# Caries arrest by topical fluorides in preschool children: 30-month results

**Short title: Caries arrest by fluorides in children**


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***Key words:*** *dental caries, fluorides, clinical trial, preschool children, silver diamine fluoride*



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## Abstract

***Objective:*** *This randomized clinical trial aimed to compare the effectiveness of different topical fluoride application protocols in arresting dental caries in preschool children.*

***Methods:*** *A total of 371 children aged 3-4 years who had at least one active caries lesion (ICDAS codes 3-6) in their primary teeth were randomly allocated to receive three intervention protocols: Group 1 - annual application of 30% silver diammine fluoride solution (SDF); Group 2 - three applications of 30% SDF at weekly interval; and Group 3 - three applications of 5% sodium fluoride (NaF) varnish at weekly interval. Follow-up examinations were performed every 6 months by the same masked examiner to investigate whether the treated carious lesions had become arrested.*

***Results:*** *After 30 months, 309 children (83%) with 1877 carious lesions remained in the study. For cavitated lesions (ICDAS codes 5 and 6), the caries arrest rate of Group 1 (48%) was significantly higher than those of Group 2 (33%) and Group 3 (34%), ($p<0.001$). However, results of multi-level survival analysis showed that the arrest times of cavitated dentine caries in both SDF solution groups were significantly shorter than that of the NaF varnish group. For moderate carious lesions without visible dentine (ICDAS codes 3 and 4), the caries arrest rates were 45%, 44% and 51% in Groups 1, 2 and 3, respectively ($p>0.05$). Presence of plaque on carious lesions, tooth type and tooth surface type had an influence on caries arrest.*

***Conclusion:*** *At 30 months, annual application of SDF is more effective in arresting active cavitated dentine caries lesions than 3 weekly applications of NaF and SDF at baseline. However, the effects of three fluoride application protocols in arresting moderate carious lesions are not significantly different.*

## Introduction

Early childhood caries (ECC) is highly prevalent, particularly in poor or socially disadvantaged children [1]. A restorative approach alone is insufficient to tackle these oral health problems, but rather perpetuate oral health inequalities, translating a skewed distribution of untreated tooth decay into caries experience [2]. A systematic review supported that the progression of dental caries can be stopped or halted without receiving any operative approaches [3]. Application of silver diammine fluoride (SDF) solution has been proposed to be effective in arresting caries progression [4, 5]. SDF solution is professionally applied once or twice a year, but these application protocols may not be feasible in mobile populations or not effective in high caries risk patients. Few studies investigated the effectiveness of the repeated topical fluoride applications in a short period of time on caries management and these results were inconclusive [6, 7]. In addition, questions remain whether there is a necessity to re-apply topical fluorides regularly to maintain its effectiveness in the long term.

Studies on caries arrest treatment was mostly conducted in children with frank cavitated lesions [8, 9] and incipient enamel caries lesions [7]. So far, there is limited information regarding the efficacy of caries arrest in moderate carious lesions according to the ICDAS system with code 3 or 4 [10]. The severity and the extent of caries lesion may affect the success of caries arrest treatment. Therefore, it was meaningful to conduct a randomized clinical trial to determine which fluoride application protocol was more efficient in slowing down the progression of tooth decay in preschool children. This trial aimed to compare the effectiveness of different fluoride interventions in arresting caries in primary teeth of preschool children. The intermediate results (18-month) on the cavitated dentine carious lesions were published [11]. The current 30-month study reports both results of moderate carious lesions (ICDAS codes 3-4) and cavitated dentine carious lesions (ICDAS codes 5-6).

## Materials and Methods

A randomized controlled trial was conducted in 16 kindergartens in Hong Kong where the fluoride concentration in drinking water is 0.5 ppm. Ethical approval was granted from the Institutional Review Board of the University of Hong Kong. This study was registered (clinicaltrials.gov # NCT02426619). Inclusion criteria were preschool children aged 3-4 years who had at least one untreated active carious lesion (ICDAS codes 3-6) [10]. Exclusion criteria were children who suffered from major systemic diseases, required long term medication, or

refused the study intervention. After screening, participating children were examined by a single dentist in kindergartens. At subject level, the dmfs index and visible plaque index (VPI) was adopted for recording dental caries and oral hygiene status. At surface level, lesion activity (arrest/active), extent of caries lesion (ICDAS codes 3 to 6), color of lesion (yellow, light brown, hard brown, black) and presence of plaque (absence or presence) was evaluated. Tooth with pulpal exposure or having any non-vital signs such as tooth discoloration was excluded.

Previous studies demonstrated that approximately 70% of the active carious lesions were arrested after 30 months [8]. A 10% difference of the caries arrest rates between intervention groups was regarded to be clinically significant. Sample size calculation was based on the anticipated proportion of arrested caries, with an 80% power ($\beta$=0.2) and with a significance level of 5% ($\alpha$=0.05). Then, 360 carious tooth surfaces were required per each group. In Hong Kong, a recent oral health survey showed that a preschool child with ECC had four carious lesions on average [12]. Therefore, approximately 90 children were required in each group. With an estimation of 10% dropout rate, 371 preschool children were recruited at baseline examination.

Due to the ethical concerns, all active lesions were treated. After baseline examination, the study children were referred to a treatment station. Then, they were classified into two strata following the number of carious tooth surfaces (having 1 to 4 carious tooth surfaces or more than 4 carious tooth surfaces). Then, they were randomly allocated to one of the three groups according to a computer-generated list using a method of stratified block randomization (block of 6):

Group 1: 30% SDF solution (Cariestop, Biodinamica, Brazil) applied once a year,
Group 2: 30% SDF solution (Cariestop, Biodinamica, Brazil) applied 3 times with weekly intervals after baseline, and
Group 3: 5% NaF varnish (Duraphat, Colgate Palmolive, USA) applied 3 times with weekly intervals after baseline.

The randomization process was maintained and kept confidentially by a research assistant who held the random allocation list and prepared the materials according to the child's assigned group. So, the dentist who was not involved in the examination and unaware of upcoming assignments performed the treatment. The randomization list was concealed from

the sole examiner, treatment providers, children, teachers and parents. The same application technique using either fluoride agent or placebo (water) was employed. The study children, their parents and the single examiner were blinded to the intervention allocation.

Regarding the study children's background (demographic and socio-economic background, behaviors related to oral health), information was collected by an anonymous questionnaire filled by their parents at baseline and the 24-month examination. Parental satisfaction on their child's oral health status was also assessed. Follow-up examinations were performed every 6 months by the same masked examiner to assess whether the active carious lesions had become arrested after receiving the topical fluoride treatment.

For cavitated dentine carious lesions diagnosed as codes 5 or 6 of ICDAS system, visual inspection and tactile detection using a 0.5 mm ball-end probe were used for assessing the lesion activity. If a wall or floor of a cavitated lesion was soft and easily penetrated by a probe using light pressure, then it was diagnosed as active caries. Carious lesions with hard and smooth surfaces were diagnosed as arrested caries [8, 13]. For moderate carious lesions without visible dentine (ICDAS codes 3 or 4), if a carious lesion did not enlarge or progress to a cavitated lesion with visible dentine (ICDAS codes 5 or 6) at the follow-up examinations [14], it was classified as arrested caries.

A 10% sample of the study children was randomly re-examined. Cohen's Kappa statistics was used to assess the intra-examiner reliability. An intention-to-treat analysis was adopted. Data were analyzed using the software SPSS 20.0 for Windows (SPSS Inc., Chicago, USA). The level of statistical significance was set at 0.05.

For moderate carious lesions, multi-level logistic regression analysis using GLIMMIX procedure, SAS/STAT® software version 9.3 (SAS Institute Inc., Cary, NC, USA) was performed to analyze the effects of independent factors on the caries arrest rates at the 30-month examination. The independent factors included gender, age, frequency of brushing, use of toothpaste, frequency of snacking, tooth type, tooth surface and the intervention group.

For cavitated dentine caries lesions, multi-level survival analysis was adopted using the software WinBUGS, version 1.4 [15]. The details of statistical procedures used in the current study were similar to our 18-month study published previously [11].

## Results

In total, 371 preschool children participated in the study. Their mean age was 41±4 months and 222 of them (60%) were boys. The respective numbers of children in Groups 1, 2 and 3 were 124, 122 and 125. There were 880, 799 and 847 active carious lesions in the Groups 1, 2 and 3, respectively. At baseline, the mean dmft score was 3.7±3.5 and the dmfs score was 5.6±6.8. The distribution of carious lesions with ICDAS codes 3, 4, 5 and 6 were 28%, 6%, 46% and 20%, respectively. Regarding the color of the lesions at baseline, yellow lesions were commonly found (73%), light brown lesions were 23%, while dark brown and black lesions were less than 5%. Approximately, 50% of the lesions were located in posterior teeth. Presence of plaque on lesion was found in most of the lesions at baseline examination. There were no statistically significant differences in children' demographic background, oral hygiene status and caries experience among three groups. All parents (100%) returned the baseline questionnaire. Most of the study children used children toothpaste (83%) and brushed their teeth at least once a day (85%). Regarding the behaviors related to oral health and parental satisfaction about child's oral health, no significant differences were found among the three treatment groups ($\chi^2$test, $p>0.05$).

At 24 months, all distributed parental questionnaires (100%) were returned. An improvement in brushing habits between baseline and 2-year examination was observed in all three groups (McNemar test, $p<0.05$). Most children brushed their teeth at least once a day (97%) and used toothpaste (98%). No differences were found among three groups regarding use of toothpaste, frequency of brushing and snacking habits at the 24-month follow-up ($\chi^2$test, $p>0.05$). There were no significant differences in parents' satisfaction about their child's oral health among the three groups ($\chi^2$test, $p>0.05$).

At the 30-month examination, 309 children remained in the study, giving an overall dropout rate of 17% (Figure 1). The subject dropout rates in Groups 1, 2 and 3 were 19%, 16% and 15%, respectively. The dropout rates were similar among three treatment groups ($\chi^2$ test, $p>0.05$). There were no significant differences in children's demographic background, behaviors, clinical parameters and caries experience between the initial and remaining children at 30 months (Table 1). Regarding the intra-examiner reliability, the respective kappa values

for the duplicate examinations of lesion activity, caries status, and color assessment were 0.98, 0.92 and 0.87, respectively.

At surface level, the caries arrest rates of cavitated dentine caries lesions in Groups 1(180/377, 48%) were significantly higher than those in Group 2 (121/367, 33%) and Group 3 (164/484, 34%) ($\chi^2$ test, $p<0.001$). However, the 24-month results showed no significant differences in caries arrest rates among three groups ($\chi^2$ test, $p>0.05$). The 24-month caries arrest rates of Groups 1, 2 and 3 were 37% (147/397), 36% (138/386) and 33% (169/505), respectively. The results of multi-level survival analysis revealed that the effect of clustering was significant ($\sigma^2$ child = 1.223; 95% credible interval = 0.861-1.767). The estimated intra-cluster correlation coefficient of the arrest times of different lesions in the same child was 0.427. Five variables including treatment group, plaque on lesion at baseline and follow-up examination, tooth type, surface type had an influence on the arrest times of cavitated dentine carious lesions. Both SDF groups with different application protocols demonstrated a shorter arrest time compared to Group 3 with NaF. However, there were no statistically significant differences between both SDF groups regarding the time to arrest. Cavitated dentine carious lesions without plaque accumulation, in buccal/lingual surfaces and in anterior teeth had higher chances to be arrested faster compared to those with plaque and located on other tooth types and surfaces types.

Regarding the moderate carious lesions (ICDAS codes 3 and 4), the caries arrest rates of all examinations are shown in Table 3. Our results showed no statistically significant differences in caries arrest rates of moderate carious lesions when treated with three different fluoride protocols in each follow-up examination ($\chi^2$ test, $p>0.05$). After 30 months, approximately half of moderate carious lesions remained stable (no progression to cavitation) regardless the different treatment protocols. The results of multi-level regression model with adjusting the cluster effect indicated five significant factors that were presence of plaque on lesion, tooth type, surface type, the extent of caries (ICDAS code) and dmfs score at 30-month follow up (Table 4). The effect of fluoride application protocols on caries arrest was not significant ($p>0.05$). Moderate carious lesions receiving different treatment protocols had a similar chance to be arrested after 30 months.

Black or dark brown staining on the carious lesions was commonly found in Group1 (65%) and Group 2 (57%), while a third in all lesions in Group 3 were dark brown or black in color. After 30 months, the prevalence of non-vital teeth was similar among three groups with the respective rate of 7%, 8% and 6% in Group 1, 2 and 3 ($\chi^2$ test, $p>0.05$). No major side effects were found during the 30-month study period.

**Discussion**

Previous studies have shown the effectiveness of SDF in arresting cavitated dentine caries in children [8, 13]. However, information about caries arrest treatment with SDF on moderate carious lesions with ICDAS code 3 and 4 is scarce. In the present study, the outcomes of topical fluoride treatments on moderate carious lesions differed significantly from those of cavitated dentine lesions.

Based on the 30-month results, annual application of SDF showed superiority in arresting cavitated dentine caries compared to the other two groups. The relatively higher treatment effect of SDF with annual application may be due to the booster effect of re-application of SDF at 12 and 24 months. It should be noted that the treatment effects of fluoride application may vary over time. If the outcomes at a single time point (such as at the end of the trial) were only analyzed, clinically important differences during the whole period of study would be obscured [16]. Therefore, we adopted time-to-event analysis which incorporates information about the study outcomes that may differ over time (time-dependent covariates). In the present study, the clustering effect could not be ignored since the observed intra-class correlation coefficient (ICC) for caries arrest rates within subjects was significant (0.427). According to the 30-month multi-level survival analysis, SDF solution with either 3 weekly applications at baseline or annual application, can shorten the arrest times of cavitated dentine carious lesions, compared to NaF with 3 weekly applications at baseline. Therefore, for relatively stable populations, the present study supports the use of SDF solution with annual application as a non-surgical approach to manage dentine caries in young children. The re-application of SDF solution at least yearly interval may be necessary to improve and maintain its efficacy in arresting dentine caries. However, for children in mobile populations, a one-off intensive SDF treatment may be an option due to a faster ability to arrest dentine caries, compared to a one-off intensive NaF treatment.

Findings of this study concur with those from previous reviews supporting the beneficial effect of SDF solution in arresting dentine caries [5]. Although the mechanisms of action of SDF on caries arrest are not truly understood, it was hypothesized to be a combined effect of its anti-cariogenic properties by inhibiting cariogenic biofilm on dentine carious surfaces [17], preserving collagens from degradation [18], and increasing dentine hardness [19].

Based on the study results, the null hypothesis that the effects of different fluoride protocols on arresting moderate carious lesions in primary teeth of preschool children are the same cannot be rejected. Possibly, the effect of NaF varnish and SDF solution on enamel lesions may be predominantly based on the role of fluoride ions in inhibiting the demineralization of dental hard tissues [20]. The synergistic effect of both fluoride and silver ions on enhancing remineralization was relatively low [21]. On the other hand, silver ions may act mainly on cariogenic microorganisms in the infected dentine carious lesions [22].

Besides the treatment effect, other confounding factors such as tooth type and surface type should also be taken into account when predicting the success of fluoride treatment. Our results are in accordance to the previous studies [9, 11] that topical fluoride treatment seems to be more beneficial for arresting lesions on labial/lingual surfaces and/or in anterior teeth, compared to those on other tooth types and other surface types. In addition, plaque accumulation had a negative effect on the success of caries arrest treatment regardless of the fluoride treatment protocol and extent of caries lesions. This highlights the significant impact of plaque control on the dental caries process.

Although the presence of black arrested caries lesions did not lead to an increase in parental dissatisfaction in the present study, the poor esthetics of black stains on the treated caries lesions can be a deterrent for patients having high esthetic concerns. Caution must be taken when transferring these study findings to other populations with different subjective considerations and acceptance. In addition, we acknowledged that these results were based on preschool children with high caries risk living in a water fluoridated area. Our findings may not generalize to other age groups with low caries risk or residing in a non-fluoridated area.

In conclusion, annual application of SDF solution is more effective in arresting cavitated dentine carious lesions than three weekly applications with NaF varnish or SDF

solution at baseline, while the three fluoride application protocols are not significantly different in arresting moderate carious lesions.

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Table 1 Background information of children in the three study groups at baseline and 30-month follow-up.

| | Baseline | | | 30-month follow-up | | |
|---|---|---|---|---|---|---|
| | **Gp1 SDF** (once a year) | **Gp 2 SDF** (3x weekly interval) | **Gp 3 NaF** (3x weekly interval) | **Gp1 SDF** (once a year) | **Gp 2 SDF** (3x weekly interval) | **Gp 3 NaF** (3x weekly interval) |
| **Gender** | | | | | | |
| % boy | 59% | 62% | 59% | 58% | 65% | 59% |
| **Visible Plaque Index (VPI)** | 56% | 55% | 53% | 56% | 56% | 52% |
| **Caries experience** | | | | | | |
| - Mean dmfs (SD) | 5.6 (6.4) | 5.0 (6.3) | 6.1 (7.7) | 5.5 (6.2)* | 4.9 (6.5)* | 6.4 (8.0)* |
| **Tooth type included** | | | | | | |
| % Anterior teeth | 50% | 48% | 52% | 50% | 48% | 54% |
| **Tooth surfaces included** | | | | | | |
| - Occlusal | 36% | 40% | 37% | 37% | 39% | 36% |
| - Proximal | 35% | 33% | 39% | 36% | 33% | 40% |
| - Buccal/Lingual | 29% | 27% | 24% | 27% | 28% | 24% |

* The dmft index scores at 30-month is the number of affected tooth surfaces in the primary canines and molars as primary incisors was excluded due to the natural exfoliation.

Table 2 Multi-level survival analysis with WinBUGS on caries arrest of cavitated dentine lesions - results from 5,000 stimulations after 5,000 burn-ins

| | **Log hazard ratio** | **95% C.I.** | **Hazard ratio** | **95% C.I.** |
|---|---|---|---|---|
| **Treatment group** | | | | |
| - Gp. 2 *vs* Gp. 1[a] | 0.147 | (-0.275, 0.580) | 1.158 | (0.760, 1.786) |
| - Gp. 3 *vs* Gp.1[a] | -1.214 | (-1.695, -0.754) | 0.297 | (0.184, 0.470) |
| - Gp. 2 *vs* Gp. 3[a] | 1.359 | (0.900, 1.842) | 3.892 | (2.460, 6.309) |
| **Tooth type** | | | | |
| - Anterior *vs* Posterior [a] | 1.191 | (0.811, 1.588) | 3.290 | (2.250, 4.894) |
| **Surface type** | | | | |
| - Buccal/Lingual vs Occlusal [a] | 0.765 | (0.332, 1.223) | 2.149 | (1.394, 3.397) |
| - Proximal *vs* Occlusal [a] | -0.453 | (-0.893, 0.022) | 0.636 | (0.409, 1.022) |
| **No plaque at baseline** | 1.296 | (0.177, 2.327) | 3.655 | (1.194, 10.247) |
| **No plaque at follow up** | 4.538 | (4.203, 4.932) | 93.504 | (66.887, 138.657) |
| **Time interval** | | | | |
| **- γ1 (Baseline-6mo)** | -2.923 | (-3.580, -2.286) | | |
| **- γ2 (6mo-12mo)** | -3.606 | (-4.309, -2.945) | | |
| **- γ3 (12mo-18mo)** | -2.196 | (-2.843, -1.566) | | |
| **- γ4 (18mo-24mo)** | -2.783 | (-3.517, -2.134) | | |
| **- γ5 (24mo-30mo)** | -2.298 | (-2.992, -1.630) | | |
| **$\sigma^2$ child** | 1.223 | (0.861, 1.767) | | |
| **Corr subject** | 0.427 | (0.344, 0.518) | | |

a = reference category

*Hazard ratio >1 corresponds to a higher chance of arrest of active dentine caries and then a shorter arrest time

*95% C.I.= 95% credible interval

Table 3 Caries arrest rates of moderate carious lesions (ICDAS codes 3 and 4) at 6-, 12-, 18-, 24-, and 30-month follow-up in the three treatment groups

| | **Caries arrest rates** | | | | |
|---|---|---|---|---|---|
| | **6-month (n=778)** | **12-month (n=768)** | **18-month (n=739)** | **24-month (n=676)** | **30-month (n=649)** |
| **Group1 SDF (once a year)** | 71% (182/257) | 63% (163/261) | 50% (126/252) | 50% (113/228) | 45% (97/218) |
| **Group 2 SDF (3x weekly interval)** | 71% (212/297) | 61% (175/285) | 53% (149/280) | 48% (125/259) | 44% (109/246) |
| **Group 3 NaF (3x weekly interval)** | 70% (157/224) | 61% (136/222) | 58% (120/207) | 54% (102/189) | 51% (95/185) |
| **$\chi^2$ test** | NS | NS | NS | NS | NS |

Table 4 Final logistic regression model of the caries arrest rate of moderate carious lesions at the 30-month follow-up with clustering effect adjustment

| Explanatory variables | Odds ratio | 95% CI | P value |
|---|---|---|---|
| **Group** | | | |
| - Gp. 1 SDF (once a year)[a] | | | |
| - Gp. 2 SDF (3x weekly) | 0.69 | 0.40-1.20 | 0.186 |
| - Gp. 3 NaF (3x weekly) | 1.37 | 0.77-2.43 | 0.286 |
| **Tooth type** | | | |
| - Anterior teeth[a] | | | |
| - Posterior teeth | 6.51 | 2.89-14.65 | <0.001 |
| **Surface type** | | | |
| - Occlusal surface[a] | | | |
| - Proximal surface | 1.46 | 0.49-4.33 | 0.500 |
| - Buccal-lingual surface | 2.90 | 1.54-5.46 | 0.001 |
| **ICDAS code** | | | |
| - code 4[a] | | | |
| - code 3 | 2.55 | 1.05-6.20 | 0.039 |
| **dmfs at 30-month** | 0.94 | 0.91-0.97 | <0.001 |
| **No plaque on lesion at 30-month** | 10.42 | 6.60-16.46 | <0.001 |

[a] reference category

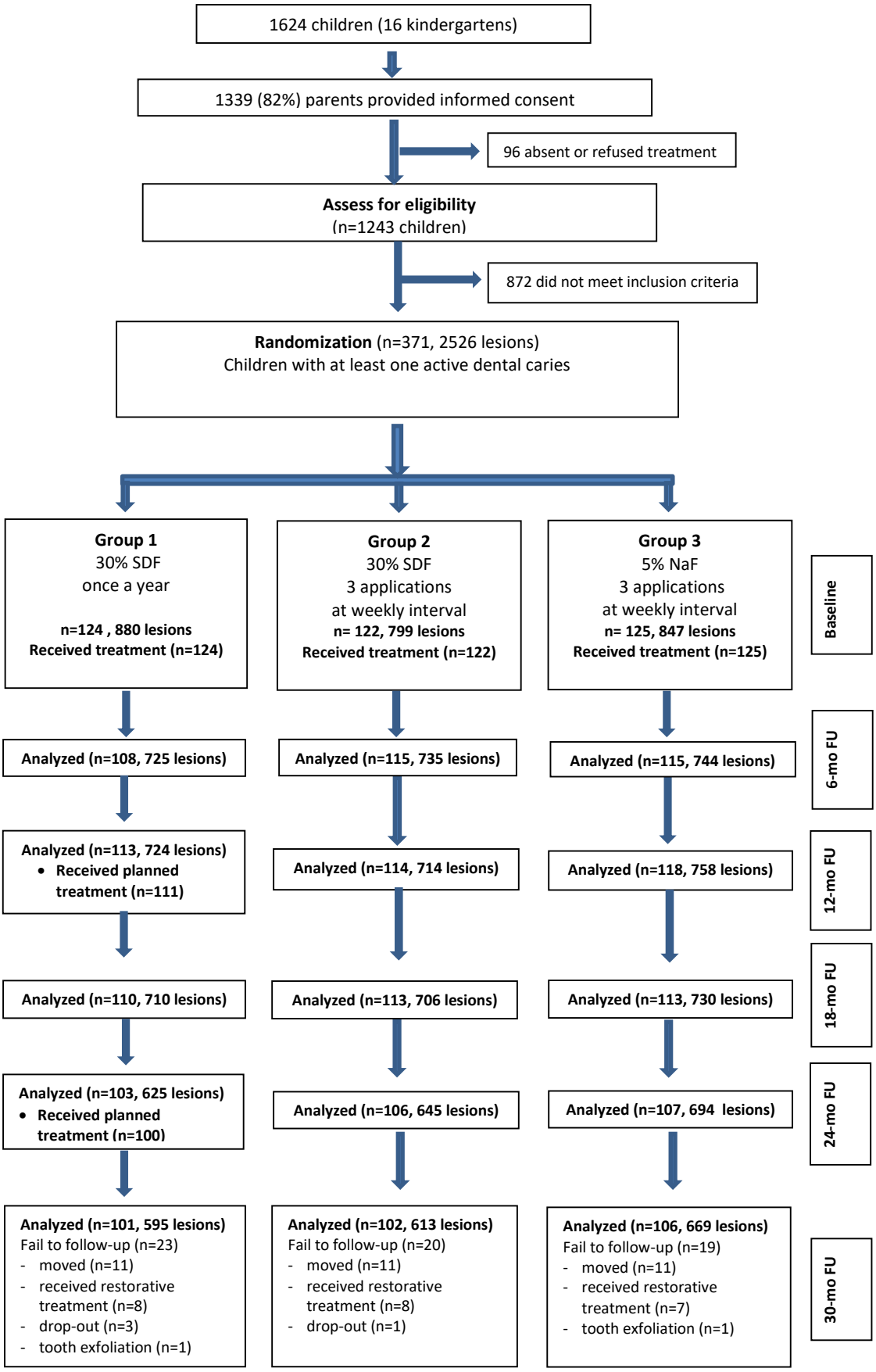


Figure 1 Flow of subjects over the 30-month study period

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