Cochrane Collaboration
Systematic Reviews of the Effects of Healthcare Interventions

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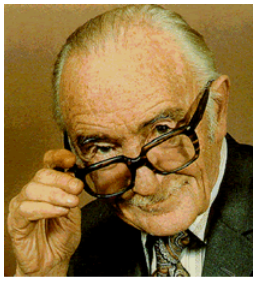
Outline

- What is the Cochrane Collaboration?
- Experience of working with Cochrane
- Resulting statistical research
- Conclusions

THE COCHRANE COLLABORATION®



"It is surely a great criticism of our profession that we have not organised a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomised controlled trials"
Archie Cochrane (1908-1988)

Systematic Reviews

- Collation of evidence fitting pre-specified eligibility criteria in order to address a specific research question; aim to minimize bias by using explicit, systematic methods
  - clearly stated set of objectives with pre-defined eligibility criteria for studies;
  - explicit, reproducible methodology;
  - systematic search that attempts to identify all studies that would meet the eligibility criteria;
  - assessment of the validity of the findings of the included studies, for example through the assessment of risk of bias; and
  - systematic presentation, and synthesis, of the characteristics and findings of the included studies.

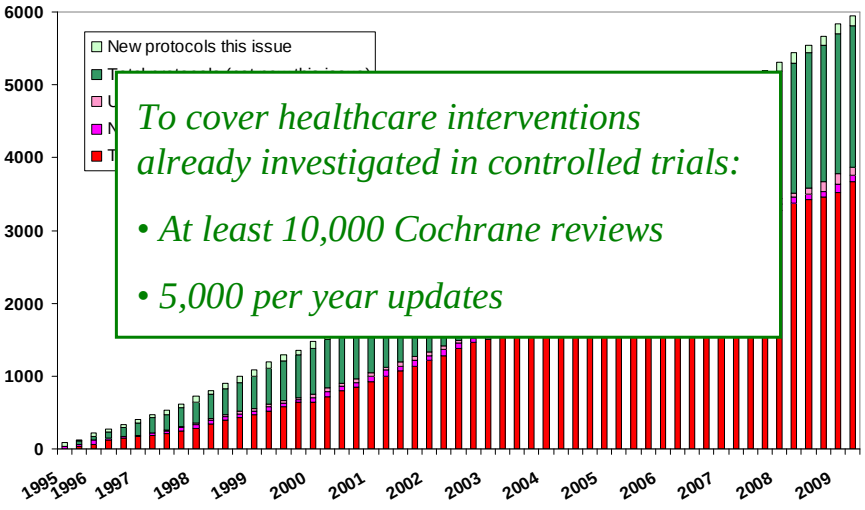
Structure of the Collaboration

- Collaborative Review Groups
  - each concentrating on a specific health care area
- Centres
  - with geographic and linguistic responsibilities
- Networks
  - draw together health care issues, such as setting of care, type of consumer, type of intervention
- Consumer Network
  - represents the interests of health care consumers
- Methods Groups
  - develop methodological techniques
- Steering Group
  - policy and decision making body

The Cochrane Library

- Cochrane Database of Systematic Reviews
  - contains Cochrane reviews and protocols
- Database of Abstracts of Reviews of Effects
  - critical assessments and structured abstracts of other systematic reviews, conforming to explicit quality criteria
- Cochrane Central Register of Controlled Trials
  - bibliographic information on studies published in sources not currently listed in other bibliographic databases
- Cochrane Database of Methodology Reviews
  - protocols and reviews of Cochrane methodological studies
- Cochrane Methodology Register
  - bibliographic information on articles and books on the science of reviewing research, prospective register of methodological studies

Growth of CDSR



To cover healthcare interventions already investigated in controlled trials:

- *At least 10,000 Cochrane reviews*
- *5,000 per year updates*

My Involvement

- Critical Appraisal Workshops 1996 - 2004
- Teaching EBM Course 1997
- Cochrane Statisticians Course 2001
- Skin Group Statistical Editor 2002 - 2004

Co-authored Reviews

- Surgical excision margins for localised cutaneous melanoma
- Topical treatments for fungal infections of the skin and nails of the foot
- Interventions for chronic palmoplantar pustulosis
- Interventions for photodamaged skin
- Interventions for rosacea
- Interventions for bullous pemphigoid
- Anticholinergics for urinary symptoms in multiple sclerosis

Statistical issues arising

- Missing data
- Time to event data
- Poor reporting of RCTs
- Use of RevMan software for routine analyses
- Assistance with non-routine analyses and data presentation

Research

- PSI Working Group on Meta-Analysis
- A graphical sensitivity analysis for clinical trials with non-ignorable missing binary outcome
  S Hollis. Stat Med 2002
- Uncertainty method improved on best-worst case analysis in a binary meta-analysis
  C Gamble, S Hollis. J Clin Epi 2005

PSI Working Group Remit

- Assess quality of published meta-analyses of drug treatments
  - Compare academic and industry analyses
  - Compare analyses before and after industry policy of online disclosure of results
- Outline statistical considerations for meta-analysis
- Publish results in a high-quality medical journal

Missing data in a single trial

- Consequences
  - Loss of precision
  - Bias, if informatively missing
  - Cannot usually determine whether informative
- Common simple strategies
  - complete-case analysis (CCA)
  - simple imputation
  - "best / worse" case analysis
  - sensitivity analysis

RCT: artemether-lumefantrine (AL) vs mefloquine plus artesunate (MA)

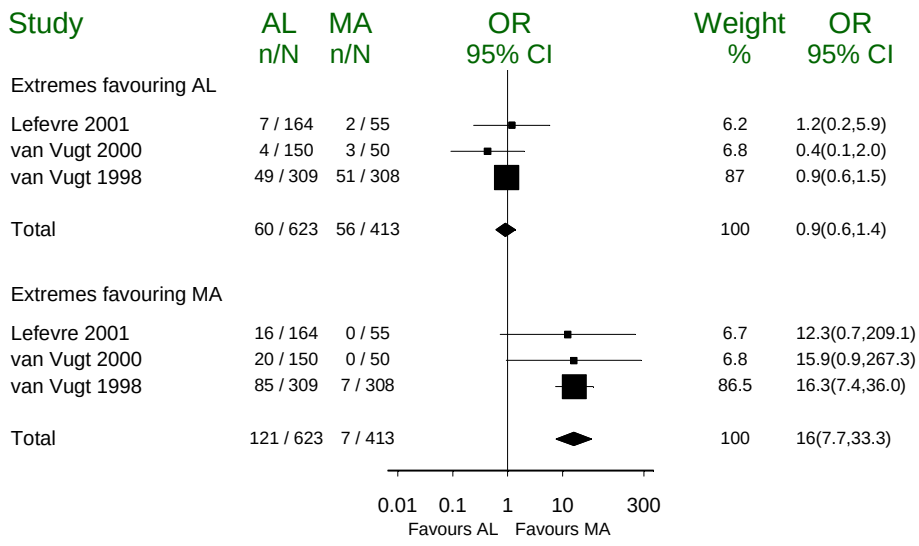
van Vught 1998	AL	MA
Parasites present	49	7
Parasites absent	224	257
~~Unobserved~~	36	44

Method	OR (95% CI)
CCA	8.0 (3.6, 18.1)
Impute failure	1.9 (1.3, 2.8)
Extremes	
favouring AL	0.9 (0.6, 1.5)
favouring MA	16.3 (7.4, 36.0)

Missing data in meta-analysis

- How should missing data be allowed for?
  - recommendations broadly based on methods for individual studies
  - sensitivity analysis commonly advocated, usually best and worst cases

Best-worst case meta-analysis



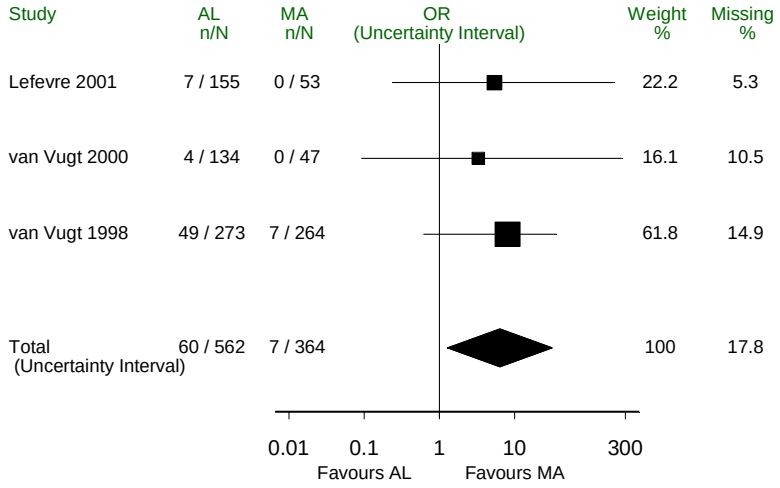
Best-worst case meta-analysis

- Shows impact of missing data
  - two estimates
  - each more precise than complete data analysis
  - all possible allocations of missing data lay between these estimates
- Is weighting appropriate?
  - weights trials according to full study size

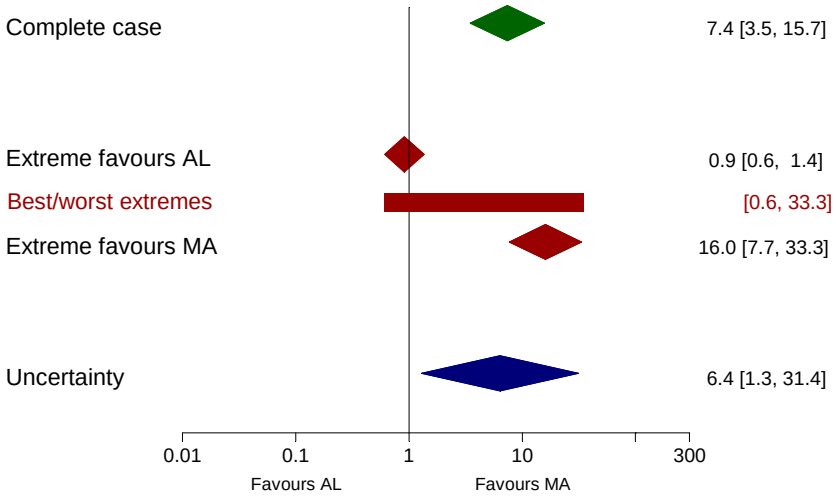
Uncertainty method

- Idea: uncertainty intervals
  - Uncertainty arises not only from *imprecision* due to sampling error, but also from *ignorance* due to incomplete data (Molenberghs *et al*., JRSSC 2001)
  - Region of uncertainty; in the spirit of a confidence region, capturing combined effects of imprecision and ignorance
  - Natural estimate is the union of confidence regions across a full range of assumptions about the missing data
- Proposed application to meta-analysis
  - Uncertainty interval for each trial: extremes of best-worst case confidence intervals
  - Meta-analysis with weights determined by interval widths (applying relationship between width and weight)

Uncertainty meta-analysis



Pooled results from each method



Uncertainty method: simulation results

- CCA cannot be recommended
  - biased unless missing data are known to be non-informative
- Best-worst case and uncertainty methods allow for informative missing data
  - but are overly-conservative
- Uncertainty method preferable to best-worst case
  - consistently narrower interval widths
  - can be implemented in any software which incorporates inverse variance meta-analysis

Conclusions

- The Cochrane Collaboration
  - produces many reviews
  - across a wide range of healthcare topics
  - with rigorous research methods
  - updated regularly, ensuring that treatment decisions can be based on the most up-to-date and reliable evidence
- My involvement
  - Interesting statistical issues to address
  - Inspiring collaboration with consumers
  - Motivated fruitful research topics
  - You should consider it too!