, adjusting for community, was conducted to control for confounders such as the decayed and filled surface (dfs) index at baseline, the child's age and sex, caregiver's high school education, number of children at home and the length of follow-up (Table 5). The adjusted OR for caries incidence over 2 years was almost two times higher for the participants in the control group than those in the varnish group. Besides the intervention, the child's age and baseline caries level were significant predictors of caries incidence.

Discussion

This study found that FV, along with caregiver counseling, reduced levels of ECC among this high-caries-risk population. The varnish promoted the remineralization of precavitated caries lesions and significantly reduced caries incidence by nearly two times in the overall study population. Remarkably high levels of decay and 'white-spot' lesions were found in the Aboriginal children, even at very young ages, which were disproportionately higher than those of non-Aboriginals of the same age. Comparisons between the convenience sample of non-Aboriginal children and the Aboriginal participants should be interpreted with some caution due to the different sampling strategies employed. However, comparable oral health inequalities among indigenous and nonindigenous children were found in Australia (38), where the prevalence of caries in primary teeth (dmft > 0) of indigenous children attending School Dental Services in South Australia was as high as 78.2% (39).

We hypothesized a 20% PF based on a Canadian trial carried out in the 1980s in Sherbrooke and Lac Mégantic, Québec which compared Duraphat/Duraflor, Fluor Protector (Ivoclar-Vivadent, Leicester, UK), and water as a negative control (14). While the study examined children 6–7 years old, it did evaluate caries on primary as well as permanent teeth. After 32 months, the dfs increment reduction in the Duraflor group was 27.2% and in the Fluor Protector group was 10.1% (40). For continuous participants after 56 months, the DMFS reductions were 27% for those in the Duraflor group and 14% for the Fluor Protector group (41). Our study observed reductions in the 24-month dmfs increment for children in the Duraflor group within the range of 18.3–50.5%. The greatest reduction was found for children aged 4–5 years (50.5%) followed by those who were caries-free at baseline (29.3%). Overall, the PF was 24.5% for the ITT population and 25.4% for those who followed the protocol to the letter.

Unlike the Sherbrooke and Lac Mégantic study (14), the present trial did not use a placebo-controlled design, as there were concerns about applying a placebo varnish to high-caries-risk children. Instead, the control group received caregiver oral health counseling and the standard restorative care which was provided to all children in both groups. A recently published FV efficacy trial among ethnic minorities in San Francisco found that the odds of developing caries was higher for children who received only caregiver counseling than those who received Duraphat varnish once per year (OR = 2.2) and twice per year (OR = 3.77) (26). Our results corroborate these findings, as the odds for caries incidence was nearly two times higher for children in the counseling only group than those receiving Duraflor at least twice per year.

FV was not only effective, but was also found to be a safe mode of fluoride delivery for very young children. This study found no case of allergic contact stomatitis from the resin component of the varnish (colophony) and the product proved safe when used on children with respiratory and asthmatic conditions. Current debates over the use of FV focus on the determination of the ideal frequency of applications. Our protocol adopted a biannual frequency of FV applications. The rationale for 6-month application intervals came from a study comparing the caries preventive effect of Duraphat varnish applications performed two and four times a year in a 2-year clinical trial with children aged 9–13 years having higher than average DMFS values (42). The study found no difference in DMFS increments between the groups. Others have proposed that a 'massive' dose – a three-application regimen in a single week during the year – may be as effective as spaced single applications and a good alternative to delivering FV to high-caries-risk patients who are mobile or difficult to reach (43, 44). However, this massive dose application method releases significantly higher fluoride concentration than the single application (44), which raises concerns about the total fluoride exposure for young children, given the fact that they may also be receiving a 'match head' amount of fluoride dentifrice twice a day through regular brushing. Future research will need to determine the risk–benefit ratio for what appears to be an unnecessarily high exposure to fluoride during a short period of time.

Although our study did not intend to compare the effect of varying frequencies of FV applications, a significant proportion of participants (55.7%) received three applications per year at 4-month intervals. An exploratory analysis using ANOVA and the Tukey honestly significant difference test showed that those who received six applications (three times per year) over the 2-year period had the lowest net caries increment rate, albeit not significantly different from those receiving the varnish twice per year.

The unit of randomization in this trial was the community and not the individual child. It was expected that by assigning treatment to whole communities this would reduce the possibility of bias that might occur if community members were aware of who was, or was not receiving treatment.

For most dental public health interventions, communities or schools are the unit of assignment by their very design (e.g. community water fluoridation and school-based sealant programs). For instance, cluster randomization was used in one trial of the effect of discontinuation of sealant or FV on the prevention of occlusal caries in permanent first molars where school classes were used as units of randomization, but children and molars were used as units of analysis (45). Another recently published trial of FV provided twice yearly at school also used a cluster-randomized design where children were clustered within the unit of randomization, the school (46). However, people living in the same community or children attending the same school may be more similar than those in different communities or schools for reasons unrelated to the intervention being tested. Children, for example, in the same school or community are more often than not from similar social backgrounds, a term epidemiologists refer to as clustering. Clustering must be accounted for in the calculation of the sample size and in the analysis of cluster-randomized trials to ensure accurate conclusions regarding treatment effectiveness.

The effect of clustering can be quantified by calculating the intra-cluster/ICC, defined as the proportion of the total variation which can be attributed to the variation between clusters (36). The value of the ICC can range from 0 to 1. In most instances, an ICC value close to 0 is desirable as this means that all observations within a cluster were independent, i.e. there was no cluster effect. When the ICC approximates 1, the cluster design effect cannot be ignored and the application of standard methods of analysing the data may lead to a substantial overstatement of the effectiveness of the intervention (47, 48).

In the current study, the observed ICC for caries increment between communities was 0.045, which was higher than the anticipated ICC of 0.025. Nevertheless, the sample size was sufficiently large with high annual participation rates, as a result of community support. In addition, the data were analysed using statistical methods that accommodated this intra-cluster correlation. However, cluster-adjusted estimates of treatment effects were more conservative than the unadjusted estimates. In other words, had clustering not been accounted for in the statistical analysis of data, most *P*-values of treatment effects would have been found significant.

In conclusion, FV applied two to three times per year in high-caries-risk children was found to be effective in preventing and reducing ECC. The present community-based FV program has the potential to reduce oral health inequalities between Aboriginal and non-Aboriginal children. But at the same time, we must offer the FV program in conjunction with caregiver oral health education and health promotion programs targeting improved prenatal and young children nutrition so that we also address the root causes of ECC. The evidence presented supports shifting some resources away from the dominant treatment and curative services towards preventive care and health promotion strategies.

Acknowledgments

We would like to thank the families and the communities of Miskeegogamang (New Osnaburgh), Weagamow (Round Lake), Frenchman's Head (Lac Seul), Wapekeka (Angling Lake), Bearskin Lake, Pikangikum, Kasabonika Lake, Sandy Lake, Kingfisher Lake, Sachigo Lake, Cat Lake, Wunnumin Lake, Poplar Hill, Deer Lake, Webequie, Kitchenuhmaykoosib Inninuwug (Big Trout Lake), Ogoki Post (in the Thunder Bay Zone), Kejick Bay, Whitefish Bay and Nibinamik (Summer Beaver) for their participation in the study. We are grateful for the support from the Institute of Aboriginal Peoples' Health of the Canadian Institutes of Health Research (Grant # MOP-64215) and the Toronto Hospital for Sick Children Foundation (Grant # XG 03-067). ClinicalTrials.gov Identifier: NCT00435500. This study could not have been done without the hard work of the RDH examiners, recorders, interviewers, community assistants, community health representatives and prenatal nutrition workers in the Sioux Lookout Zone (SLZ). Special thanks go to the dental hygienists in the SLZ – Lynn Cappel and Jan Douglas (study coordinators in the SLZ), Michael St. Pierre, Laura Thomson, Tracey Kitt, Glenda Law, Linda Pieniniemi, Elaine Powell, Kathy Walker and the recorders – Darlene Binguis, Steven Young, Jennifer Gilbart/Sitar, Aleena Mason, Martha Meekis, Shanna Switzer. Special thanks also to the dental hygienists from the Thunder Bay District – Lynda McKeown (study coordinator in Thunder Bay), Debbie Vanderstelt, Ruth Currie, Barbara Grosjean, Linda Pieniniemi and the recorders – Kathi Rotar, Susan Beese, Ann Marie Smith-Remus. Thanks to the dentists: Dr Valerie Dorward, Dr Andrew Madej and Dr Marlene Bloom who served as the gold standard dental examiners during examiner and recorder training and calibration sessions. We thank all the staff at the SLZ Dental Program and the Thunder Bay District Health Unit (TBHU) for their invaluable administrative assistance and advice, particularly Bonita Switzer, Jean Davies, Tina Quequish at the SLZ and Dr Brad Holmes, Janine Piovasano, Dr William Campbell at the TBDHU. In addition, we would like to thank the following community partners for their support: Lynda Ducharme, Georgina Lentz, Rayanne Waboose, Lynn Baxter (Program Managers in the SLZ); Community Chiefs and Tribal Council; all the nurses in charge during the study; our partners in Thunder Bay and its neighboring regions (Northwest Community Health Centres – Ogden Site; W.J. Griffis Day Care Centre; Footsteps Family Centre; Our Kids Count – Academy Family Resource Centre; Communities Together for Children – Ontario Early Years Centre; Anishnawbe-Mushkiki Thunder Bay Aboriginal Community Health Centre; Salvation Army Single Parents Program; Eagles Nest Family Centre/Our Kids Count in Upsala; Dr Marlene Bloom, DDS). Finally, we would like to thank Dr James Rogers, Dr Hal Leitch, Dr Peter Cooney and Dr Margaret Reade from Health Canada for their feedback at different stages of the project.

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