Using meta-analysis to inform the design of subsequent studies

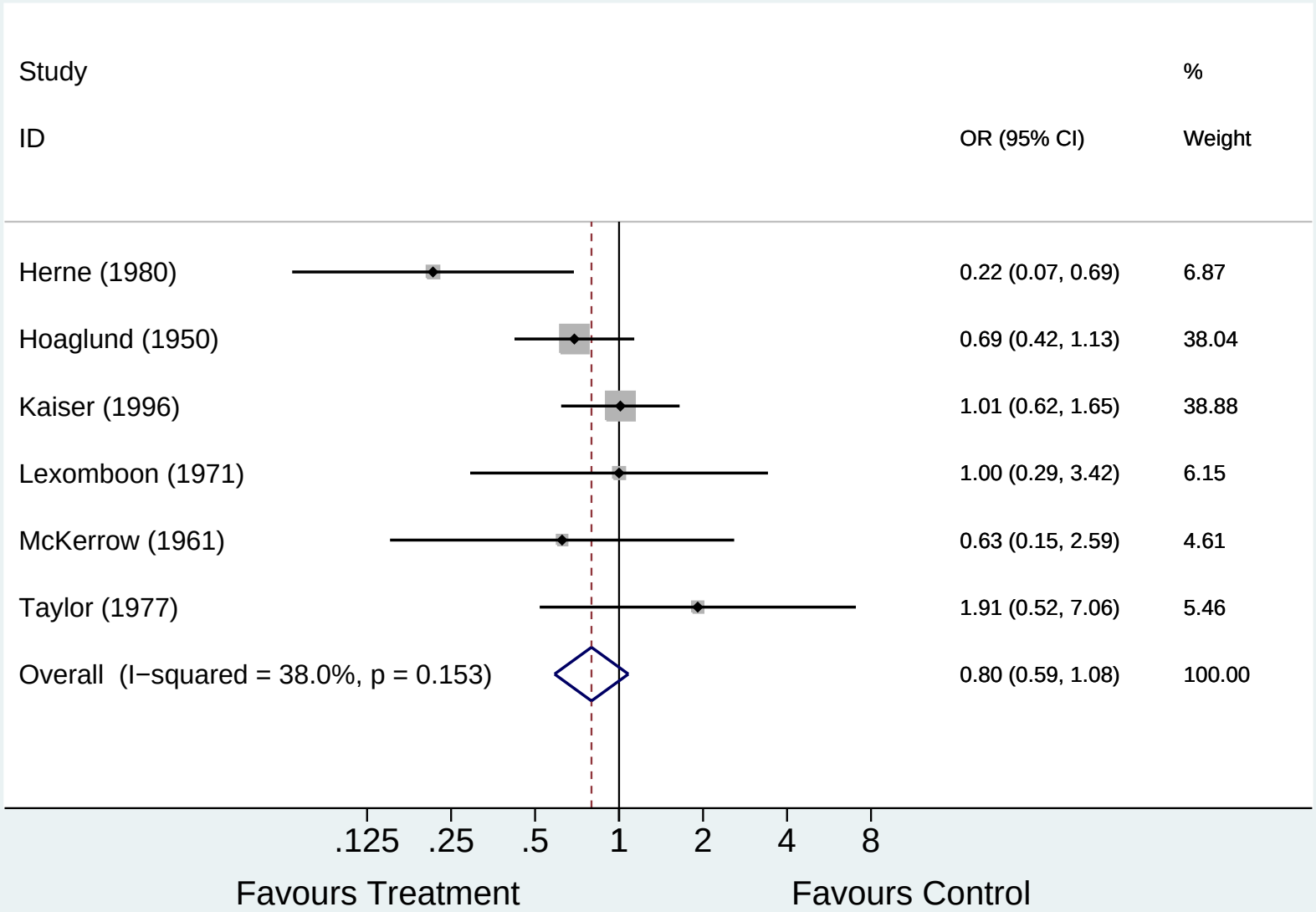
Sally R. Hinchliffe, Michael J. Crowther, Alison Donald and Alex J. Sutton

Centre for Biostatistics and Genetic Epidemiology, Department of Health Sciences, University of Leicester

Motivating Example

- Systematic review of antibiotic use for common cold from Cochrane database of systematic reviews (1).
- Six trials were conducted to compare antibiotics versus placebo for outcome symptoms persisting beyond 7 days.
- There were a total of 1147 subjects, 664 in the treatment group and 483 in the control group.

Motivating Example



Motivating Example

- The review concluded that "there was insufficient evidence of benefit to warrant the use of antibiotics". Further trials could be potentially beneficial.
- It is possible that additional information in the form of another trial could change this result.

The Concept

- Individual clinical trials or diagnostic accuracy studies rarely provide enough information to make conclusive recommendations.
- Sutton et al. (2) proposed when designing a new trial would be reasonable to consider power of updated meta-analysis including new trial rather than power of new trial itself.
- The subsequent updated meta-analysis would be more influential than results of new study on its own.
- The methods have recently been adapted for diagnostic test accuracy (3).

Power by Simulation

1. A distribution for the effect size expected to be seen in the new study is derived from the M-A of existing evidence. A starting sample size is specified indicating the initial size of the new study considered. Data relating to a new study is generated stochastically.

2. The simulated study is then included in the meta-analysis and a rule used to establish whether the result is "decisive".

3. Steps 1 and 2 are repeated a large (N) number of times recording whether the result is "decisive or not".

4. Power is estimated by calculating what proportion of the N simulations are deemed to give "decisive" results.

5. Procedure is iterative using different sample sizes until the desired level of power is achieved.

What is a Decisive Result?

Possible options are:

1. Conventional: statistical significance of pooled effect - say 5% level.

2. Variance minimisation: reduce the variance of the pooled effect to a specified level (irrespective of statistical significance).

3. Limits of equivalence (minimal clinical worthwhile benefit): decisive when pooled effect and (95%) confidence interval lie completely within, or outside, pre-specified limits of equivalence.

Overview of Stata Software

- Collection of three programs to implement the frequentist version of the methodology for (2-arm) randomised controlled trials and diagnostic test accuracy contexts.

  1. `metasim`
  2. `metapow`
  3. `metapowplot`

Overview of Stata Software

`metasim`

- Simulates specified number of new studies based on estimate/s obtained from pre-existing meta-analysis assuming effect size seen in new study will be consistent with existing studies in meta-analysis.

- Program can be used independently, but was designed to be used in conjunction with `metapow`.

Overview of Stata Software

`metapow`

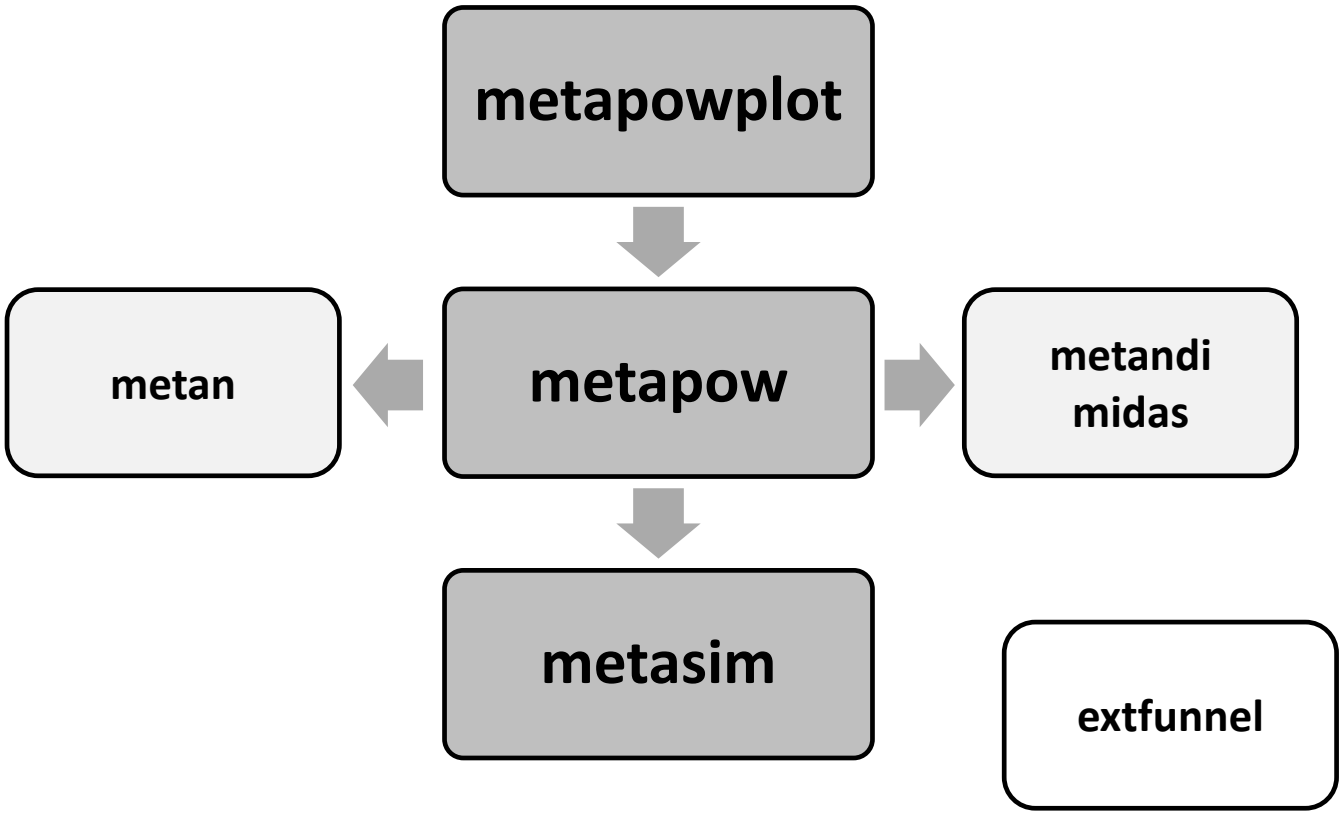
- Power is determined through simulation, with data for new studies being generated using program `metasim`.
- For certain inferences can also estimate power of new study when analysed on its own.

Overview of Stata Software

`metapowplot`

- Produces plot of power values for a range of sample sizes.
- Calls on program `metapow` which in turn calls on `metasim`.

Software Relationship Diagram



Using metapowplot

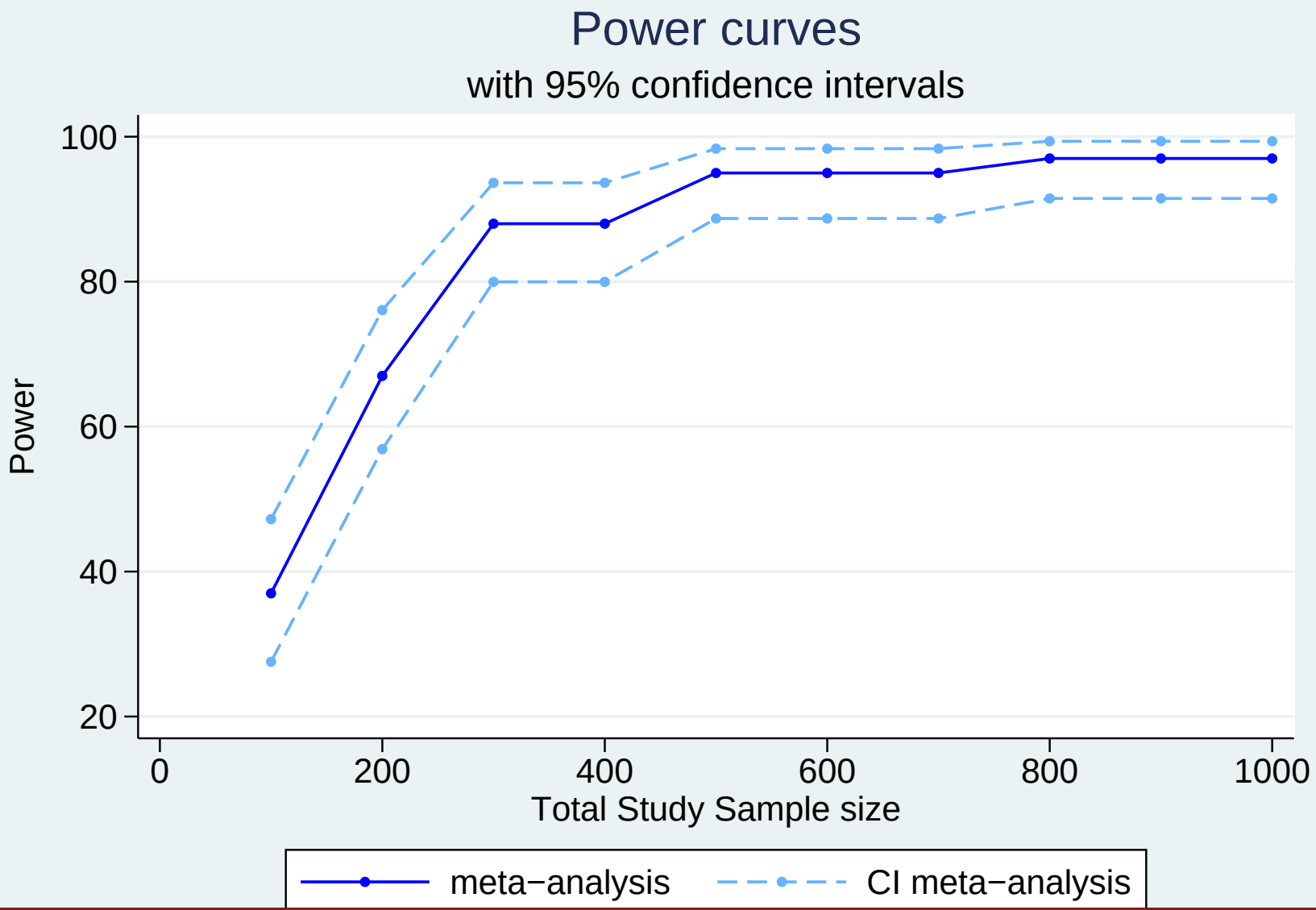
```
. metapowplot event_t noevent_t event_c noevent_c, start(100) step(100)
  stop(1000) type(clinical) measure(or) model(fixedi) nit(100)
  inference(pvalue) pow(0.05)

  Sample size

  t=100       Treatment/Control=50/50
  t=200       Treatment/Control=100/100
  t=300       Treatment/Control=150/150
  t=400       Treatment/Control=200/200
  t=500       Treatment/Control=250/250
  t=600       Treatment/Control=300/300
  t=700       Treatment/Control=350/350
  t=800       Treatment/Control=400/400
  t=900       Treatment/Control=450/450
  t=1000      Treatment/Control=500/500


  Fixed effect inverse variance-weighted model
  Statistic used was odds ratio
  Level of significance used to estimate power = 0.05
  Power estimates used to plot the graph are saved in file
   called C:\Documents\temppow3.dta
```

Using `metapowplot`



Discussion

- It is hoped the suite of programs will be useful to
  1. trialists who want to assess the impact potential new trials will have on the overall evidence base.
  2. meta-analysts who want to assess the robustness of the current meta-analysis to the inclusion of future data.
- Have created prototype set of programs to allow same calculations using Bayesian approach to all meta-analyses estimation.

References

[1] B. Arroll and T. Kenealy. Antibiotics versus placebo for the common cold (cochrane review). *Cochrane Library Oxford*, Issue 2, 1999.

[2] Alexander J. Sutton, Nicola J. Cooper, David R. Jones, Paul C. Lambert, John R. Thompson, and Keith R. Abrams. Evidence-based sample size calculations based upon updated meta-analysis. *Statist. Med.*, 26(12):2479–2500, 2007.

[3] Sally R. Hinchliffe, Alex J. Sutton, Robert S. Phillips, and Michael J. Crowther. Using meta-analysis to inform the design of subsequent studies of diagnostic test accuracy. *Submitted*, 2011.