Site-specific Periodontal Data Revisited – Results From a Recent RCT on Triclosan in Toothpaste

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Background

- Individual variation of inflammatory responses in gingiva to dental plaque
  - Löe et al. 1965
  - Abbas et al. 1986
  - Müller et al. 2000
  - Trombelli et al. 2004

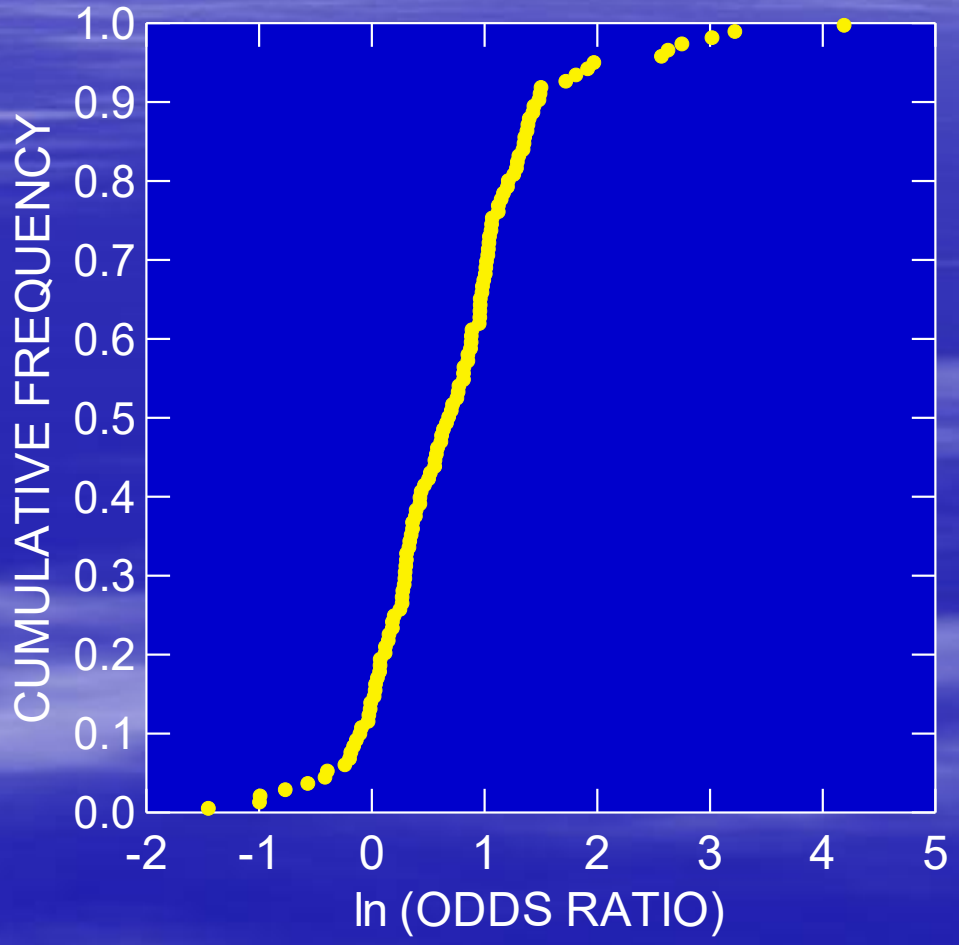
Clin Oral Invest (2000) 4: 212-218

ORIGINAL ARTICLE

H.-P. Müller • A. Heinecke • T. Eger

Site-specific association between supragingival plaque and bleeding upon probing in young adults

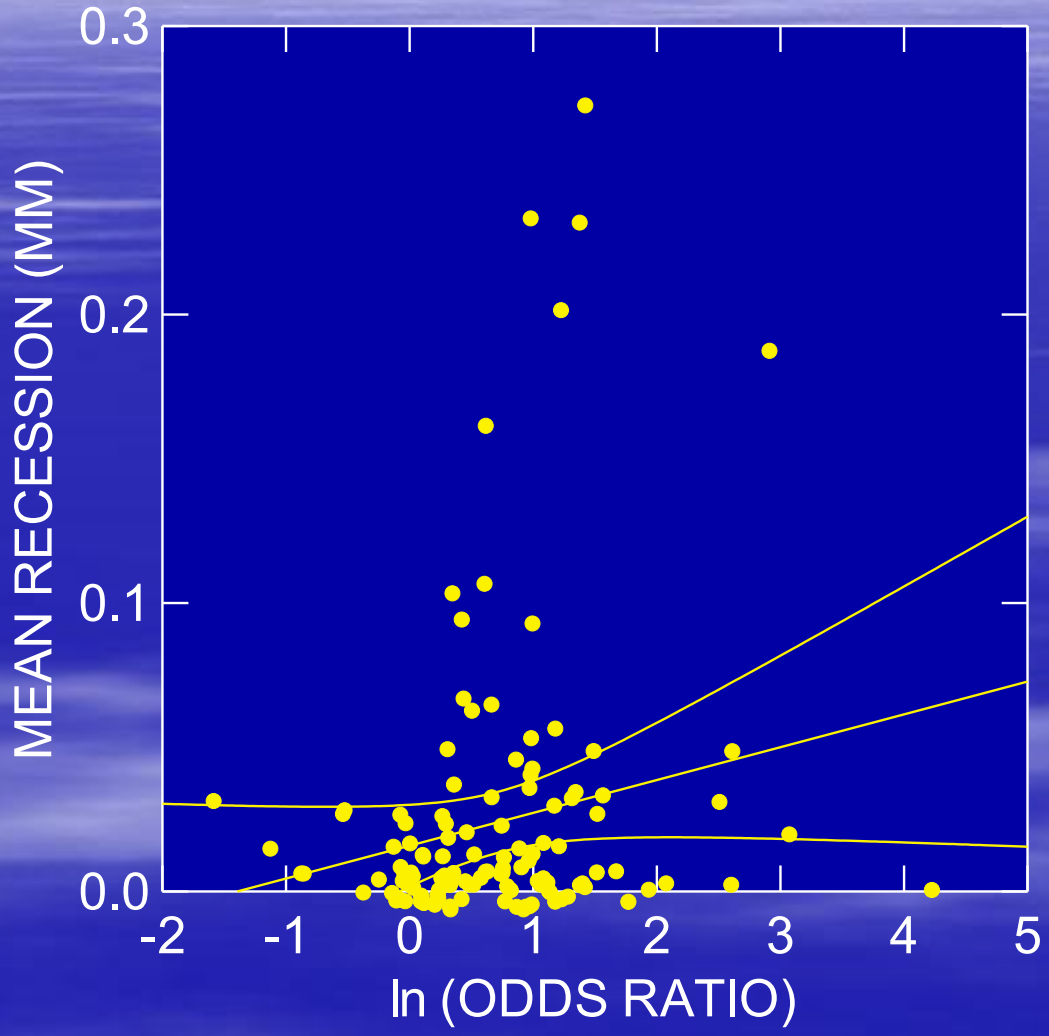
DISTRIBUTION OF LOG-TRANSFORMED ODDS RATIOS



CLINICAL CONDITIONS IN SUBJECTS WITH EXTREME ASSOCIATION BETWEEN PLAQUE AND BLEEDING ON PROBING

	Lower 20% OR	Upper 20% OR	*p*
Mean PPD	1.94 ± 0.25	1.92 ± 0.22	n.s.
Maximum PPD	3.44 ± 0.56	3.68 ± 0.90	n.s.
Mean CAL	0.02 ± 0.03	0.10 ± 0.16	<0.05
Maximum CAL	1.32 ± 1.46	2.48 ± 1.93	<0.05
Mean REC	0.01 ± 0.01	0.05 ± 0.08	<0.05
Maximum REC	0.64 ± 0.81	1.44 ± 1.61	<0.05
% BOP	24 ± 10	25 ± 14	n.s.
% PLAQUE	54 ± 24	53 ± 23	n.s.

CORRELATION BETWEEN LOG-TRANSFORMED ODDS RATIO AND MEAN GINGIVAL RECESSION



r=0.21, p=0.02

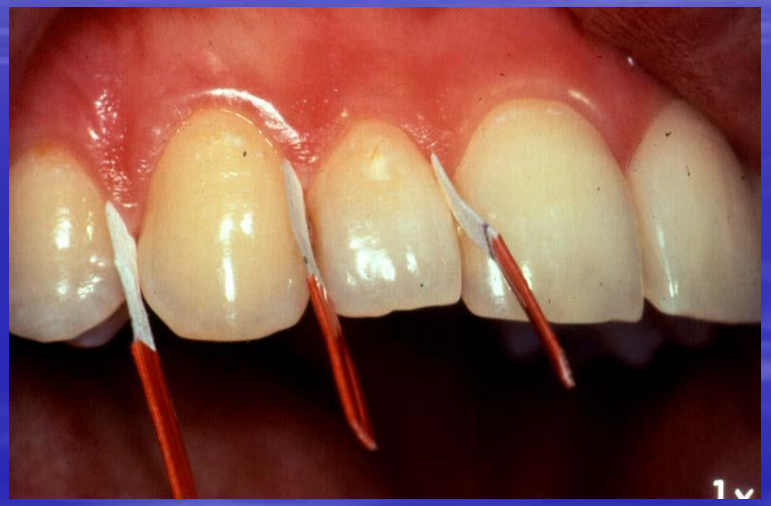
- Internal Factors
  - Sex hormones
  - Stress
  - Diabetes mellitus
  - Genetics?

- External Factors
  - Smoking
  - NSAIDs
  - Steroids
  - Toothpaste?

The Data Analysis

- Inflammatory processes of the periodontium are hierarchical
  - The subject
  - The tooth
  - The site

- Observations made at lower levels nested in higher levels cannot be regarded independent



- Popular strategy
  - Summarize at the subject level!
  - Make the subject the statistical unit
  - However … there are several serious caveats:
    - Loss of most of the collected albeit valuable information
    - Any correlation between aggregate responses are prone to the so-called ecological fallacy
    - Any inference might thus be spurious

Association of *Eubacterium nodatum* and *Treponema denticola* with human periodontitis lesions

A. D. Haffajee, R.P. Teles, S. S. Socransky

Department of Periodontology, The Forsyth Institute, Boston, MA, USA

Haffajee AD, Teles RP, Socransky SS. Associations of Eubacterium nodatum *and* Treponema denticola *with human periodontitis lesions.*
Oral Microbiol Immunol 2006: 21: 269-282.

….

Methods: Subgingival plaque samples were taken from the mesial aspect of each tooth in 635 subjects with chronic periodontitis and 189 periodontally healthy subjects. The samples were individually analyzed for their content of 40 bacterial species using checkerboard DNA-DNA hybridization (total samples = 21,832). Mean counts, % DNA probe counts and percentage of sites colonized at $>10^5$ were determined for each species in each subject and then averaged in each clinical group. Significance of difference between groups was determined using Mann-Whitney test. Association between combinations of species and periodontal status was examined by stepwise logistic regression analysis.

….

- So-called marginal models, such as Generalized Estimating Equations as possible solution
  - They usually start with the formulation for a covariance structure which is not necessarily based upon a multilevel structure
  - They aim to provide estimates with acceptable properties only for the fixed parameters in the model

- They treat existence of any random parameter as a necessary nuisance without providing explicit estimates for them
- They may be inefficient if they utilize a covariance structure that is substantially incorrect
- Instead, they ignore the correct covariance structure (Lindsay and Lambert 1998) which is explicitly addressed in Multilevel Modeling

Why Triclosan?

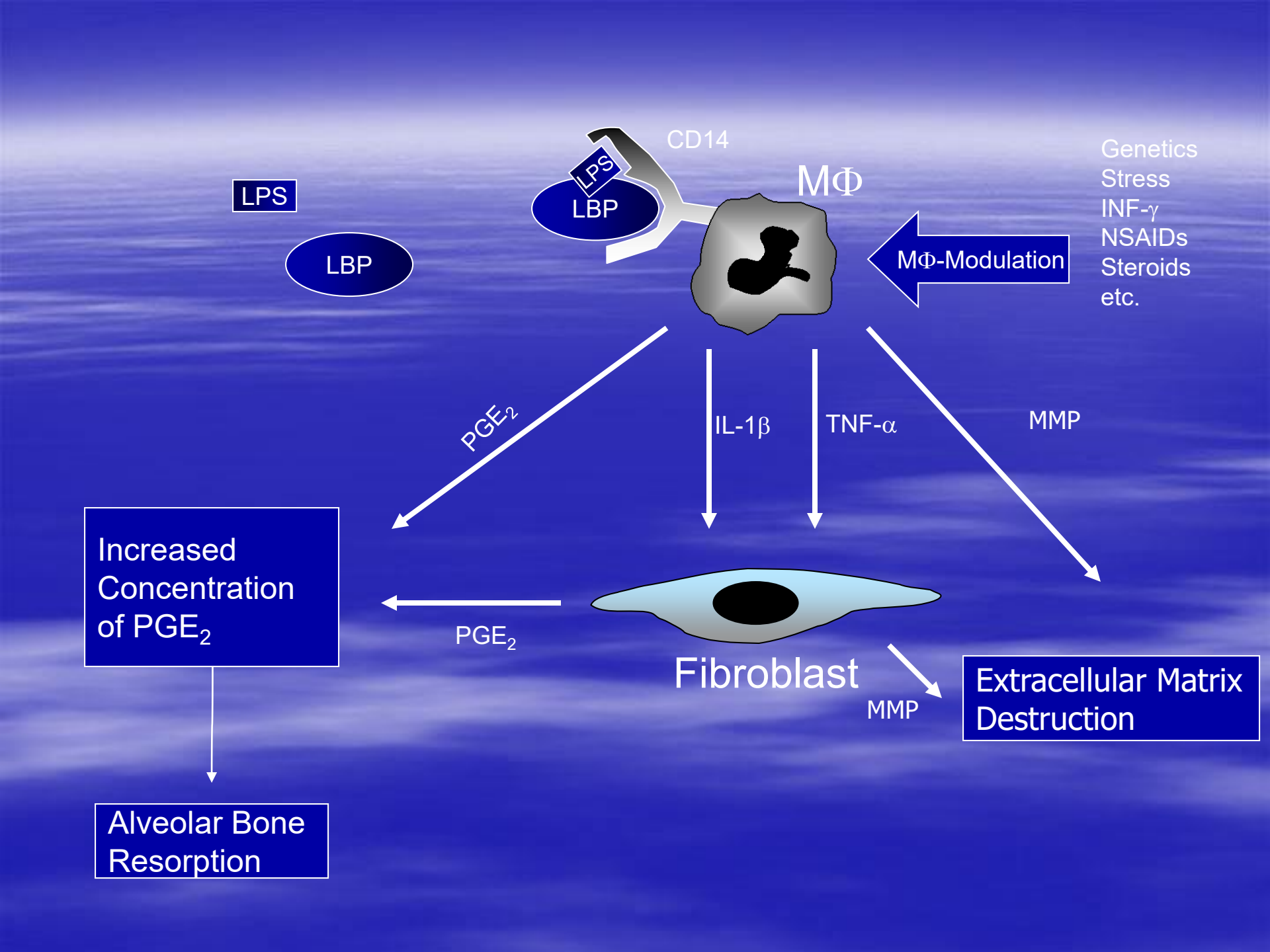
- Part of a multilevel representation of the steady-state plaque environment
- Example for a potential external factor with the capacity of modulating the ‘causal’ relationship between plaque and gingivitis

- Triclosan has been shown to dampen the inflammatory response during experimental gingivitis
- Early reports indicate that the anti-inflammatory action might be independent of its plaque-reducing effect
- Recent gingivitis experiments were, however, inconclusive (McClanahan & Bartizek 2002)

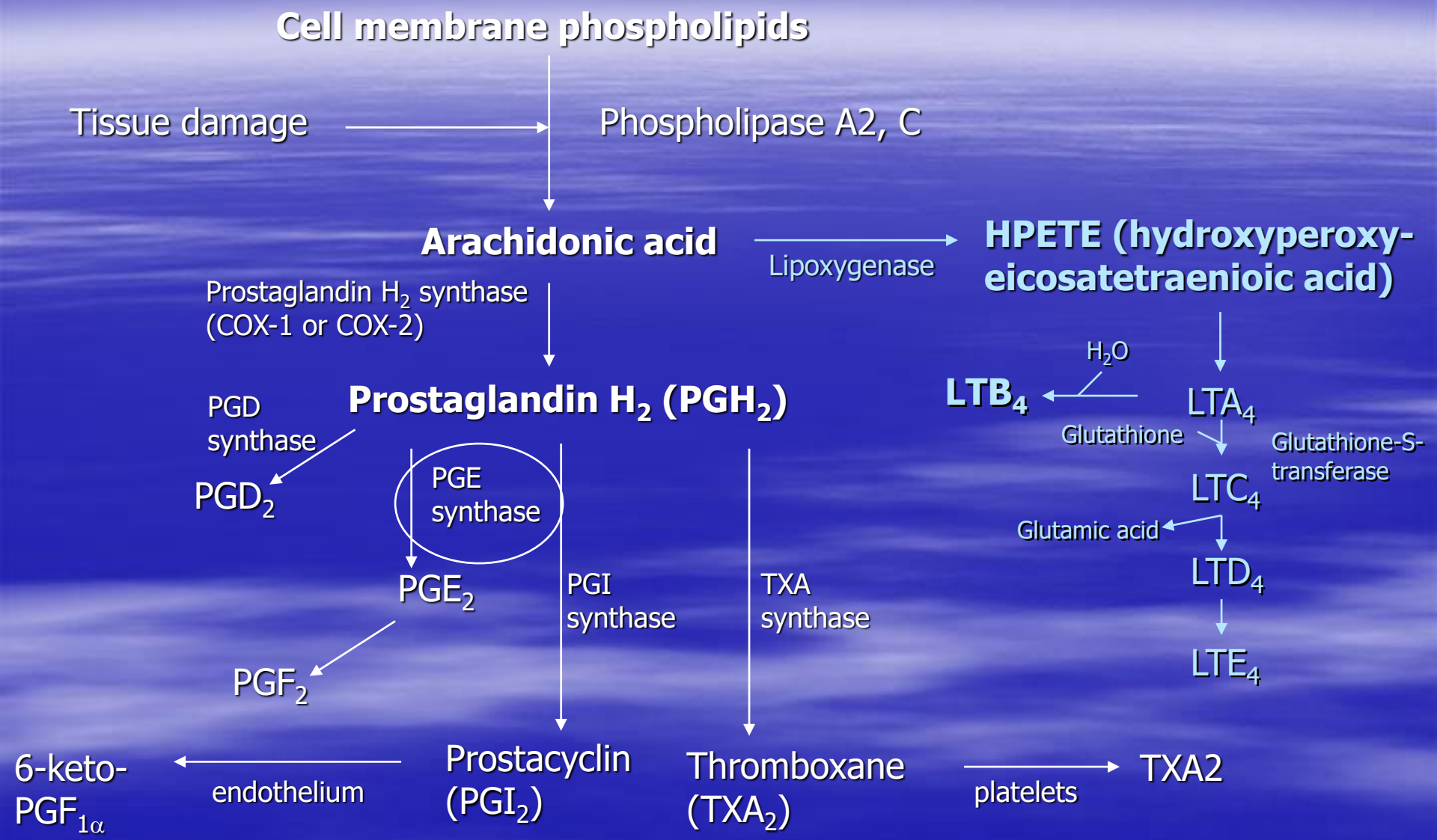
- In a recent meta-analysis of 16 RCT of at least 6 months duration both plaque and gingivitis levels were reduced (Davies et al. 2004)
- Thus, it remains unclear whether the association between plaque and gingivitis is attenuated when triclosan-containing toothpaste is introduced

How Does It Work?

- Triclosan affects both cyclooxygenase and lipoxygenase pathways of arachidonic acid with similar efficacy (Gaffar et al. 1995)
- It inhibits IL-1β induced PGE_2 production of human gingival fibroblasts in a dose-dependent manner (Modeer et al. 1996)


LPS
LBP
CD14
LPS
LBP
MΦ
MΦ-Modulation
Genetics
Stress
INF-γ
NSAIDs
Steroids
etc.
PGE2
IL-1β
TNF-α
MMP
Increased Concentration of PGE2
PGE2
Fibroblast
MMP
Extracellular Matrix Destruction
Alveolar Bone Resorption

- It reduces the stimulatory effect of TNFα on the expression of microsomal PGE synthase-1 at both mRNA and protein level and subsequently production of PGE_2
- It does not affect translocation of NF-κB or expression of COX-2 in TNFα stimulated cells (Mustafa et al. 2005)


Cell membrane phospholipids
Tissue damage
Phospholipase A2, C
Arachidonic acid
Lipoxygenase
HPETE (hydroxyperoxy-eicosatetraenioic acid)
Prostaglandin H2 synthase (COX-1 or COX-2)
Prostaglandin H2 (PGH2)
H2O
LTB4
LTA4
Glutathione
Glutathione-S-transferase
LTC4
Glutamic acid
LTD4
LTE4
PGD synthase
PGD2
PGE synthase
PGE2
PGI synthase
TXA synthase
PGF2
6-keto-PGF1α
endothelium
Prostacyclin (PGI2)
Thromboxane (TXA2)
platelets
TXA2

Effect of triclosan/copolymer-containing toothpaste on the association between plaque and gingival bleeding: a randomized controlled clinical trial

H. P. Müller[1], K.M. Barrieshi-Nusair[1], E. Könönen[1,2] and M. Yang[3]

[1]Faculty of Dentistry, Kuwait University, Kuwait; [2]Anaerrobe Reference Laboratory, National Public Health Institute, Helsinki, Finland; [3]Institute of Community Health Sciences, Queen Mary, University of London, London, UK

Müller HP, Barrieshi-Nusair KM, Könönen E, Yang M. Effect of triclosan/copolymer-containing toothpaste on the association between plaque and gingival bleeding: a randomized controlled clinical trial. J Clin Periodontol 2006: 33: 811-818; doi: 10.1111/j.1600-051X.2006.00993.x

Objectives

- Short-term RCT in a steady-state plaque environment
- Effects of triclosan-containing toothpaste on longitudinal associations between amount of supragingival plaque and gingival bleeding tendency
- Application of advanced statistical methodology (multivariate multilevel modelling) using all available site-specific data

Material and Methods

- 10-week, randomized, 2-arm, double-masked, controlled clinical trial
- CONSORT guidelines were followed, see http://www.consort-statement.org/newene.htm
- Ethical approval by KU FOD Ethical Committee as conforming to Ethical Principles for Medical Research Involving Human Subjects, see http://www.wma.net/e/policy/b3.htm

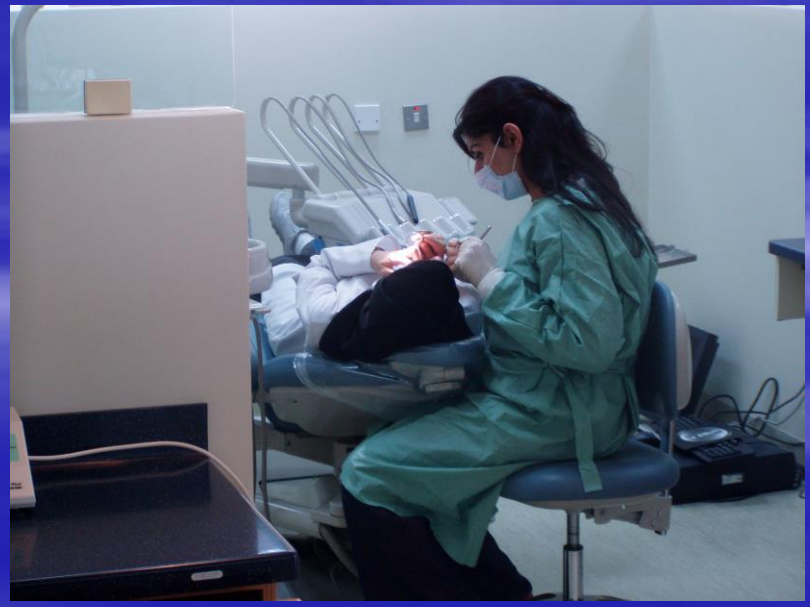
- Sample size calculation based on previous information (Müller et al. 2002)
  - Estimate of SD of Log Mantel-Haenszel's OR of 0.5
  - Clinically relevant difference of Log MH's OR of 0.5
  - Alpha of 5%
  - 1-beta (power) of 80%, result in

  17 volunteers in each group
- Study period September 2003 until September 2004

Volunteers

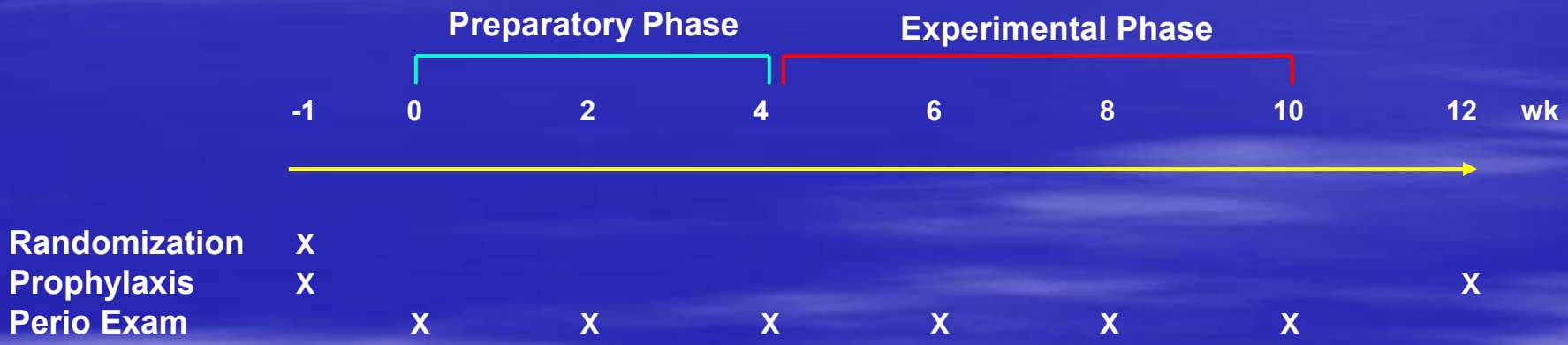
- Sampling among 5th and 6th year Dental students and Dental hygienists
  - *N* = 34
  - 19-28 yr of age (mean 22.2 ± 1.4 yr)
  - Minimum of 23 teeth (mean 28.7 ± 2.7)
- Randomization according to computer-generated list of random numbers
- Allocation concealment of PI until finalizing of statistical analysis

- Inclusion criteria
  - Female gender
  - Mild plaque-induced gingival disease
  - Minimum amounts of supragingival calculus



- Exclusion criteria
  - Indication for antibiotic prophylaxis
  - Pregnancy/lactation
  - Long-term medication with possible effects on periodontal tissues
  - Non-plaque-induced gingival disease
  - Destructive periodontal disease w/ possible exception localized gingival recession
  - Extensive tooth restoration or tooth replacement
  - Orthodontic treatment
  - Smoking

Experimental Design



- Preparatory Phase
  - Recording of frequencies of tooth brushing, toothpaste used, use of dental floss
  - No attempt was made to improve oral hygiene
  - Instead, volunteers were advised not to change oral hygiene habits
  - In case of usage of triclosan-containing toothpaste, the volunteer was asked to change
  - To investigate variation of site-specific associations between plaque and bleeding on probing
  - To study a possible Hawthorne effect
  - Wash-out period for subjects already using triclosan-containing toothpaste

- Experimental Phase (according to randomization)
  - Experimental toothpaste (*N* = 17)
    - Colgate Total®
      - 0.24% sodium monofluorophosphate
      - 0.3% triclosan
      - 2% polyvinyl-methyl ether maleic acid (PMMA)

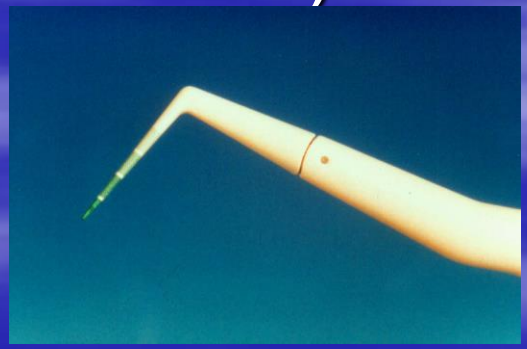
  - Control toothpaste (*N* = 17)
    - Colgate Maximum Cavity Protection®
      - 0.76% sodium monofluorophosphate
      - 0.1% sodium fluoride

      corresponding to 1450 ppm F^-

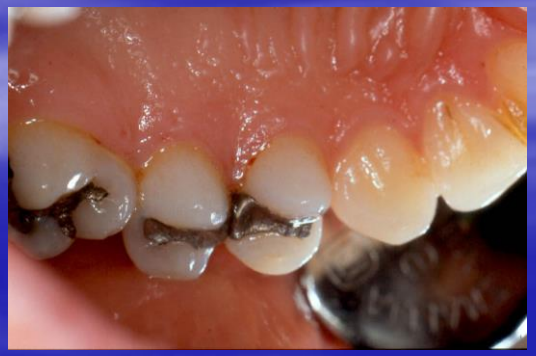
Both experimental toothpastes were provided in white neutral containers

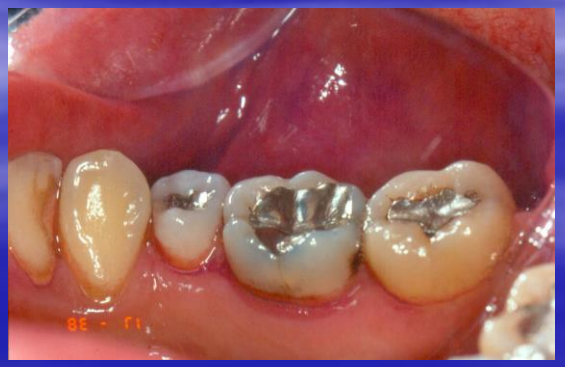
Clinical Examinations

- One blinded examiner (PI)
- Periodontal examination at 6 sites of every tooth present
- Periodontal probing using a pressure-controlled probe (ClickProbe, KerrHawe) at 1.27 MPa
  - Periodontal probing depth (mm)
  - Clinical attachment level (mm)



  - Bleeding on probing (BI 0, 1, 2)
- Presence of supragingival calculus
- Plaque Index (Silness & Löe 1964) after disclosing of supragingival plaque (D&C Red-28, Sultan Chemists Inc.)





Data Analysis

- *MLwiN* 2.02, Center for Multilevel Modelling, University of Bristol, UK
- Variance components multivariate repeated measures 4-level model of binary response BOP, where
  - n occasions (treated as repetitions at level 1, indicated by t) are nested
  - within sites (indicated by j), and
  - teeth (indicated by k), which are nested in
  - subjects l
  - Vectors of indicator variables (0, 1) for t = 1, 2, …, n are described by z_t

$$y_{tjkl} \sim Bin(1, \pi_{tjkl}),$$

$$\log it(\pi_{tjkl}) = \sum_{t=1}^{n} \beta_{0,t} z_{tjkl} +$$

- Residual terms at the subject (f_{tl}) and tooth levels (v_{tkl}) are associated with the intercepts for each examination ($\beta_{0,t}z_{tjkl}$)
- No level 1 (occasion) variation as at level 2 (site) binomial variates among occasions are allowed to covary
  - At this level, a covariance structure is estimated in which diagonal terms are constrained to have binomial variance, and
  - off-diagonal terms are estimated
  - In this way, dependence of observations is fully accounted (Yang et al. 2000)
- The model can then be extended by including covariates

$$\text{resp}_{1jkl} \sim \text{Binomial}(\text{denom.old}_{1jkl}, \pi_{1jkl})$$
$$\text{resp}_{2jkl} \sim \text{Binomial}(\text{denom.old}_{2jkl}, \pi_{2jkl})$$
$$\text{resp}_{3jkl} \sim \text{Binomial}(\text{denom.old}_{3jkl}, \pi_{3jkl})$$
$$\text{logit}(\pi_{1jkl}) = \beta_{0kl}\text{cons.bp1}_{ijkl}$$
$$\beta_{0kl} = \beta_0 + f_{0l} + v_{0kl}$$
$$\text{logit}(\pi_{2jkl}) = \beta_{1kl}\text{cons.bp2}_{ijkl}$$
$$\beta_{1kl} = \beta_1 + f_{1l} + v_{1kl}$$
$$\text{logit}(\pi_{3jkl}) = \beta_{2kl}\text{cons.bp3}_{ijkl}$$
$$\beta_{2kl} = \beta_2 + f_{2l} + v_{2kl}$$

$$\begin{bmatrix} f_{0l} \\ f_{1l} \\ f_{2l} \end{bmatrix} \sim \text{N}(0,\ \Omega_f) \ :\ \Omega_f = \begin{bmatrix} \sigma^2_{f0} & & \\ \sigma_{f0\,1} & \sigma^2_{f1} & \\ \sigma_{f0\,2} & \sigma_{f1\,2} & \sigma^2_{f2} \end{bmatrix}$$

$$\begin{bmatrix} v_{0kl} \\ v_{1kl} \\ v_{2kl} \end{bmatrix} \sim \text{N}(0,\ \Omega_v) \ :\ \Omega_v = \begin{bmatrix} \sigma^2_{v0} & & \\ \sigma_{v0\,1} & \sigma^2_{v1} & \\ \sigma_{v0\,2} & \sigma_{v1\,2} & \sigma^2_{v2} \end{bmatrix}$$

$$\text{cov}\begin{bmatrix} \text{resp}_{1jkl}|\pi_{1jkl} \\ \text{resp}_{2jkl}|\pi_{2jkl} \\ \text{resp}_{3jkl}|\pi_{3jkl} \end{bmatrix} = \begin{bmatrix} \alpha g(\pi_{1jkl}) & & \\ \rho\,[g(\pi_{1jkl})g(\pi_{2jkl})]^{0.5} & \alpha g(\pi_{2jkl}) & \\ \rho\,[g(\pi_{1jkl})g(\pi_{3jkl})]^{0.5} & \rho\,[g(\pi_{2jkl})g(\pi_{3jkl})]^{0.5} & \alpha g(\pi_{3jkl}) \end{bmatrix}$$

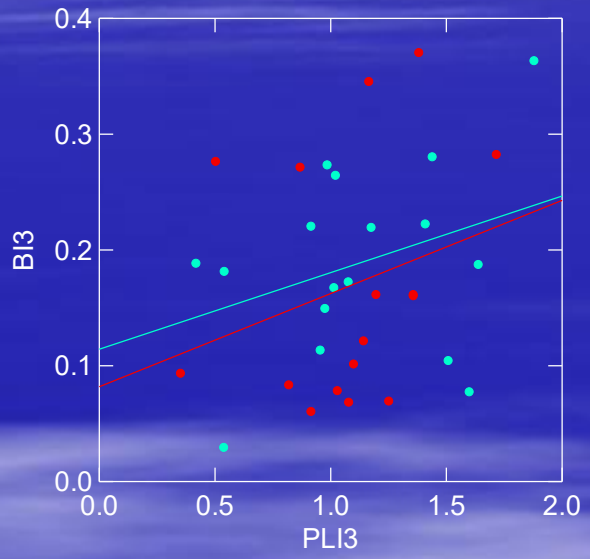
$$g(\pi) = \pi(1 - \pi)/n$$

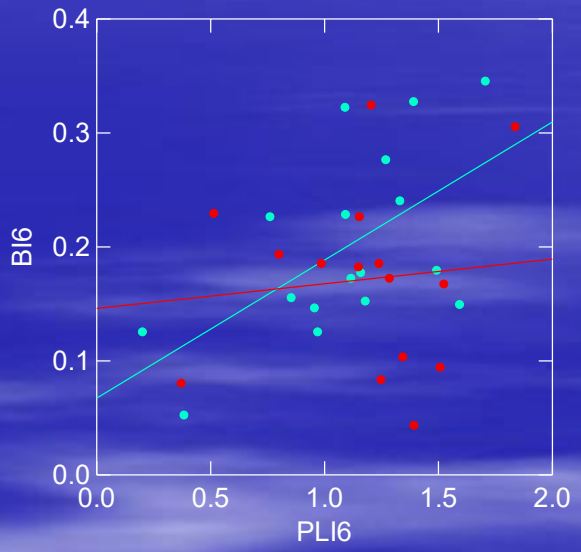
Results

	Baseline		Difference at wk 10	
	Control (*N* = 17)	Test (*N* = 17)	Control (*N* = 17)	Test (*N* = 15)
PPD (mm)	1.84 ± 0.24	1.76 ± 0.30	-0.08 ± 0.24	-0.04 ± 0.18
CAL (mm)	0.01 ± 0.01	0.01 ± 0.01	+0.00 ± 0.02	+0.00 ± 0.01
BI (0-2)	0.26 ± 0.10	0.20 ± 0.14	-0.06 ± 0.08	-0.05 ± 0.12
% BOP	23.8 ± 8.7	18.9 ± 12.7	-5.5 ± 7.3	-5.7 ± 8.6
PLI (0-3)	1.09 ± 0.42	1.09 ± 0.37	+0.00 ± 0.49	+0.09 ± 0.33
% Plaque	66.1 ± 19.0	64.4 ± 18.8	-1.8 ± 22.9	+2.5 ± 15.2
% CLS	1.9 ± 2.6	3.4 ± 3.7	+4.6 ± 4.4	+2.7 ± 6.3

Significant differences ($p<0.05$) as compared to baseline in red

Ecological Analysis





Multivariate Multilevel Models

- Preparatory Phase

$$\text{resp}_{1jkl} \sim \text{Binomial}(\text{denom.old}_{1jkl}, \pi_{1jkl})$$
$$\text{resp}_{2jkl} \sim \text{Binomial}(\text{denom.old}_{2jkl}, \pi_{2jkl})$$
$$\text{resp}_{3jkl} \sim \text{Binomial}(\text{denom.old}_{3jkl}, \pi_{3jkl})$$
$$\text{logit}(\pi_{1jkl}) = \beta_{0kl}\text{cons.bp1}_{ijkl} + \beta_3\text{pli1.bp1}_{ijkl} + \beta_6\text{ppd1.bp1}_{ijkl} + \beta_9\text{cls1.bp1}_{ijkl}$$
$$\beta_{0kl} = \beta_0 + f_{0l} + v_{0kl}$$
$$\text{logit}(\pi_{2jkl}) = \beta_{1kl}\text{cons.bp2}_{ijkl} + \beta_4\text{pli2.bp2}_{ijkl} + \beta_7\text{ppd2.bp2}_{ijkl} + \beta_{10}\text{cls2.bp2}_{ijkl}$$
$$\beta_{1kl} = \beta_1 + f_{1l} + v_{1kl}$$
$$\text{logit}(\pi_{3jkl}) = \beta_{2kl}\text{cons.bp3}_{ijkl} + \beta_5\text{pli3.bp3}_{ijkl} + \beta_8\text{ppd3.bp3}_{ijkl} + \beta_{11}\text{cls3.bp3}_{ijkl}$$
$$\beta_{2kl} = \beta_2 + f_{2l} + v_{2kl}$$

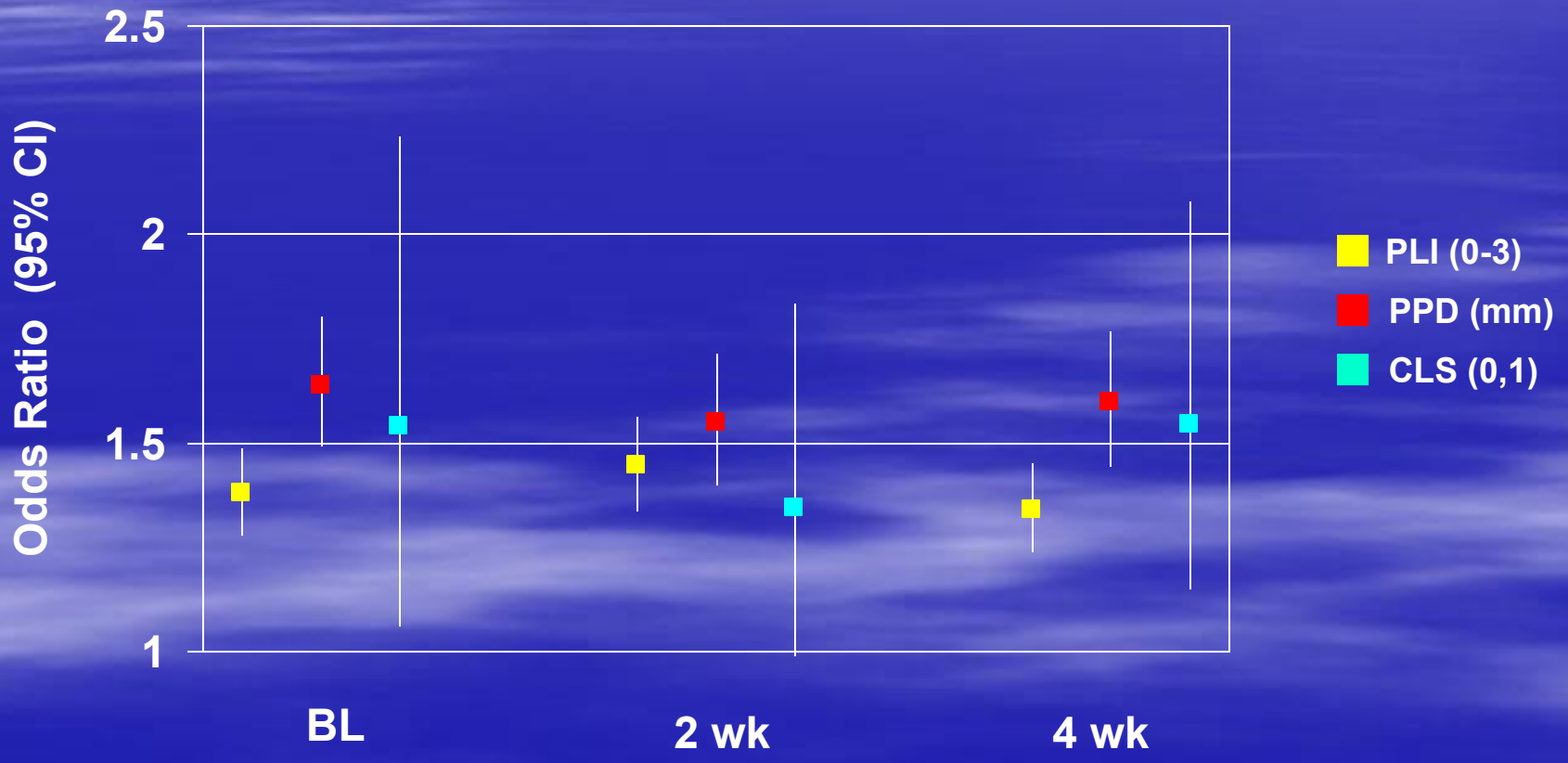
$$\begin{bmatrix} f_{0l} \\ f_{1l} \\ f_{2l} \end{bmatrix} \sim \text{N}(0,\ \Omega_f) \ :\ \Omega_f = \begin{bmatrix} \sigma^2_{f0} & & \\ \sigma_{f01} & \sigma^2_{f1} & \\ \sigma_{f02} & \sigma_{f12} & \sigma^2_{f2} \end{bmatrix}$$

$$\begin{bmatrix} v_{0kl} \\ v_{1kl} \\ v_{2kl} \end{bmatrix} \sim \text{N}(0,\ \Omega_v) \ :\ \Omega_v = \begin{bmatrix} \sigma^2_{v0} & & \\ \sigma_{v01} & \sigma^2_{v1} & \\ \sigma_{v02} & \sigma_{v12} & \sigma^2_{v2} \end{bmatrix}$$

$$\text{cov}\begin{bmatrix} \text{resp}_{1jkl}|\pi_{1jkl} \\ \text{resp}_{2jkl}|\pi_{2jkl} \\ \text{resp}_{3jkl}|\pi_{3jkl} \end{bmatrix} = \begin{bmatrix} \alpha g(\pi_{1jkl}) & & \\ \rho\,[g(\pi_{1jkl})g(\pi_{2jkl})]^{0.5} & \alpha g(\pi_{2jkl}) & \\ \rho\,[g(\pi_{1jkl})g(\pi_{3jkl})]^{0.5} & \rho\,[g(\pi_{2jkl})g(\pi_{3jkl})]^{0.5} & \alpha g(\pi_{3jkl}) \end{bmatrix}$$

$$g(\pi) = \pi(1 - \pi)/n$$

Fixed Effects of Multivariate Repeated Measures
4-level Model of BOP



Biserial Correlation Estimates Derived from Random Part of Multivariate Repeated Measures 4-level Model of BOP

		2 wk	4 wk
Subject	BL	0.888	0.871
	2 wk		0.726
Tooth	BL	0.336	0.336
	2 wk		0.260
Site	BL	0.113	0.109
	2 wk		0.134

Prep Phase, Conclusions

- Consistent positive associations between BOP and (i) plaque, (ii) periodontal probing depth, and (iii) calculus
- High correlations of biserial BOP at the subject level, moderate correlations at the tooth level
- Very low correlations of biserial BOP at the site level
- No Hawthorne effect discernable

- Experimental Phase

$$\text{resp}_{1jkl} \sim \text{Binomial}(\text{denom.old}_{1jkl}, \pi_{1jkl})$$
$$\text{resp}_{2jkl} \sim \text{Binomial}(\text{denom.old}_{2jkl}, \pi_{2jkl})$$
$$\text{resp}_{3jkl} \sim \text{Binomial}(\text{denom.old}_{3jkl}, \pi_{3jkl})$$
$$\text{resp}_{4jkl} \sim \text{Binomial}(\text{denom.old}_{4jkl}, \pi_{4jkl})$$
$$\text{logit}(\pi_{1jkl}) = \beta_{0kl}\text{cons.bp3}_{ijkl} + \beta_{7}\text{pli3.bp3}_{ijkl} + \beta_{11}\text{ppd3.bp3}_{ijkl} + \beta_{15}\text{cls3.bp3}_{ijkl}$$
$$\beta_{0kl} = \beta_0 + f_{0l} + v_{0kl}$$
$$\text{logit}(\pi_{2jkl}) = \beta_{1kl}\text{cons.bp4}_{ijkl} + \beta_{4}\text{test.bp4}_{ijkl} + \beta_{8}\text{pli4.bp4}_{ijkl} + \beta_{12}\text{ppd4.bp4}_{ijkl} + \beta_{16}\text{cls4.bp4}_{ijkl}$$
$$\beta_{1kl} = \beta_1 + f_{1l} + v_{1kl}$$
$$\text{logit}(\pi_{3jkl}) = \beta_{2kl}\text{cons.bp5}_{ijkl} + \beta_{5}\text{test.bp5}_{ijkl} + \beta_{9}\text{pli5.bp5}_{ijkl} + \beta_{13}\text{ppd5.bp5}_{ijkl} + \beta_{17}\text{cls5.bp5}_{ijkl}$$
$$\beta_{2kl} = \beta_2 + f_{2l} + v_{2kl}$$
$$\text{logit}(\pi_{4jkl}) = \beta_{3kl}\text{cons.bp6}_{ijkl} + \beta_{6}\text{test.bp6}_{ijkl} + \beta_{10}\text{pli6.bp6}_{ijkl} + \beta_{14}\text{ppd6.bp6}_{ijkl} + \beta_{18}\text{cls6.bp6}_{ijkl}$$
$$\beta_{3kl} = \beta_3 + f_{3l} + v_{3kl}$$

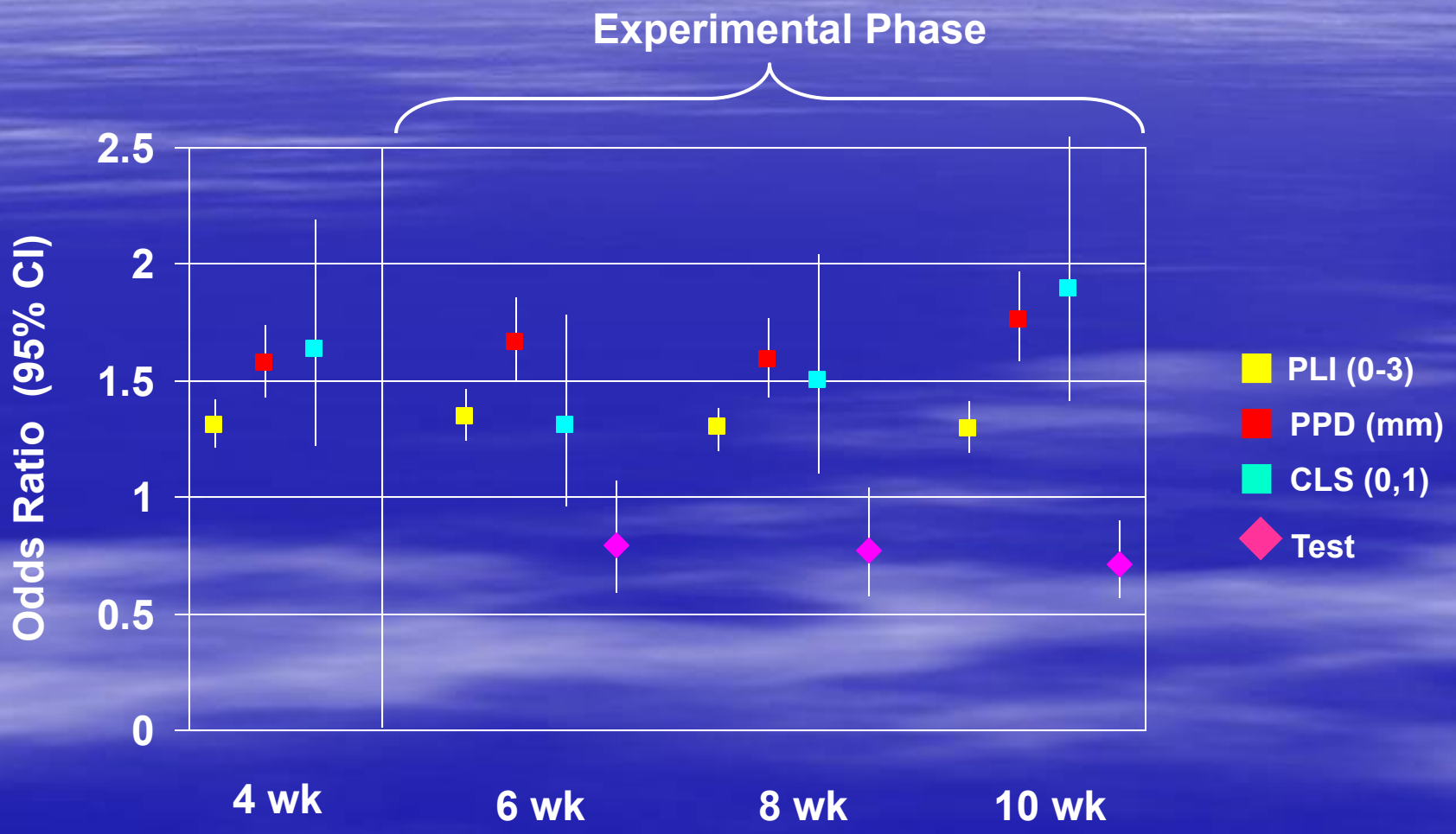
$$\begin{bmatrix} f_{0l} \\ f_{1l} \\ f_{2l} \\ f_{3l} \end{bmatrix} \sim \text{N}(0,\ \Omega_f) \ :\ \Omega_f = \begin{bmatrix} \sigma^2_{f0} & & & \\ \sigma_{f0\,1} & \sigma^2_{f1} & & \\ \sigma_{f0\,2} & \sigma_{f1\,2} & \sigma^2_{f2} & \\ \sigma_{f0\,3} & \sigma_{f1\,3} & \sigma_{f2\,3} & \sigma^2_{f3} \end{bmatrix}$$

$$\begin{bmatrix} v_{0kl} \\ v_{1kl} \\ v_{2kl} \\ v_{3kl} \end{bmatrix} \sim \text{N}(0,\ \Omega_v) \ :\ \Omega_v = \begin{bmatrix} \sigma^2_{v0} & & & \\ \sigma_{v0\,1} & \sigma^2_{v1} & & \\ \sigma_{v0\,2} & \sigma_{v1\,2} & \sigma^2_{v2} & \\ \sigma_{v0\,3} & \sigma_{v1\,3} & \sigma_{v2\,3} & \sigma^2_{v3} \end{bmatrix}$$

$$\text{cov}\begin{bmatrix} \text{resp}_{1jkl}|\pi_{1jkl} \\ \text{resp}_{2jkl}|\pi_{2jkl} \\ \text{resp}_{3jkl}|\pi_{3jkl} \\ \text{resp}_{4jkl}|\pi_{4jkl} \end{bmatrix} = \begin{bmatrix} \alpha g(\pi_{1jkl}) & & & \\ \rho\,[g(\pi_{1jkl})g(\pi_{2jkl})]^{0.5} & \alpha g(\pi_{2jkl}) & & \\ \rho\,[g(\pi_{1jkl})g(\pi_{3jkl})]^{0.5} & \rho\,[g(\pi_{2jkl})g(\pi_{3jkl})]^{0.5} & \alpha g(\pi_{3jkl}) & \\ \rho\,[g(\pi_{1jkl})g(\pi_{4jkl})]^{0.5} & \rho\,[g(\pi_{2jkl})g(\pi_{4jkl})]^{0.5} & \rho\,[g(\pi_{3jkl})g(\pi_{4jkl})]^{0.5} & \alpha g(\pi_{4jkl}) \end{bmatrix}$$

$$g(\pi) = \pi(1 - \pi)/n$$

Fixed Effects of Multivariate Repeated Measures
4-level Model of BOP



Subject, Tooth and Site Level Variance Estimates Derived from Random Part of Multivariate Repeated Measures 4-level Model of BOP

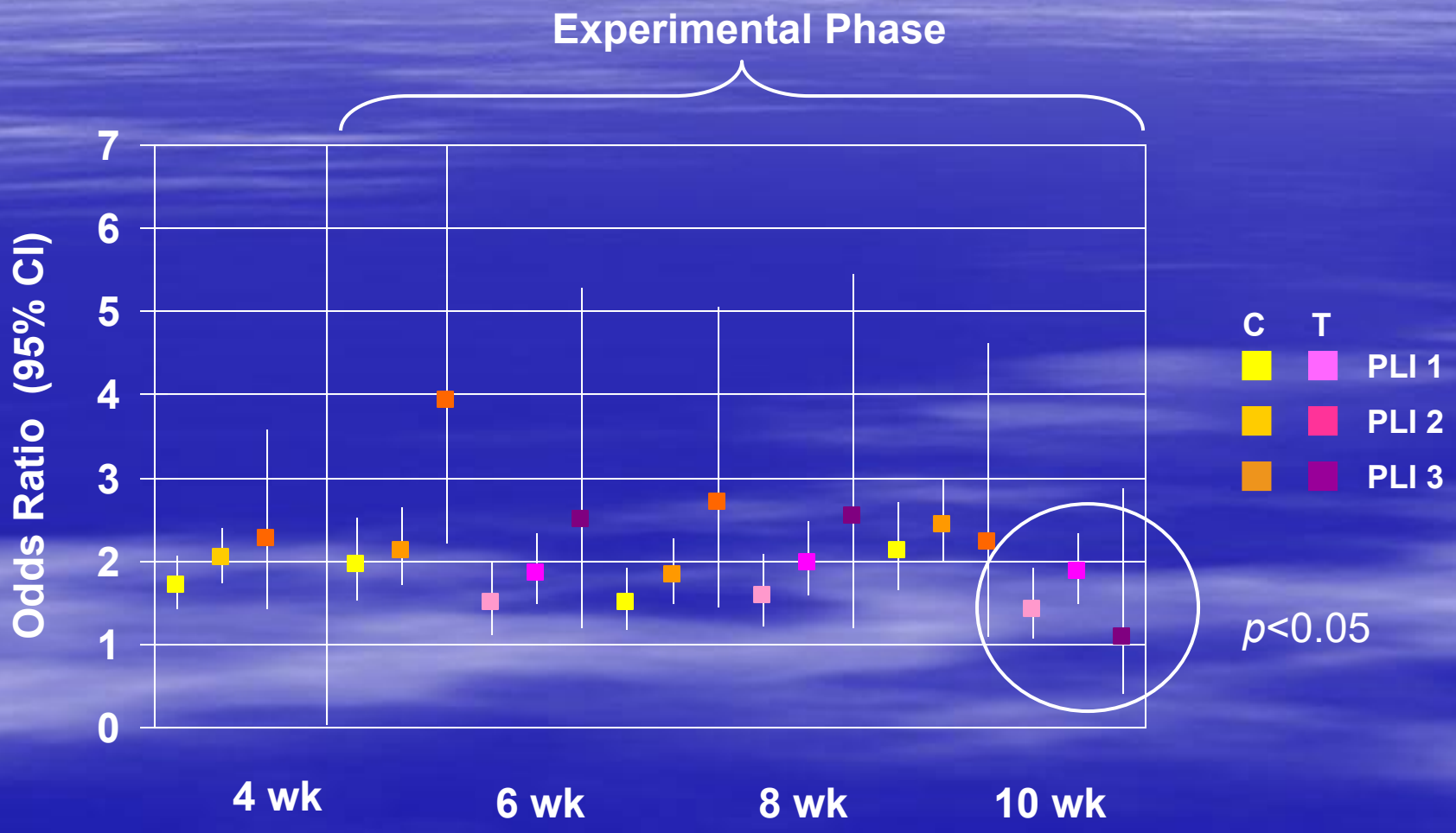
	4 wk	6 wk	8 wk	10 wk
σ^2_f	0.600 (0.158)	0.304 (0.089)	0.344 (0.099)	0.173 (0.057)
σ^2_v	0.552 (0.067)	0.405 (0.073)	0.472 (0.074)	0.411 (0.076)
σ^2_e	0.830 (0.017)	0.902 (0.019)	0.895 (0.018)	0.922 (0.019)

Up to 16 brands of toothpaste; change was allowed

2 experimental toothpastes

Experimental Phase, Conclusions (I)

- Consistent positive associations between BOP and (i) plaque, (ii) periodontal probing depth, and (iii) calculus
- Gradually decreasing odds of BOP in subjects using TEST toothpaste, significant 6 weeks after introduction
- Standardizing experimental conditions may result in large attenuation of subject (and tooth) level variances of BOP


Experimental Phase
Odds Ratio (95% CI)
0
1
2
3
4
5
6
7
4 wk
6 wk
8 wk
10 wk
C
T
PLI 1
PLI 2
PLI 3
p<0.05

Experimental Phase, Conclusions (II)

- The strong dose response of plaque usually leading to higher odds ratios of BOP at sites with higher plaque scores was attenuated in subjects using triclosan-containing toothpaste
- This effect could be observed already 6 weeks after introduction of experimental toothpaste

Conclusions regarding MLM

- MLM of site-specific periodontal data (170’000 in the present study) has great potential of providing deep insights into the pathogenesis and therapeutic mechanisms at the level of interest, the periodontal site
- Random parameters (variances, covariances, correlations) at the site, tooth and subject levels can be considered as well

- Understanding of underlying theory may be demanding for the common ‘dental’ reader, but editors and reviewers as well

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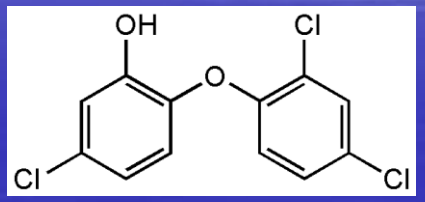
The Controversy

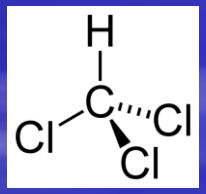
- Usage of triclosan is regulated by both the U.S. Food and Drug Administration and by the European Union
- Triclosan had been criticized, in particular by environmentalists, for various concerns
  - Development of bacterial resistance
  - Generation of carcinogenic chloroform
  - Generation of highly toxic dioxin

- Development of bacterial resistance (McMurry, Oethinger, Levy. Nature 1998; 394(6693): 531
  - In 2003, some UK supermarkets and other retailers were considering phasing out products containing triclosan

- Since then it has been demonstrated that the laboratory methods used by McMurry et al. (1998) were not effective in predicting bacterial resistance for biocides like triclosan (McBain, Bartolo, Catrenich et al. Appl Environ Microbiol 2003; 69: 5433)
- At least 7 peer-reviewed and published studies have been conducted demonstrating that triclosan is not significantly associated with bacterial resistance (e.g., Aiello, Marshall, Levy et al. Antimicrob Agents Chemother 2004; 48: 2973)

- Possible conversion to probable carcinogenic chloroform in the presence of chlorine in water (Rule, Ebbet, Vikesland. Environ Sci Technol 2005; 39: 3176
  - Triclosan became the target of a UK cancer alert,
  - even though the respective study showed that the amount of chloroform generated was less than amounts often present in chlorinated drinking waters





- Triclosan may react with free chlorine in tap water to produce compounds like 2,4-dichlorophenol (Rule et al. Environ Sci Technol 2005; 39: 3176)
- Upon exposure to UV radiation, these intermediates may convert into dioxins, e.g., in river waters (Latch et al. Environ Toxicol Chem 2005; 24: 517).
  - Extremely toxic
  - Very potent endocrine disruptors (adverse effects on physiologic function of hormones)
  - Chemically very stable
  - May bio-accumulate to dangerous levels
  - May persist in the environment for a long time

- Showering or bathing with 2% triclosan has become a recommended regime for decolonization of patients whose skin is carrying methicillin resistant *Staphylococcus aureus* (Coia et al. J Hosp Infect 2006; 63(Suppl 1): S1-S44)
- Triclosan is infused in an increasing number of consumer products
  - Kitchen utensils
  - Toys
  - Bedding
  - Socks
  - Trash bags

- Presently, triclosan is found in soaps, deodorants, toothpastes, and mouthwash
- A supermarket survey revealed that the vast majority of manufacturers of toothpaste have at least one product containing triclosan
  - Colgate
  - Procter & Gamble
  - Unilever