How to determine the best treatment: a mixed-treatment-comparisons meta-analysis (MTM) of trials of topical fluoride therapies for the prevention of dental caries
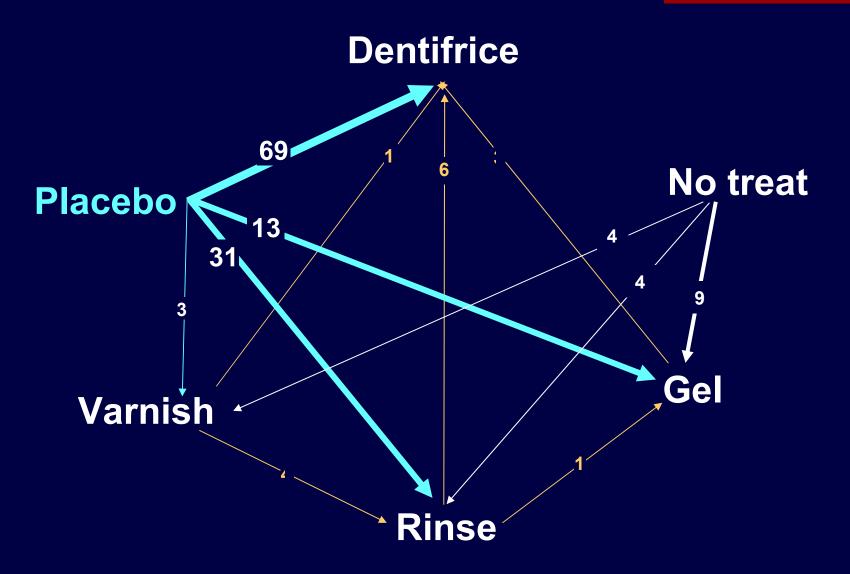
Georgia Salanti, Julian Higgins, Valeria Marinho
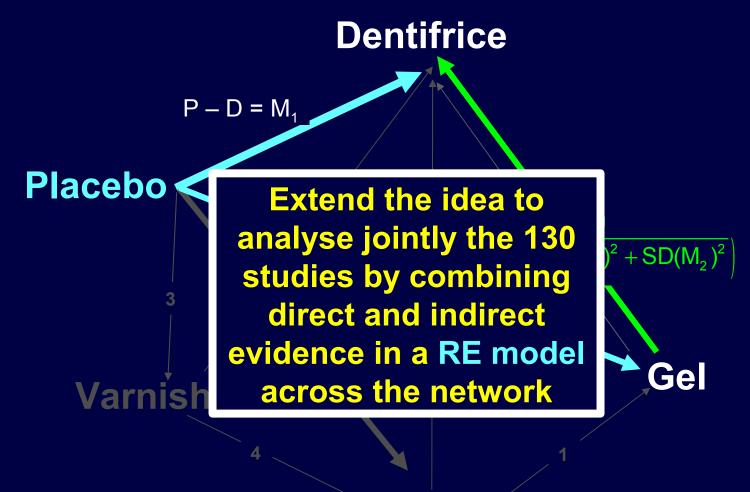
XIII Cochrane Colloquium

Melbourne 2005

MRC | Biostatistics Unit

• A series of <u>seven</u> Cochrane reviews examines the effect of fluoride in preventing caries Marinho, Higgins, Sheiham, Logan. *CDSR* 2002-2004

<u>Fluoride in</u>

• Dentifrice

• Rinse

• Placebo, No treatment

• Gel

• Varnish

• Outcome measure: SMD compares caries increment across the two groups

(P−D > 0 favours D)

- RE model, fitted in WinBUGS, taking into account correlation in multi-arm trials (I spare you the technical details)

- Joint analysis of all trials by taking advantage of indirect evidence: we gain precision!

- Should we be tempted do so?

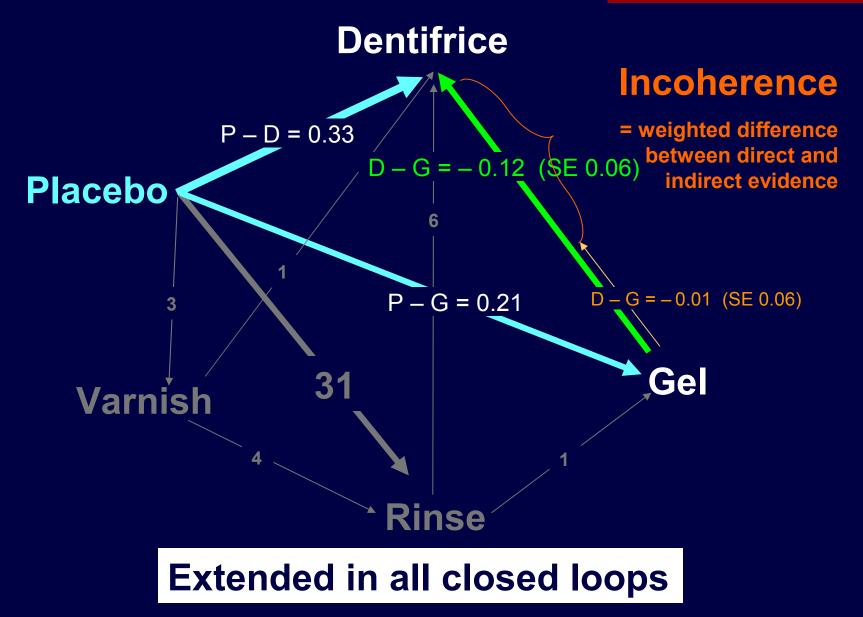- Check the validity of multiple treatments meta-analysis

Intervention	Effect size	Probability it's the best
No treatment	0	0%
Placebo	0.23(0.09,0.34)	0%
Dentifrice	0.55(0.41,0.70)	61%
Gel	0.45(0.32,0.58)	3%
Rinse	0.51(0.37,0.65)	12%
Varnish	0.51(0.34,0.67)	24%

DIC= – 82.12,   Heterogeneity standard deviation = 0.20 (0.16,0.24)

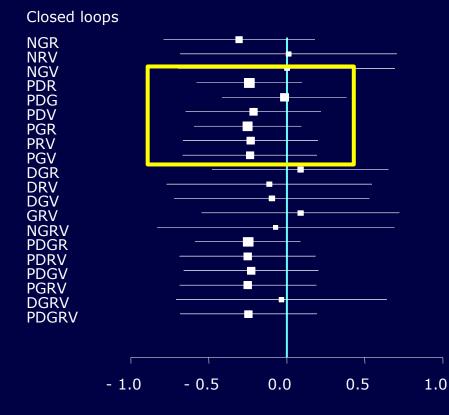- **Dentifrice appears as the best treatment**

- **Placebo seems to have an effect?**

- How important is the apparent conflict between direct and indirect evidence?

- Can we identify sources of incoherence?

- What can we do to improve the agreement?

Incoherence in each loop

Estimates with 95% confidence intervals

Closed loops

NGR
NRV
NGV
PDR
PDG
PDV
PGR
PRV
PGV
DGR
DRV
DGV
GRV
NGRV
PDGR
PDRV
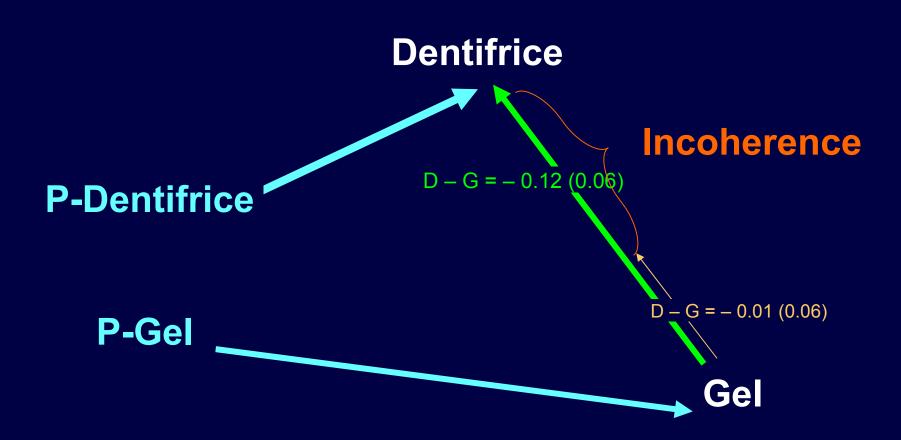PDGV
PGRV
DGRV
PDGRV

- 1.0   - 0.5   0.0   0.5   1.0

Indirect and direct evidence combined using the inverse variance method

Head to head comparison is overestimated when going through placebo

Coherence seems better when we use another treatment as the intermediate step

Compare different placebo effects

Reference	Placebo configuration	DIC
Placebo or NT	$(NT, P_{D,G,R,V})$	-70.5
NT	$P_{D,G,R,V}$	-82.1
NT	$P_D, P_{G,R,V}$	-81.8
NT	$P_D, P_{G,V}, P_R,$	-81.0
NT	P_D, P_G, P_R, P_V	-80.7

- **All placebos work the same**

- **Analyse separately NT and placebo controlled trials**

Possible confounders

No. studies	D	G	R	V	P	Fup	Baseline	Year	Water F (yes/no)
69	■				■	2.6	11.8	1968	0.2
13		■			■	2.3	3.8	1973	0.2
30			■		■	2.4	5.9	1973	0.1
3				■	■	2.3	2.7	1983	0
3	■	■				2.7	NA	1968	0.66
6	■		■			2.8	14.7	1969	0
1	■			■		2	0.9	1978	0
1		■		■		1	NA	1977	0
1		■		■		3	7.4	1991	NA
4			■			2.5	7.6	1981	0.33

Differences in year reflect differences in baseline

$$\text{SMD}_i^{P-T} = \theta_i^{P-T} + \beta\,(\text{year}_i)$$

Intervention	Meta-analysis		Meta-regression $\beta=-0.04\,(-0.08,-0.01)$	
	Effect size	Probability it's the best	Effect size	Probability it's the best
Placebo	0	0%	0	0%
Dentifrice	0.31(0.27,0.36)	62%	0.30(0.25,0.35)	31%
Gel	0.23(0.13,0.34)	6%	0.24(0.13,0.35)	5%
Rinse	0.29(0.22,0.36)	21%	0.30(0.23,0.36)	23%
Varnish	0.24(0.09,0.38)	11%	0.30(0.14,0.45)	41%
τ^2	0.17(0.14,0.21)		0.17(0.14,0.21)	

No. studies	D	G	R	V	P	Fup	Baseline	Year	Water F (yes/no)
69								1968	
3								1983	
1								1978	
1								1991	
4								1981	

Is this the future of meta-analysis in the Cochrane collaboration?

- Need 'umbrella reviews' to compare multiple interventions

  for the same condition

  - Increased precision

  - Comprehensive ranking

- <u>But don't get too excited!!!</u>

  - **Need very careful examination of the underlying assumptions (especially absence of confounders)**

  - **We need user-friendly tools to assess incoherence**

  - Expertise is needed (Bayesian models, multi-arms studies)