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Fluoride Varnish Efficacy in Preventing Early Childhood Caries

ABSTRACT

To determine the efficacy of fluoride varnish (5% NaF, Duraphat®, Colgate) added to caregiver counseling to prevent early childhood caries, we conducted a two-year randomized, dental-examiner-masked clinical trial. Initially, 376 caries-free children, from low-income Chinese or Hispanic San Francisco families, were enrolled (mean age ± standard deviation, 1.8 ± 0.6 yrs). All families received counseling, and children were randomized to the following groups: no fluoride varnish, fluoride varnish once/year, or fluoride varnish twice/year. An unexpected protocol deviation resulted in some children receiving less active fluoride varnish than assigned. Intent-to-treat analyses showed a fluoride varnish protective effect in caries incidence, $p < 0.01$. Analyzing the number of actual, active fluoride varnish applications received resulted in a dose-response effect, $p < 0.01$. Caries incidence was higher for 'counseling only' *vs.* 'counseling + fluoride varnish assigned once/year' (OR = 2.20, 95% CI 1.19-4.08) and 'twice/year' (OR = 3.77, 95% CI 1.88-7.58). No related adverse events were reported. Fluoride varnish added to caregiver counseling is efficacious in reducing early childhood caries incidence.

KEY WORDS: dental caries, prevention, fluorides, preschool child, randomized controlled trial.

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A supplemental appendix to this article is published electronically only at http://www.dentalresearch.org.

INTRODUCTION

Early childhood caries is a public health problem sometimes affecting young children almost as soon as their teeth erupt. In severe cases, pediatric dental services may require anesthesia in the operating room, services often unavailable, especially for low-income, underserved groups. In California, the early childhood caries prevalence is particularly high in some low-income racial/ethnic populations. Findings from the 1993-94 statewide oral health needs assessment (Pollick *et al.*, 1999; Shiboski *et al.*, 2003) showed early childhood caries prevalence (≥ 1 decayed, extracted, or filled primary maxillary incisor) was 14% among all preschool children, but higher in children from low-income families enrolled in Head Start programs: 44% among Asians and 39% among Latinos.

Fluoride varnish is a concentrated topical fluoride with a resin or synthetic base. At least 19 fluoride varnish reviews (Weintraub, 2003), including a systematic review (Bader *et al.*, 2001) and three meta-analyses (Helfenstein and Steiner, 1994; Strohmenger and Brambilla, 2001; Marinho *et al.*, 2002) have been published in English. Most studies examined fluoride varnish efficacy in the permanent teeth of school-aged children. Consensus statements (NIH, 2001) regarding fluoride varnish differed for permanent and primary teeth. They stated, "The evidence for the benefit of applying fluoride varnish to permanent teeth is generally positive. In contrast, the evidence for the effectiveness of fluoride varnish applied to primary teeth is incomplete and inconsistent."

The objective of this two-year randomized controlled trial was to determine the efficacy of different fluoride varnish application frequencies with parental/caregiver oral health counseling *vs.* counseling alone in preventing early childhood caries incidence in young, initially caries-free children.

MATERIALS & METHODS

Before implementation, the University of California, San Francisco Institutional Review Board approved this study. An NIH-appointed Data and Safety Monitoring Board provided additional oversight.

Participants

This trial occurred at two public health centers, the Family Dental Center at San Francisco General Hospital (SFGH), and the San Francisco Department of Public Health's Chinatown Public Health Center (CPHC), serving primarily low-income, underserved Hispanic and Chinese populations, respectively. San Francisco has been optimally fluoridated (~ 1 ppm) since 1952.

Inclusion criteria for children at enrollment were: four erupted maxillary incisors; all primary teeth caries-free without demineralized, white spots; age 6-44 months; born in San Francisco or a fluoridated community in the San Francisco Bay Area and planning to reside in San Francisco for at least two years (eliminating water fluoridation as a potential confounder and

demonstrating geographic stability); and a parent providing informed consent in English, Spanish, or Chinese. Children were excluded from the study if they had: medical problems or medications possibly affecting oral health; cleft lip/palate; developmental disabilities; transient residence; or another household member participating.

Recruitment and Follow-up

Between October, 2000, and August, 2002, families were recruited primarily from Well Child Clinics, Women, Infants and Children Supplemental Nutrition Programs, and dental clinics. Follow-up was completed in August, 2004.

Randomization

Children with parental consent were randomly assigned to one of three arms: parental counseling plus fluoride varnish twice/year (baseline, 6, 12, and 18 months) with four intended applications (4FV); parental counseling plus fluoride varnish once/year (baseline and 12 months) with two intended applications (2FV); or counseling only, with no fluoride varnish (0FV). The study team's biostatisticians conducted the computer-generated random assignment of participants, stratified by center, using permuted blocks of various sizes unknown to the clinicians. Assignment was concealed in sealed, opaque, labeled envelopes, unopened until time for treatment by the clinician.

Intervention and Measurements

Dental Examinations

Dental examinations, without radiographs, were conducted three times: at baseline prior to the intervention, and one and two years post-intervention. Older children's examinations were conducted in a dental office; very young children had a knee to-knee examination (Ramos-Gomez *et al.,* 2002). Universal infection control procedures were followed. Children's saliva samples were collected during dental examinations, before any fluoride varnish application, for the assessment of salivary mutans streptococci (MS), lactobacilli (LB), and fluoride concentrations. Salivary assay results will be reported separately.

Parental Interview

The Project Director trained and calibrated staff in conducting interviews. Questionnaires were translated into Spanish and Cantonese, back translated into English for the assessment accuracy, and revised if necessary. The family member/caregiver was interviewed about factors associated with early childhood caries or dental caries, potential confounders, and effect modifiers, including sociodemographic, biologic, and behavioral factors, including questions about bottle use, diet, and dental utilization.

Parental Counseling

The annual counseling protocol followed the American Academy of Pediatric Dentistry's (AAPD) anticipatory guidance recommendations (Nowak and Casamassimo, 1995; Nowak, 1998). Thus, it was inappropriate for the control group to receive an examination without counseling or education having been provided. Individualized counseling visits followed these age-specific recommendations (6-12 months, 12-24 months, 2-5 years), in the parents' preferred language, by a trained team member.

Fluoride Varnish Application

Duraphat® (Colgate Oral Pharmaceuticals, New York, NY, USA) fluoride varnish was used with 0.1 mL (1 drop) applied *per* arch. Parents/caregivers were asked to refrain from brushing their children's teeth with a fluoride dentifrice the day of varnish treatment, to minimize total fluoride exposure that day. Teeth were dried with gauze, and varnish was brushed onto all surfaces of the maxillary and mandibular anterior teeth, and the proximal and occlusal surfaces of the posteriors. One dentist (BJ) who spoke English, Spanish, and Cantonese provided clinical interventions at both sites. Masking accompanying caregivers to the control group assignment was attempted. The control group's tray set-up was the same. For children in this group, fluoride varnish was placed on gauze, which was then folded. The dry area was used to wipe the child's teeth, and no fluoride varnish was applied.

Primary Outcome Measures

The primary outcome was any caries incidence. We used the NIDCR diagnostic criteria for dental caries (USDHHS, 1991) for assessing cavitated, decayed (d_{2+}), and filled surfaces on primary teeth (d_{2+}fs). We used supplemental criteria (Drury *et al.*, 1999) to diagnosis pre-cavitated lesions (d_1). One pediatric dentist (FRG), masked to treatment group, conducted all dental examinations. Intra-examiner reliability, from repeat examinations of 21 children, yielded a kappa statistic of 0.96, indicating excellent agreement. Two years of follow-up were planned unless caries was detected at the one-year follow-up examination, in which case children were considered treatment failures and were referred for dental care.

Sample Size

We planned a sample size of 384 participants (128/study arm) (alpha = 0.05, power = 90%, 50% attrition, χ^2 test) to detect caries incidence differences, based on caries incidence in the literature (20% to 50% over two years). A similar study (Weinstein *et al.*, 1994) reported 53% attrition in six months.

Data Analysis

For primary analysis, we used the intention-to-treat (ITT) approach (Fisher *et al.*, 1990). Protocol-compatible analyses used number of actual active fluoride varnish applications. Analyses used data from all children with a follow-up dental examination. Primary analysis tested two-year caries incidence among treatment groups, with a two-degree-of-freedom (d.f.) non-parametric extended Mantel-Haenszel (EMH) test stratifying on center (Koch and Edwards, 1988). *A priori* step-down comparisons (Koch and Gansky, 1996) of each varnish group *vs.* control were performed, each at $p \leq 0.05$: (1) 4FV *vs.* 0FV and (2) 2FV *vs.* 0FV; step (2) was performed only if step (1) was significant. A 1 d.f. EMH test, stratifying on center, tested trends across intended and actual number of applications. Logistic regression tested treatment group differences in incidence, with adjustment for covariates and treatment x center homogeneity. Supplemental analyses used linear regression to compare log (d_{2+}fs +1) and log (d_{1+}fs +1) among groups, adjusted for covariates (since d_{n+}fs is skewed). Confounders were defined as changing model treatment coefficients by ≥ 20%. Since 96 children had no follow-up examination, multiple imputation (Schafer, 1997) with the Markov Chain Monte Carlo estimation (20 imputations) used center, assigned group, number of actual fluoride varnish applications, factors related to loss-to-follow-up (mother's age, dental pain barrier, dental fear barrier, and fluoride toothpaste use), and salivary measures ($\log_{10}$MS and $\log_{10}$LB) to impute log (d_{2+}fs +1) scores.

RESULTS

Enrollment and Retention

There were 376 children enrolled and randomized, with a mean

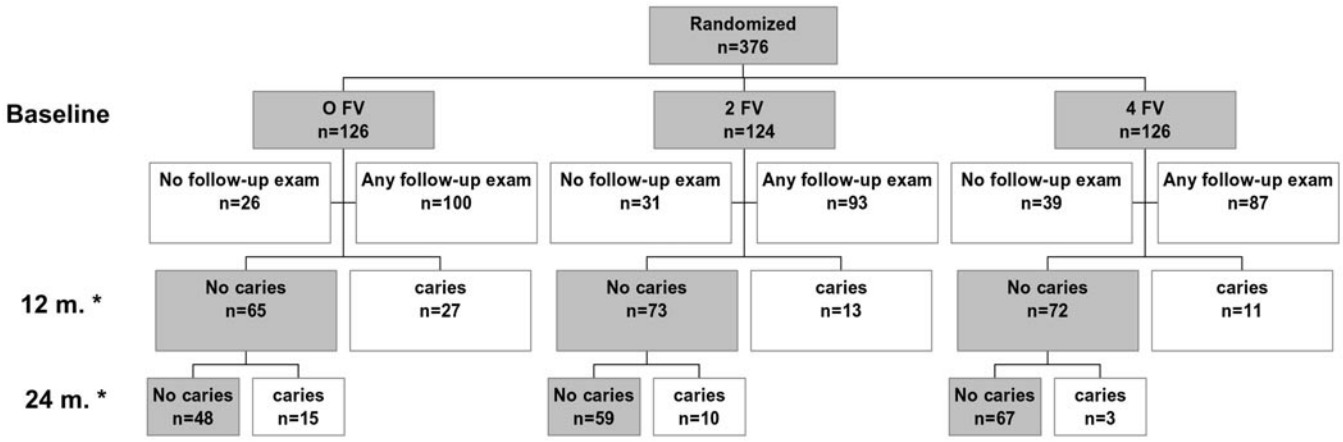

Figure 1. Flow of study participants. Children with and without dental caries at each examination by intended (randomized) fluoride varnish (FV) treatment group. * 27 children with no caries at 12 months were not seen at 24 months; 19 children with a 24-month examination missed the 12-month examination.

(standard deviation) age of 1.8 (0.6) yrs: 200 at SFGH and 176 at CPHC. Overall, 53% were girls, 47% were Hispanic, 46% were Asian, and 7% were other race/ethnicity. No randomization imbalances were apparent. About 60% of those screened and found to be ineligible had existing dental caries. At the 12-month follow-up examination, 70% of enrolled children (n = 261) were seen; 51 of them were discontinued from the study due to caries, and were referred for care (Fig. 1). Twenty-seven caries-free children seen at 12 months were not seen at 24 months. Thus, 78 children had their last follow-up examination at 12 months. At the final, 24-month follow-up, 202 children were seen (67% retention, including the 51 children with caries at 12 months). There were 280 (74%) children with a 12- or 24-month follow-up visit.

Protocol Deviation

Due to an unexpected protocol violation (see APPENDIX), children unintentionally received a placebo varnish instead of active product during a 10-month period, even though this study had no planned placebo varnish. Among children with follow-up examinations, most (75%) who were intended to receive two applications received only one with active product; 15% received two. About half (49%) who were intended to receive four applications received only two, and 29% received three. Only one child received four active applications. For five weeks, a total of 21 varnish applications could not be confirmed as active. We conservatively assumed, for analytical purposes, that they were placebo applications.

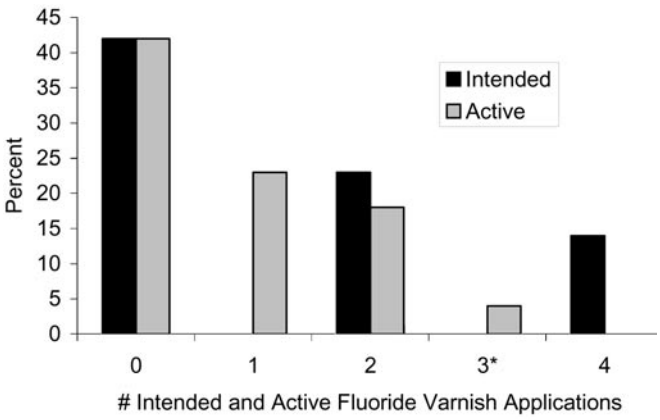

Figure 2. Caries incidence at last follow-up examination by intended treatment group and number of active fluoride varnish applications (n = 280). * 3 active applications + one child with 4 active applications. Intended groups are the groups randomized to receive 0, 2, or 4 fluoride varnish applications. Active groups are the children stratified by number of actual fluoride-containing varnish applications received (see text and APPENDIX).

Clinical Outcomes

Primary analysis showed a statistically significant reduced percentage of children with any caries incidence (any decayed or filled surfaces at the last follow-up examination), when children in groups with any intended fluoride (2 or 4 treatments) were compared with the control group (Fig. 2) (2 d.f. EMH $p < 0.001$; 1 d.f. step-down 4FV *vs.* 0FV and 2FV *vs.* 0FV both $p < 0.003$; multiple imputation 2 d.f. $p < 0.034$), or actual active applications *vs.* none (3 d.f. EMH $p < 0.001$; multiple imputation 3.d.f. $p < 0.001$). The percentage of children with caries decreased with increasing numbers of intended or actual active applications linearly (both $p < 0.001$).

Supplemental analyses showed that the child who received four fluoride varnish applications had no caries, but did have a pre-cavitated lesion at the final visit. The magnitude of caries experience at the last examination, by intended treatment group and number of active fluoride varnish applications, was analyzed two ways, with and without pre-cavitated lesions ($d_{1+}fs$ and $d_{2+}fs$). For both, results showed significant inverse dose-response effects (Table 1). Linear regression of log ($d_{2+}fs$ +1) and log ($d_{1+}fs$ +1), adjusted for center, showed statistically significant decreases in caries experience with increasing number of intended or actual active fluoride varnish treatments (both $p < 0.001$; both multiple imputation $p < 0.002$). Of the 79 children with d2+fs, only 12 had any restorations. The magnitude of caries experience was also reduced for a single dose of fluoride against none ($p = 0.004$). However, this comparison is not significant when the proportion of children with caries is compared ($p = 0.121$). Significant odds ratios

were obtained when the caries incidence in the counseling only group was compared with the intended and actual number of fluoride varnish applications (Table 2). Center was never a significant predictor or effect modifier of caries incidence or magnitude ($p > 0.540$). No adverse events or safety issues resulting from the fluoride varnish use were reported by accompanying adults.

Table 1. Mean dfs and dfs + Pre-cavitated Lesions at Last Follow-up Visit by Intended Treatment Group and Number of Active Fluoride Varnish Applications (n = 280)

	n	Mean $d_{2+}fs$*	SD	Mean $d_{1+}fs$	SD	PF% $d_{2+}fs$
Intended Treatment Group						
0	100	1.7 **	3.1	2.7 **	3.4	-
2	93	0.7 **	1.8	1.3 **	2.3	58
4	87	0.7	2.1	1.4	3.1	61
# Active Fluoride Varnish Applications						
0	118	1.6 **	3.0	2.8 **	3.7	-
1	79	0.8	2.1	1.2	2.3	53
2	57	0.7	2.1	1.2	2.4	58
3-4	26	0.1	0.6	0.6	1.6	93

* $d_{2+}fs$ = number of cavitated decayed or filled surfaces.
$d_{1+}fs$ = number of pre-cavitated or cavitated decayed or filled surfaces.
SD = standard deviation.
PF% = prevented fraction: [(control mean - intervention mean)/control mean] x 100.
Intended Group = as randomized, intention-to-treat analysis.
Active Applications = number of varnish applications containing fluoride actually received (see text and APPENDIX).
3-4 includes one child with 4 applications.
** p-values ≤ 0.01 for comparisons with group receiving no fluoride varnish applications.

DISCUSSION

Study findings support the use of fluoride varnish to prevent early childhood caries and reduce caries increment in very young children. AAPD (www.aapd.org, 2004) and AAPHD (www.aaphd.org, 2004) guidelines support a dental assessment by a child's first birthday or first tooth eruption. Fluoride varnish efficacy in this age group provides additional rationale for an early dental visit, especially for high-caries-risk children, since the application of fluoride varnish at this first visit will help reduce future disease. Some children were even younger than age 1 at the first visit. We had little difficulty with cooperation of the young infants with the fluoride varnish. Collecting saliva was more problematic, but was possible with parental help. Public facilities sometimes find it difficult to see children at regular six-month intervals. Thus, determining the efficacy of only one application of varnish a year was important. Although more frequent varnish applications were more beneficial, one application was preferable to none.

The Cochrane collaboration meta-analysis (Marinho *et al.*, 2002) obtained a pooled d(e/m)fs prevented fraction of 33% (95% CI, 19-48%) based on three clinical trials. In our study, it ranged from 52 to 92%, by treatment group. The systematic review (Rozier, 2001) for the NIH Consensus Conference compared seven studies of fluoride varnish showing mixed effectiveness on primary teeth. Some were not randomized clinical trials, and none included children as young as those in our study (see APPENDIX).

The Cochrane reviewers (Marinho *et al.*, 2002) recommended that fluoride varnish studies include reports of adverse events or safety concerns. At each visit, families were asked about adverse events; only 1 adverse event was noted for a child in the four-fluoride-varnish group, with "ulcer on the cheek" at the 18-month visit having onset 2 months after the last fluoride varnish application, which was "fluoride-free". The ulcer was gone at the 24-month visit. Some concerns about applying fluoride varnish to asthmatic children have been noted (Blinkhorn and Davies, 1998). However, from parental report, of the 21 children with asthma, none of the fluoride varnish recipients had adverse events. A 95% upper bound on adverse event incidence in asthmatic children was 0.14 (Hanley and Lippman-Hand, 1983).

Many children with caries at the screening examination were ineligible. This study was intended to determine the success of preventing caries incidence, not increment. It did not address fluoride varnish efficacy for children with extant caries.

An important lesson in efficacy trials is always to test the presence and quantity of the product's active ingredient prior to and during study implementation, and to implement quality control measures to identify and correct protocol deviations as soon as possible. Most studies' non-compliance/non-adherence is participant-generated. In this study, only the entry time was related to number of active treatments, making results more generalizable. This study provides support for the conduct of future caries-prevention clinical research in community health centers serving vulnerable and minority populations. Because the study occurred at these sites, findings are more generalizable to settings serving many high-caries-risk children than other potential locations. Similar results from the two

Table 2. Caries Incidence Comparisons, Adjusted for Center, by Intended Treatment Group and Actual # Active Fluoride Varnish Applications (n = 280)

Comparison by Intended Treatment Group	Odds Ratio	95% Confidence Interval
0 *vs.* 4	3.8	1.9, 7.6
0 *vs.* 2	2.2	1.2, 4.1
Comparison by # Active Fluoride Varnish Applications		
0 *vs.* 3-4*	18.3	2.4, 138.5
0 *vs.* 2	3.4	1.6, 7.5
0 *vs.* 1	2.5	1.3, 4.7

* Includes one child with 4 active fluoride applications.

clinical sites with different populations increase generalizability of the findings. Fluoride varnish and parental counseling should be recommended as part of caries prevention programs targeting infants and toddlers.

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REFERENCES

American Academy of Pediatric Dentistry (2004). Clinical guidelines on infant oral health care. Revised 2004. http://www.aapd.org/media/Policies_Guidelines/G_InfantOralHealthCare.pdf (accessed 3/29/05).

American Association of Public Health Dentistry (2004). First oral health assessment policy, adopted May 2004. http://aaphd.org/default.asp?page=FirstHealthPolicy.htm (accessed 3/29/05).

Bader JD, Shugars DA, Bonito AJ (2001). Systematic reviews of selected dental caries diagnostic and management methods. *J Dent Educ* 65:960-968.

Blinkhorn A, Davies R (1998). Using fluoride varnish in the practice. *Br Dent J* 185:280-281.

Drury TF, Horowitz AM, Ismail AI, Maertens MP, Rozier RG, Selwitz RH (1999). Diagnosing and reporting early childhood caries for research purposes. *J Public Health Dent* 59:192-197.

Fisher LD, Dixon DO, Herson J, Frankowski RK, Hearron MS, Peace KE (1990). Intention to treat in clinical trials. In: Statistical issues in drug research and development. Peace KE, editor. New York: Marcel Dekker, Inc., pp. 331-350.

Hanley JA, Lippman-Hand A (1983). If nothing goes wrong, is everything all right? Interpreting zero numerators. *J Am Med Assoc* 249:1743-1745.

Helfenstein U, Steiner M (1994). Fluoride varnishes (Duraphat): a meta-analysis. *Community Dent Oral Epidemiol* 22:1-5.

Koch GG, Edwards S (1988). Clinical efficacy trials with categorical data. In: Biopharmaceutical statistics for drug development. Peace KE, editor. New York: Marcel Dekker, pp. 403-458.

Koch GG, Gansky SA (1996). Statistical considerations for multiplicity in confirmatory protocols. *Drug Info J* 30:523-534.

Marinho VC, Higgins JP, Logan S, Sheiham A (2002). Fluoride varnishes for preventing dental caries in children and adolescents. *Cochrane Database Syst Rev* 3:CD002279.

NIH (2001). Diagnosis and management of dental caries throughout life. National Institutes of Health Consensus Development Conference statement, March 26-28, 2001. *J Dent Educ* 65:1162-1168.

Nowak AJ (1998). Early intervention and the pediatric dentist. *J Southeastern Soc Ped Dent* 4:9.

Nowak AJ, Casamassimo PS (1995). Using anticipatory guidance to provide early dental intervention. *J Am Dent Assoc* 126:1156-1163.

Pollick HF, Isman R, Fine JI, Wellman J, Kipnis P, Ellison J (1999). Report of the California oral health needs assessment of children, 1993-94: background, methodology, findings. Oakland, CA: The Dental Health Foundation.

Ramos-Gomez F, Jue B, Bonta CY (2002). Implementing an infant oral care program. *J CA Dent Assoc* 30:752-761

Rozier RG (2001). Effectiveness of methods used by dental professionals for the primary prevention of dental caries. *J Dent Educ* 65:1063-1072.

Schafer JL (1997). Analysis of incomplete multivariate data. New York: Chapman & Hall.

Shiboski CH, Gansky SA, Ramos-Gomez F, Ngo L, Isman R, Pollick HF (2003). The association of early childhood caries and race/ethnicity among California preschool children. *J Public Health Dent* 63:38-46.

Strohmenger L, Brambilla E (2001). The use of fluoride varnishes in the prevention of dental caries: a short review. *Oral Dis* 7:71-80.

USDHHS, PHS, NIH, NIDR (1991). Oral health surveys of the National Institute of Dental Research: diagnostic criteria and procedures. NIH Publication No. 91-2870. Bethesda, MD: US Department of Health and Human Services, NIH.

Weinstein P, Domoto P, Koday M, Leroux B (1994). Results of a promising open trial to prevent baby bottle tooth decay: a fluoride varnish study. *ASDC J Dent Child* 61:338-341.

Weintraub JA (2003). Fluoride varnish for caries prevention: comparisons with other preventive agents and recommendations for a community-based protocol. *Spec Care Dentist* 23:180-186.