CRAFT OF EVIDENCE SYNTHESIS WITH QUANTITATIVE DATA

(META ANALYSIS)

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Outline of the talk

Systematic review and Meta analysis - Basics

Models in meta analysis

Heterogeneity

Subgroup analysis

Publication bias

Caution in the use of meta analysis

Acknowledgement

Thanks to the Cochrane collaboration especially to the Cochrane community for many of the materials used in this presentation.

Creating Research evidence

Primary research

Secondary data analysis

Narrative reviews

Systematic reviews and meta analysis

Systematic Reviews

Answering a focused research question, based on existing literature with the application of scientific strategies that limit bias to the systematic assembly, critical appraisal, and synthesis of all relevant studies.

Steps in conducting a systematic review

STEP 1: Framing the review question

STEP 2: Writing protocol

STEP 3: Locating and selecting studies

STEP 4: Critical appraisal of studies

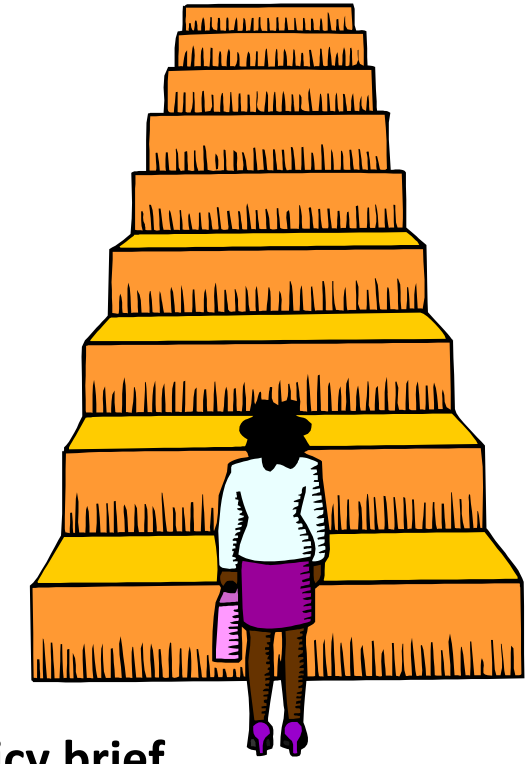
STEP 5: Collecting data

STEP 6: Analysing and presenting results

STEP 7: Interpreting results

STEP 8: Writing & publishing review

Step 9: Writing evidence summary and Policy brief



Meta analysis - summarising effects across studies

‘The statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings’

Glass GV. Primary, Secondary and meta analysis of research. Educ rese ; 1976;5:3-8

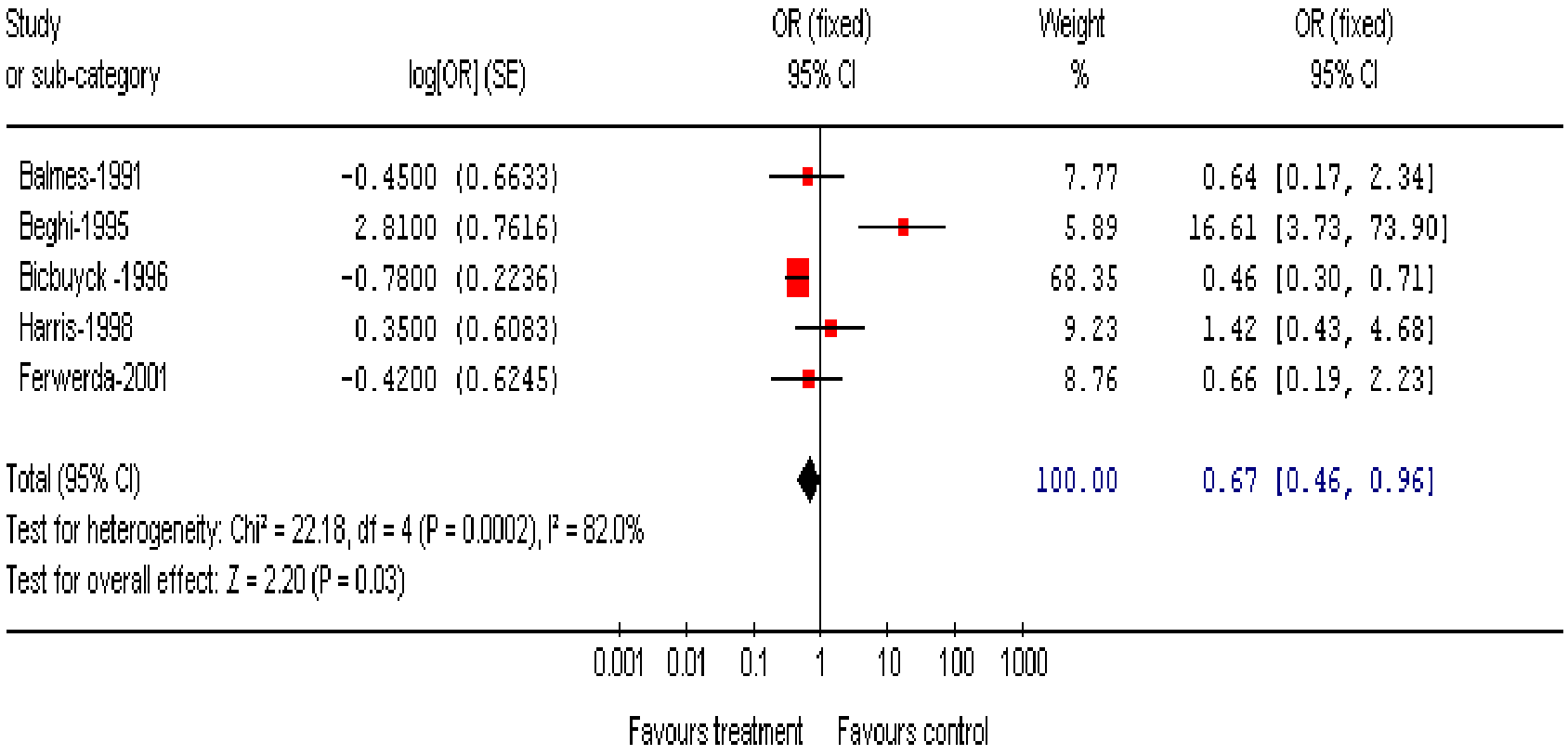
R A Fisher, Karl Pearson

Efficacy of Azithromycin in comparison with Amoxicillin for acute lower respiratory tract infection

Study	OR	95% CI
Study 1	0.64	0.14 – 2.65
Study 2	16.6	3.52 – 107.5
Study 3	0.46	0.30 – 0.71
Study 4	1.42	0.40 – 5.57
Study 5	0.66	0.17 – 2.53
Pooled	**0.66**	**0.46 – 0.96**

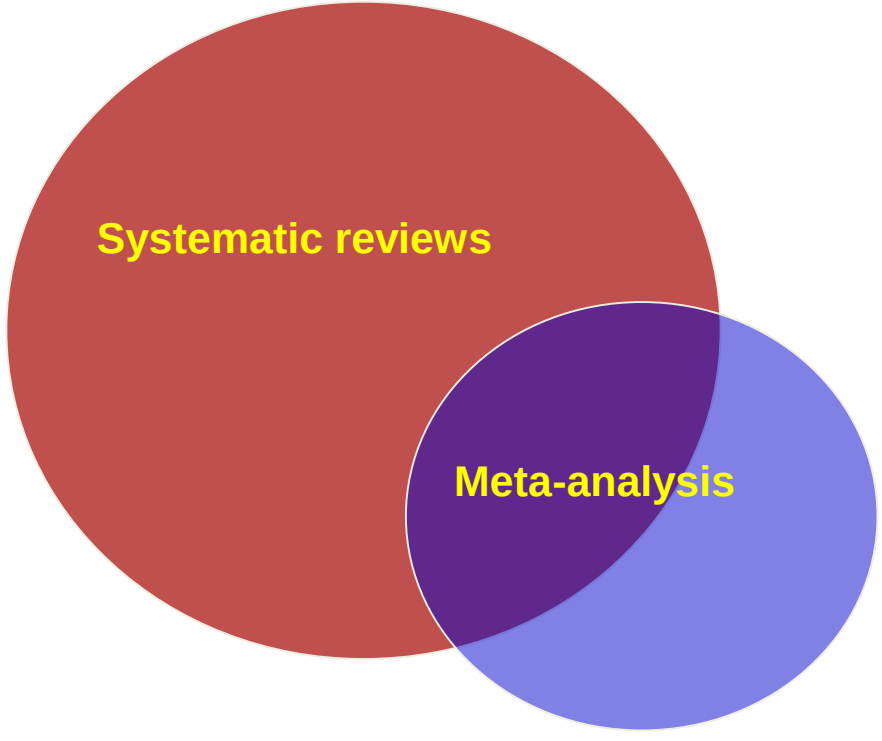
Meta analysis- Forest plot

Review: Azithromycin for acute lower respiratory tract infection
Comparison: 01 Azithromycin vs Amoxycilin
Outcome: 02 Clinical failure



Systematic review and Meta analysis

Optional part of a systematic review



Method of meta analysis – Fixed effect model (one source of variation)

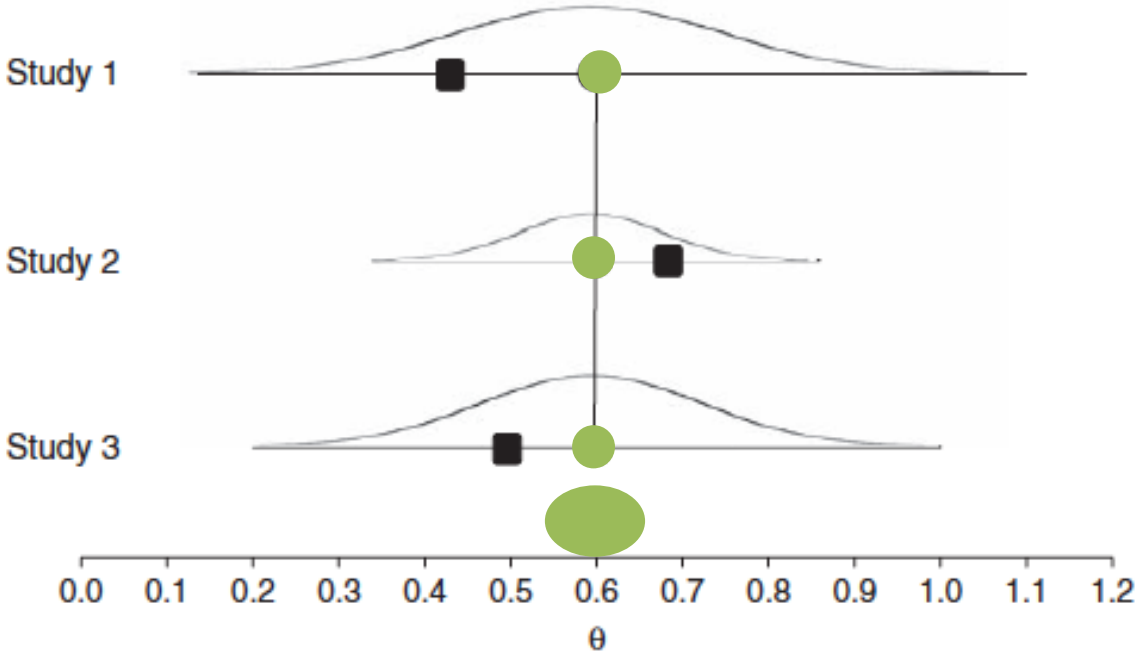


Figure 11.3 Fixed-effect model – distribution of sampling error.

One source of variance

(ie, random errors inherent in the study) and the width of the normal curve is based on the variance in that study

More generally, the observed effect *Yi* for any study is given by the population mean plus the sampling error in that study.

$$Y_i = \theta + \varepsilon_i$$

Borenstein M et al. Chapter 11. Fixed-Effect Model. Introduction to Meta-analysis. 2009

Azithromycin for acute lower respiratory tract infection

Study	Azithromycin Total	Azithromycin Events*	Amoxycillin Total	Amoxycillin Events*	OR
Study 1	48	4	56	7	0.64
Study 2	69	22	73	2	16.6
Study 3	497	53	257	53	0.46
Study 4	125	11	63	4	1.42
Study 5	55	5	53	7	0.66

*** Clinical failure**

Pooled 0.66 (0.46 – 0.96)

Variance estimate & Weight

Study 1	Clinical failure	No event	Total
Azithro	4	44	48
Amoxy	7	49	56
Total	11	93	104

Variance of ln(OR) $= 1/a + 1/b + 1/c + 1/d$

$= 1/4 + 1/44 + 1/7 + 1/49$

$= 0.25 + 0.023 + 0.143 + 0.020 = 0.436$

Weight = Inverse variance

$W_i = 1/V_i = 1/0.44 = 2.27$

Azithromycin for acute lower respiratory tract infection

Study	OR	ln OR y	Var v	Weight w	%
Study 1	0.64	-0.45	0.44	2.27	7.76
Study 2	16.6	2.81	0.58	1.72	5.88
Study 3	0.46	-0.78	0.05	20.0	68.4
Study 4	1.42	0.35	0.37	2.70	9.23
Study 5	0.66	-0.42	0.39	2.56	8.75
Total				29.25	100

Pooled effect measures

Results for log odds ratios

$M = \sum(wy) / \sum w = -11.92 / 29.25 = -0.41$

$SE(M) = 1 / \sqrt{\sum w} = 1 / \sqrt{29.25} = 0.19$

95% C.I. = $M \pm 1.96\ SE(M)$ = -0.78 to -0.04

Results in odds ratio scale

Pooled OR = Exp(M) = Exp(-0.41) = **0.67**

95 % CI = Exp(-0.78) to Exp(-0.04)
= 0.46 to 0.96

Meta analysis- Forest plot

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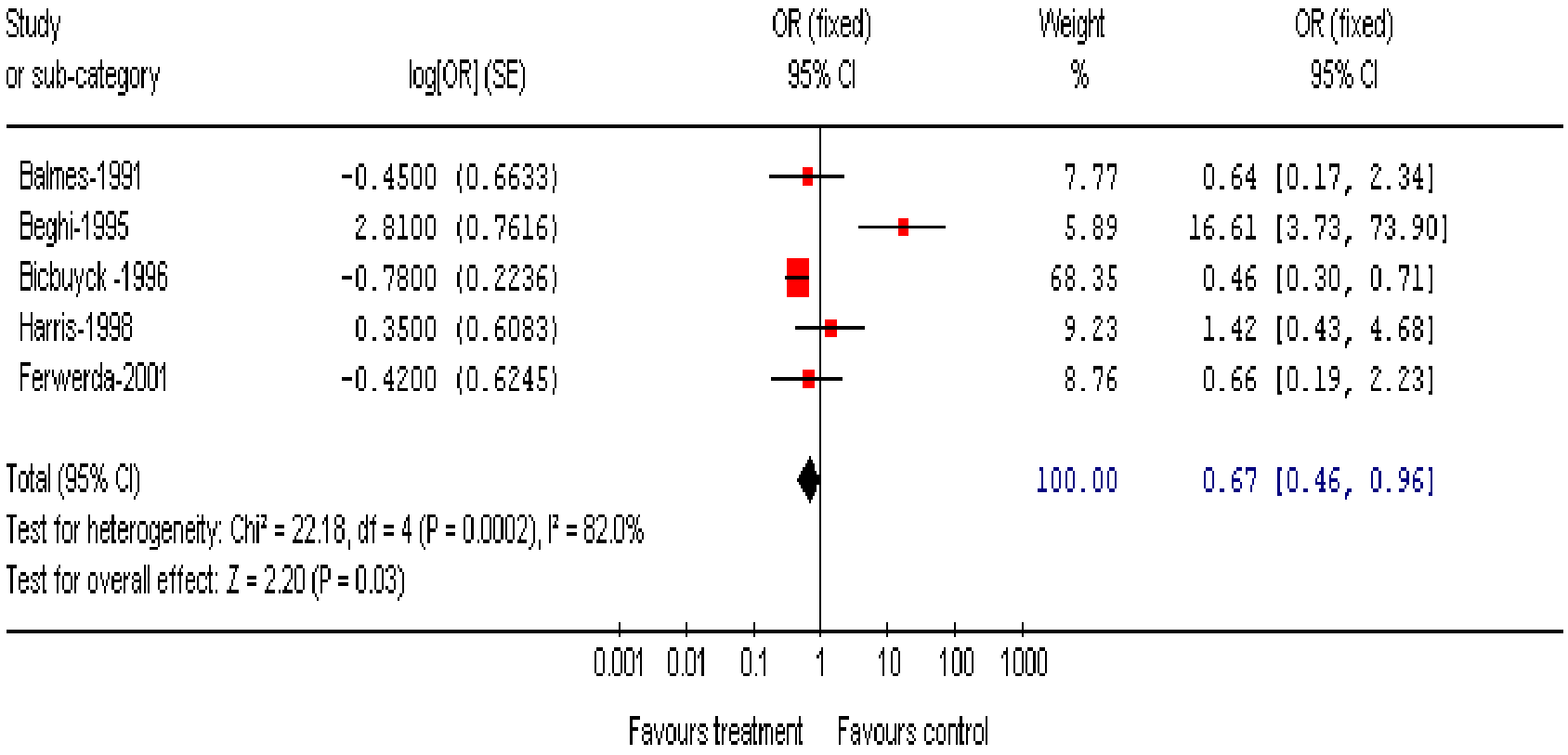

Method of meta analysis- Random-effects Model – Two Sources of Variance

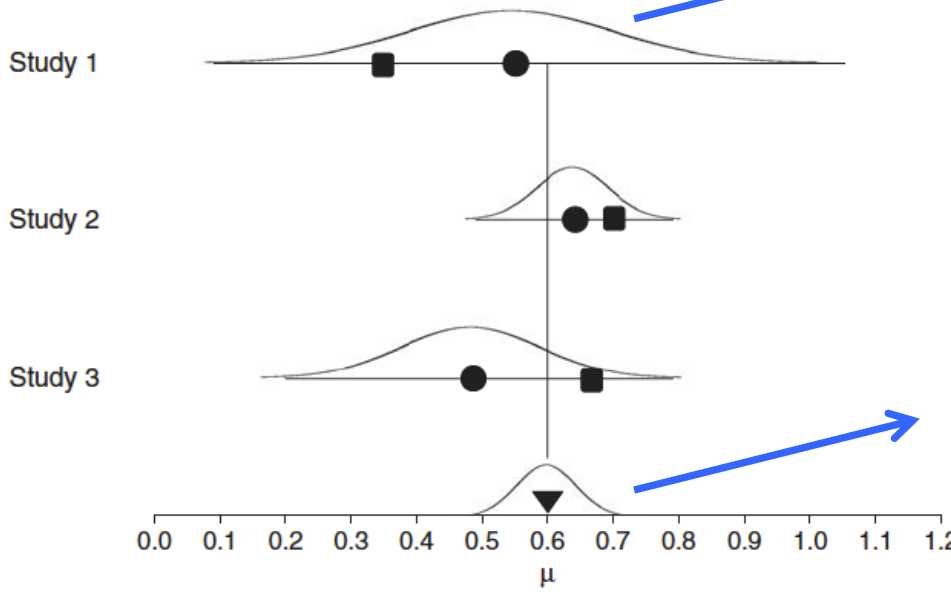

Figure 12.4 Random-effects model – between-study and within-study variance.

Within studies variance:
The distance from $\boldsymbol{\theta_i}$ (the circles) to $\boldsymbol{Y_i}$ (the square) depends on within study variance (ie., random errors within study) $\boldsymbol{V_{Yi}}$

Between studies variance:
The distance from $\boldsymbol{\mu}$ (the triangle) to each $\boldsymbol{\theta_i}$ (the circles) depends on the variance of the distribution of the true effects across studies, called $\boldsymbol{\tau^2}$

	True effect	Observed effect
Study	●	■
Combined	▼	◆

$$Y_i = \mu + \zeta_i + \varepsilon_i$$

Borenstein M et al. Chapter 12. Random-Effects Model. Introduction to Meta-analysis. 2009

Performing a Random-effects Meta-analysis

Start with the observed effects and try to estimate the population effect through computing a weighted mean.

- **Weight** assigned to each study in a ***random-effects*** meta-analysis is

$$W_i^* = \frac{1}{V_{Y_i}^*}$$

$$V_{Y_i}^* = V_{Y_i} + T^2$$

$V_{Y_i}^*$ is the within studies variance for study *i* plus the estimate of between studies variance T^2

- **Weighted mean (*M**):** $M^* = \frac{\sum Y_i W_i^*}{\sum W_i^*}$

- **Variance of the summary effect (V_{M^*}):** $V_{M^*} = \frac{1}{\sum W_i^*}$

- **Standard error of the summary effect (SE_{M^*}):** $SE_{M^*} = \sqrt{V_{M^*}}$

Borenstein M et al. Chapter 12. Random-Effects Model. Introduction to Meta-analysis. 2009

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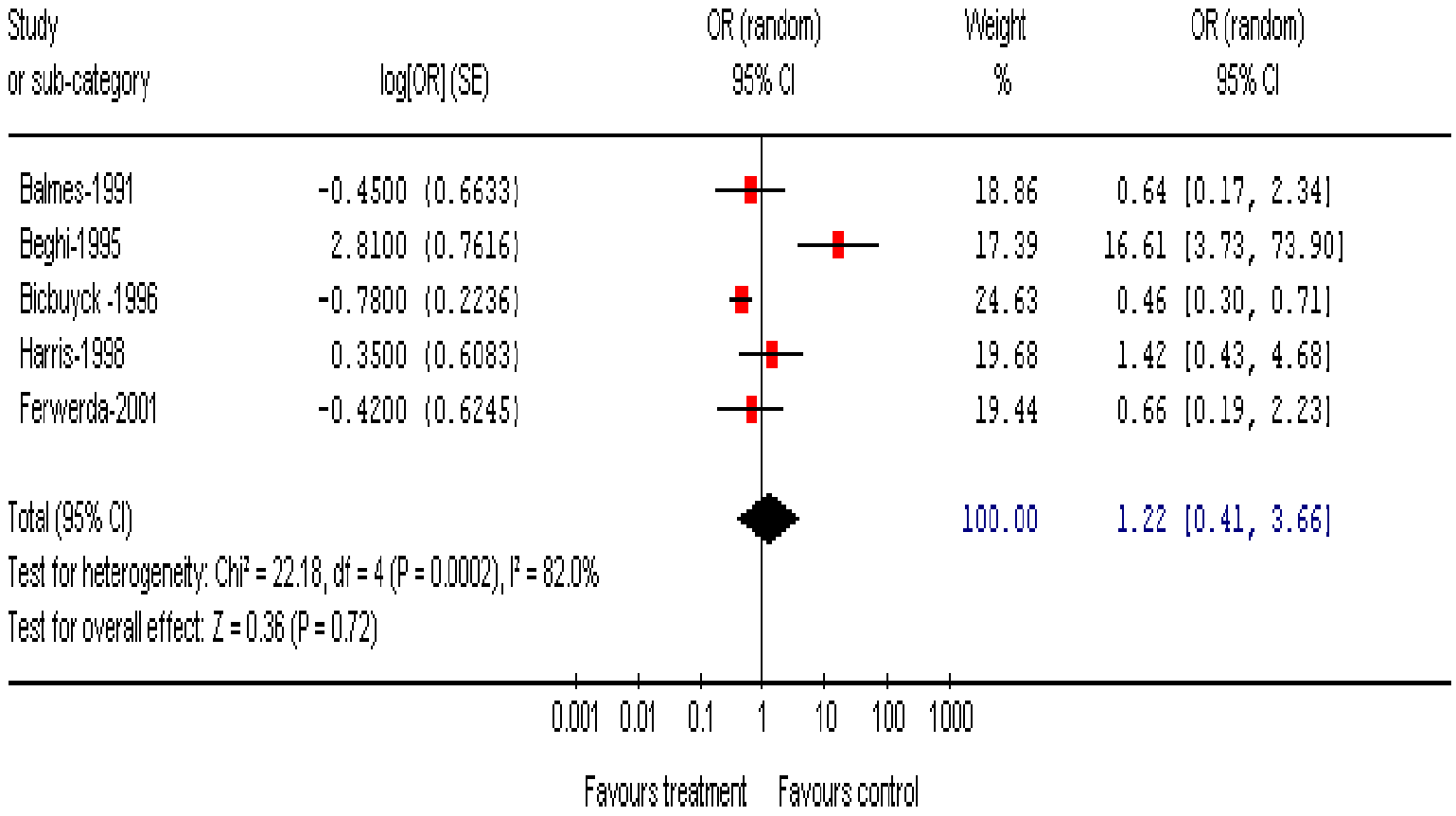

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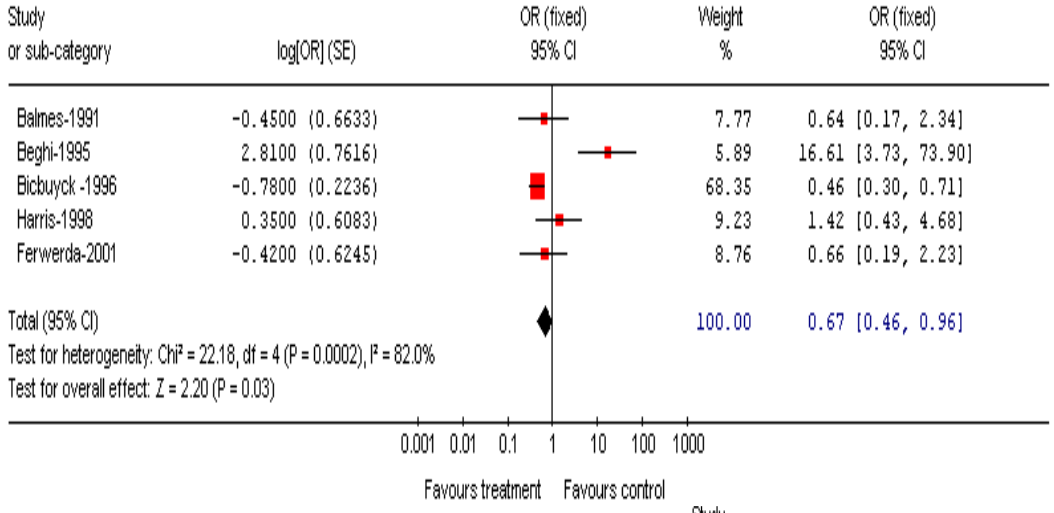

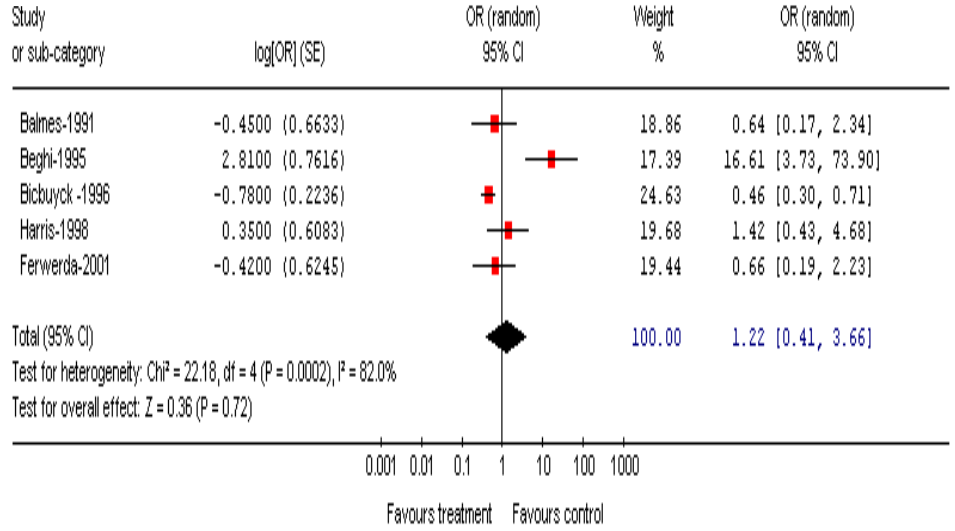

Heterogeneity issues in systematic reviews

Clinical heterogeneity

Population
Dose
Materials
Inclusion & exclusion criteria

Subgroup analysis

Methodological heterogeneity

Study design:
Case control,
Cohort ,
RCT, Cluster RCT & N-RCT

Subgroup analysis

Statistical heterogeneity

More variation between results of studies than would be expected by chance

Treat statistically using appropriate models

Statistical heterogeneity

More variation between results of studies than would be expected by chance

lack of overlap in confidence interval indicate heterogeneity

Statistical tests

Q statistics, I^2 statistic, τ^2

Note of caution

With very few studies, statistical test has low power to detect important heterogeneity

With large number of studies, statistical test has excessive power to detect clinically unimportant heterogeneity

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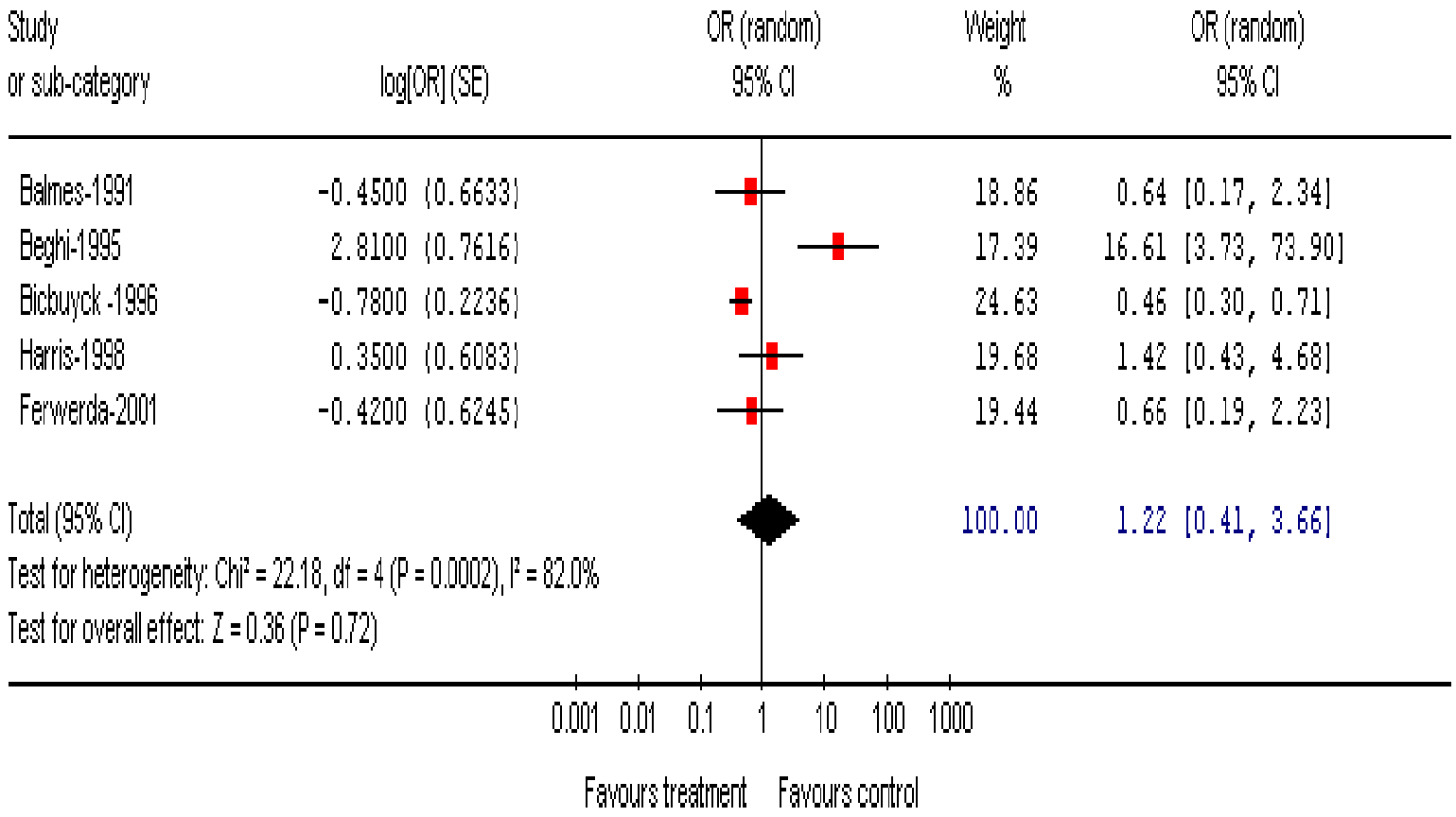
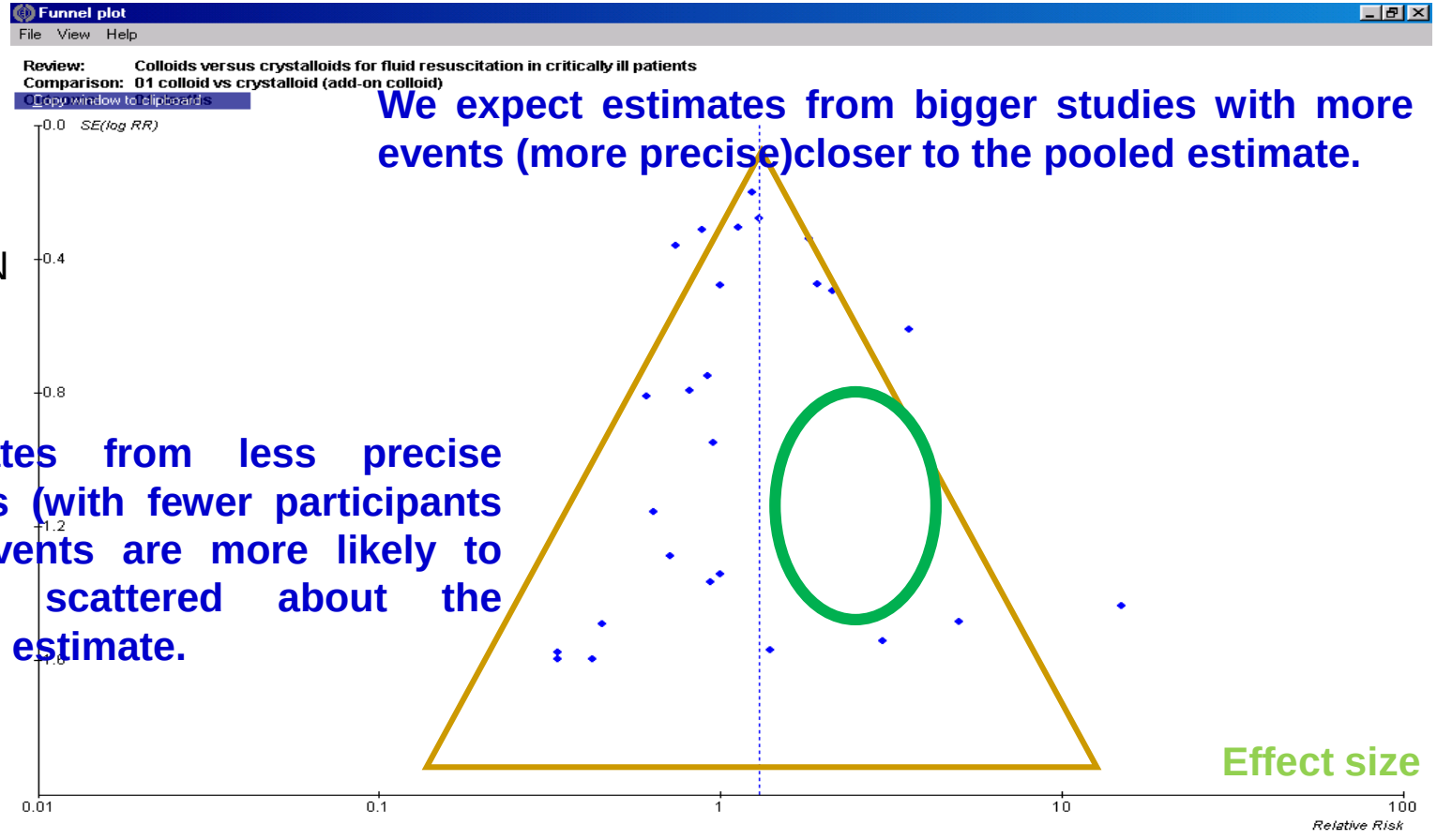


Detecting publication bias – the funnel plot



We expect estimates from bigger studies with more events (more precise)closer to the pooled estimate.

SEor N

Estimates from less precise studies (with fewer participants and events are more likely to widely scattered about the pooled estimate.

Effect size

In the absence of bias, this should produce a triangular shape, an inverted funnel, and we would expect the funnel to be symmetrical

Other topics in meta analysis

Network meta analysis

Meta regression

Bayesian meta analysis

Multivariate meta analysis

Meta analysis of complex interventions

Caution in the use of meta analysis

Search should be complete, unbiased and studies selected with robust inclusion/exclusion criteria

Studies must address same question and possibly get the same effect measures

Clinical and methodological homogeneity should be guaranteed

GIGO

Effect measure of combination of biased studies will much more dangerous than a single biased study.


Thank you