Critical appraisal of a meta-analysis study

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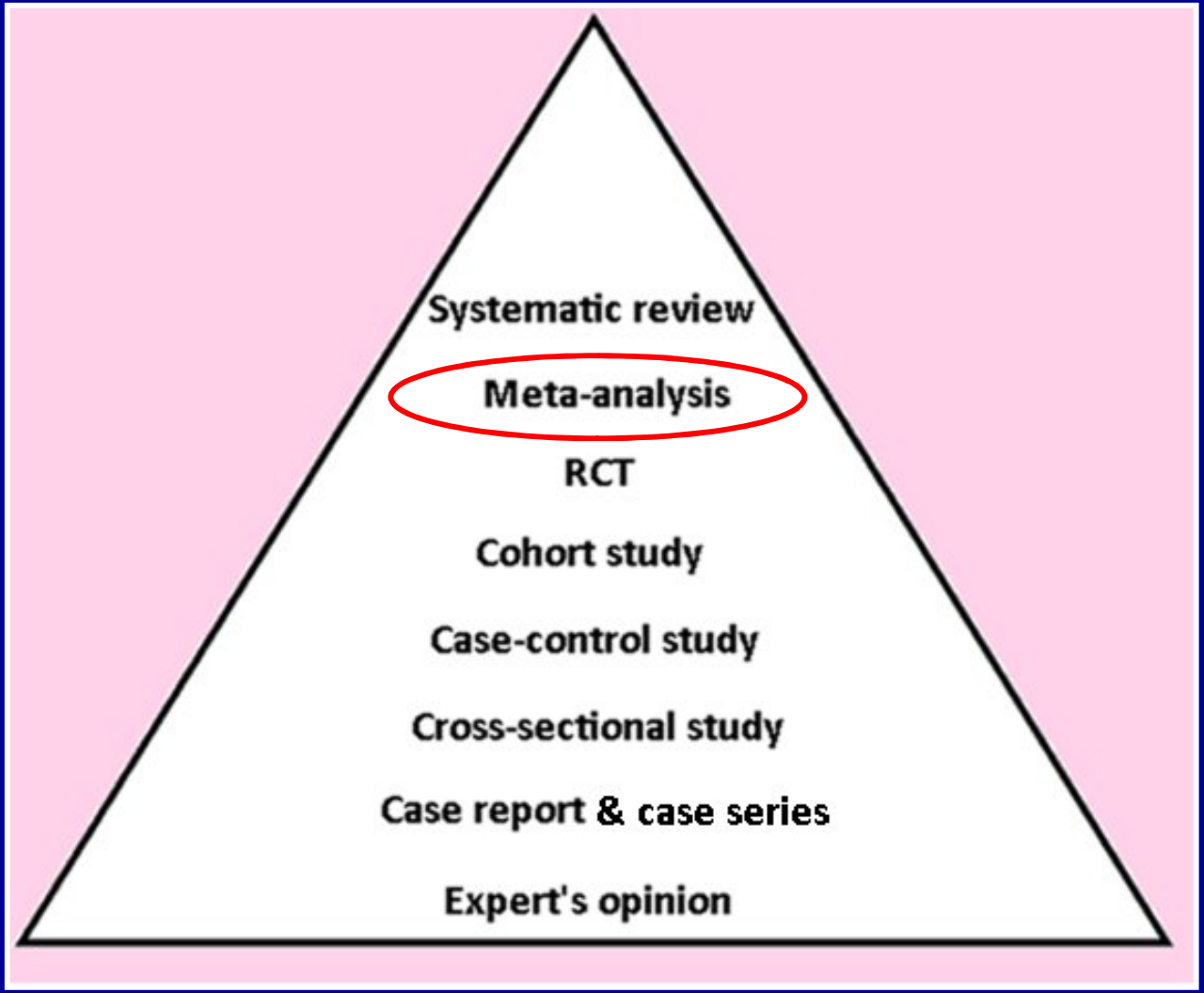
Hierarchy of evidence in quantitative studies



McGovern D, Summerskill W, Valori R, Levi M. Key topics in EBM. BIOS Scientific Publishers, 1st Edition, Oxford, 2001.

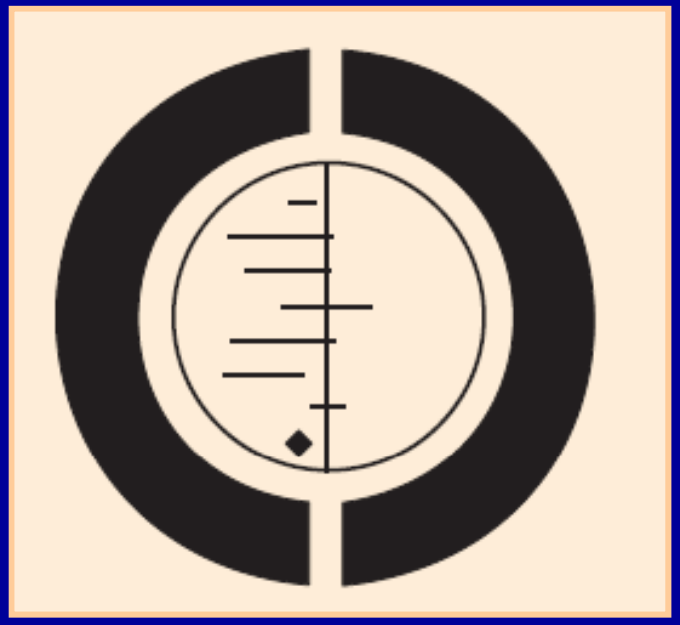
Gene Glass

American statistician – University of Colorado

Involved in social science research

He coined the term meta-analysis in 1976

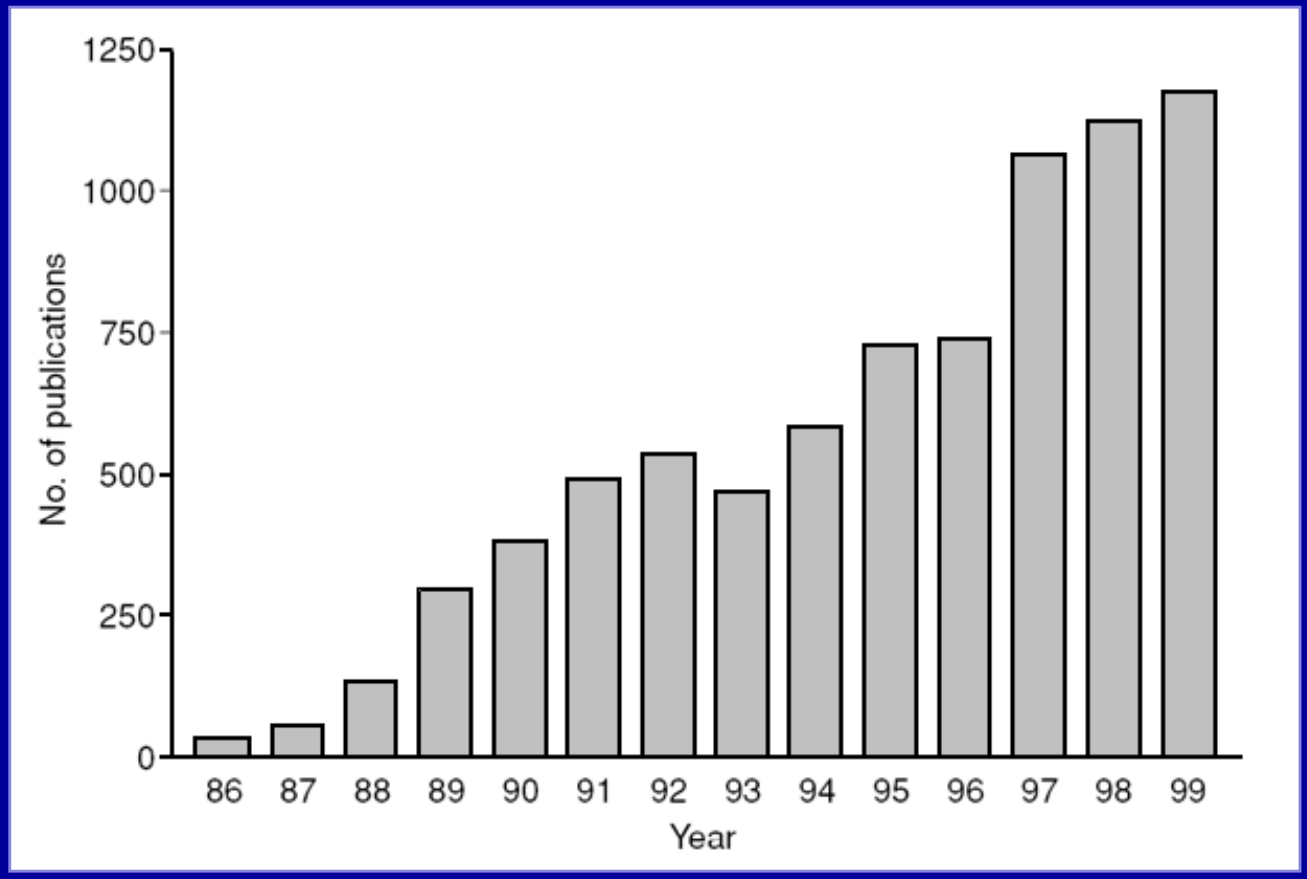
Logo of Cochrane collaboration



http://www.cochrane.org

Database available free online in many countries

Number of publications about MA (1986 - 1999)



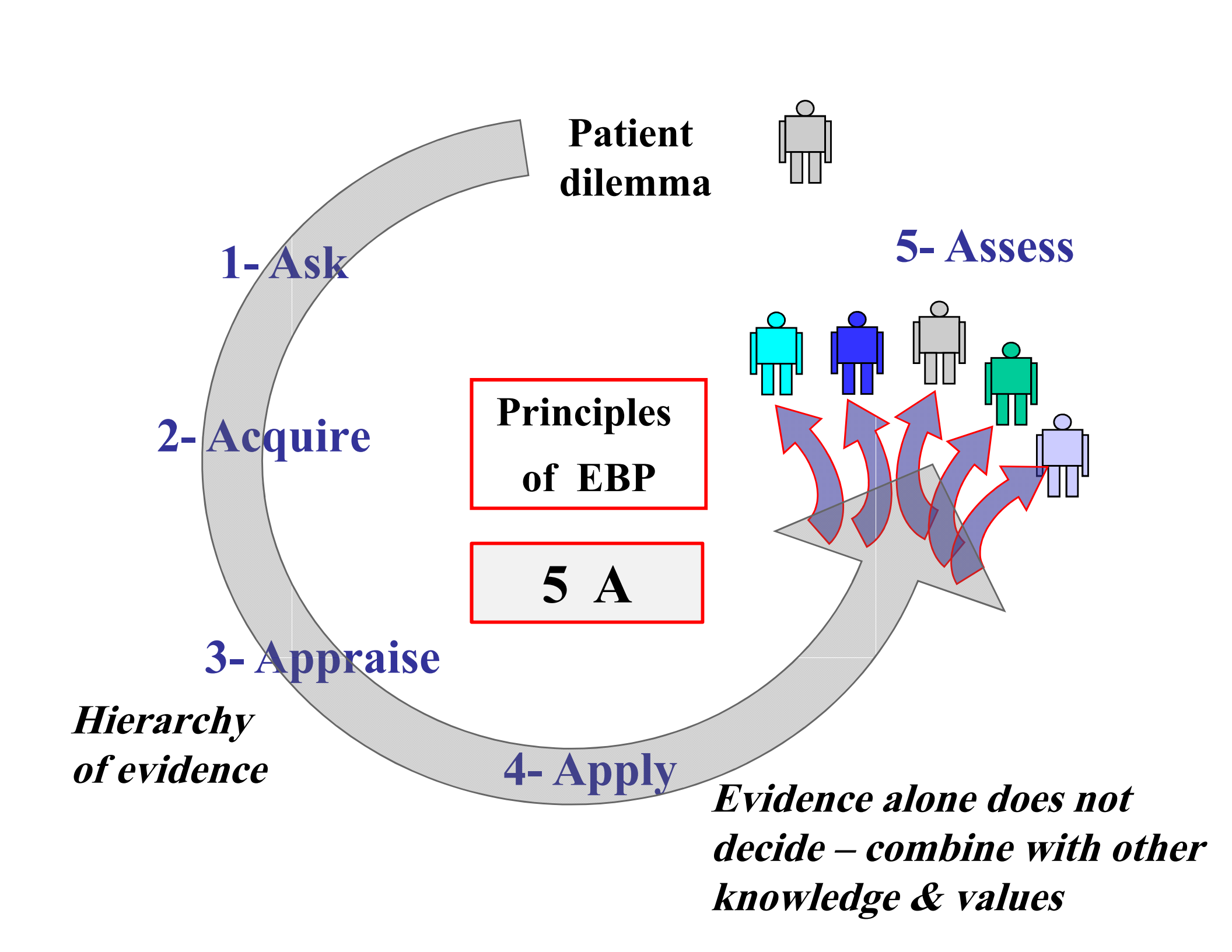
Results from Medline search using MeSH
"meta-analysis" & text word "systematic review"

Egger M et all. Systematic reviews in health care: Meta-analysis in context. BMJ Publishing Group, London, 2nd edition, 2001.

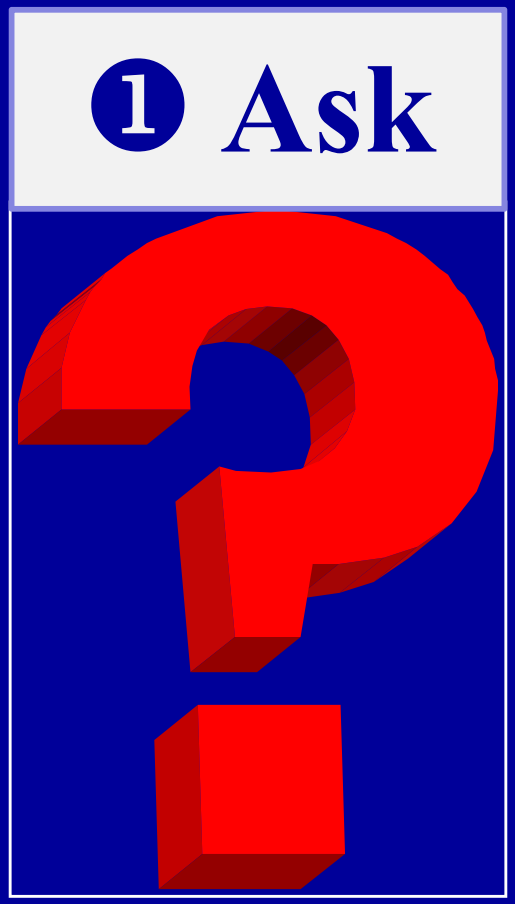
" If I had to pick one word which exemplifies the fear felt by so many students, clinicians, & consumers towards evidence-based medicine, that word would be **meta-analysis**"

Trisha Greenhalgh

Greenhalgh T. How to read a paper - The basics of evidence based medicine. BMJ Publishing Group -2nd Edition - London - 2001.


Patient dilemma
1- Ask
2- Acquire
3- Appraise
4- Apply
5- Assess
Principles of EBP
5 A
Hierarchy of evidence
Evidence alone does not decide – combine with other knowledge & values

Steps of EBM



Clinical history

- 60-year-old man with acute biliary pancreatitis
- **Ranson's score: 4** – No fever – Normal WBCs
- CECT* on day 7: CT grading system of Balthazar 3
  Necrosis score 2
  CT severity index 5
- You wonder if prophylactic antibiotics prevents infection of non-infected pancreatic necrosis & decreases mortality

*CECT: Contrast-Enhanced Computed Tomography

Ranson's score for gallstone pancreatitis

At presentation	During initial 48 hr
Age > 70 yr	Ht >10% decrease
Blood glucose >220 mg/dl	Serum calcium < 8 mg/dl
WBC >18,000/mm^3	Base deficit > 5 mEq/L
LDH > 400 IU/L	BUN > 2 mg/dl increase
ASAT > 250 IU/L	Fluid sequestration > 4 L

1 point for each positive factor

Severe acute pancreatitis: ≥ 3

Ranson JHC. Am J Gastroenterol 1982;77:633.

CT grading system of Balthazar

Grade	Description	Points
A	Normal pancreas	0
B	Pancreatic enlargement	1
C	Inflammation of pancreas or peripancreatic fat	2
D	Single peripancreatic fluid collection	3
E	≥ 2 fluid collections or retroperitoneal air	4

Balthazar EJ et al. Radiology 1990 ; 174 : 331 – 6.

Necrosis score

Necrosis	Points
No pancreatic necrosis	0 points
One third of pancreas	2 points
One half of pancreas	4 points
> one half of pancreas	6 points

CT severity index

CT grading of Balthazar (0 – 4 points) + **Necrosis score (0 – 6 points)**

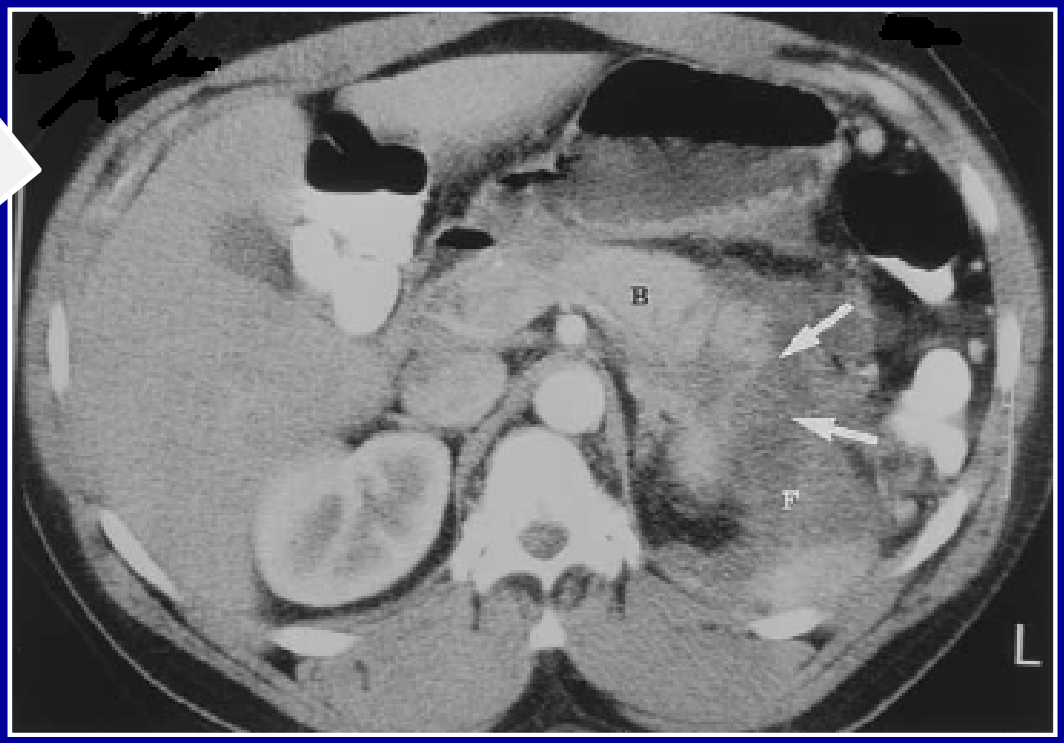
The index ranges from 0 to 10

Severe acute pancreatitis ≥ 3

Morgan DE. Clin Gastroenterol Hepatol 2008 ; 6 : 1077 – 1085.

CT Severity Index (CTSI)

CT severity index 5



Localized fluid collection adjacent to tail: CT grading (**3 points**)

Lack of enhancement of pancreatic tail: Necrosis <30 % (**2 points**)

Absence of **retroperitoneal air**

Key components of your clinical question

PICO

Prophylactic antibiotics in pancreatic necrosis

P	Patient	Severe AP with CT-proven necrosis
I	Intervention	Prophylactic antibiotics
C	Comparaison	Placebo or no treatment
O	Outcome	Infected pancreatic necrosis – Mortality

Steps of EBM

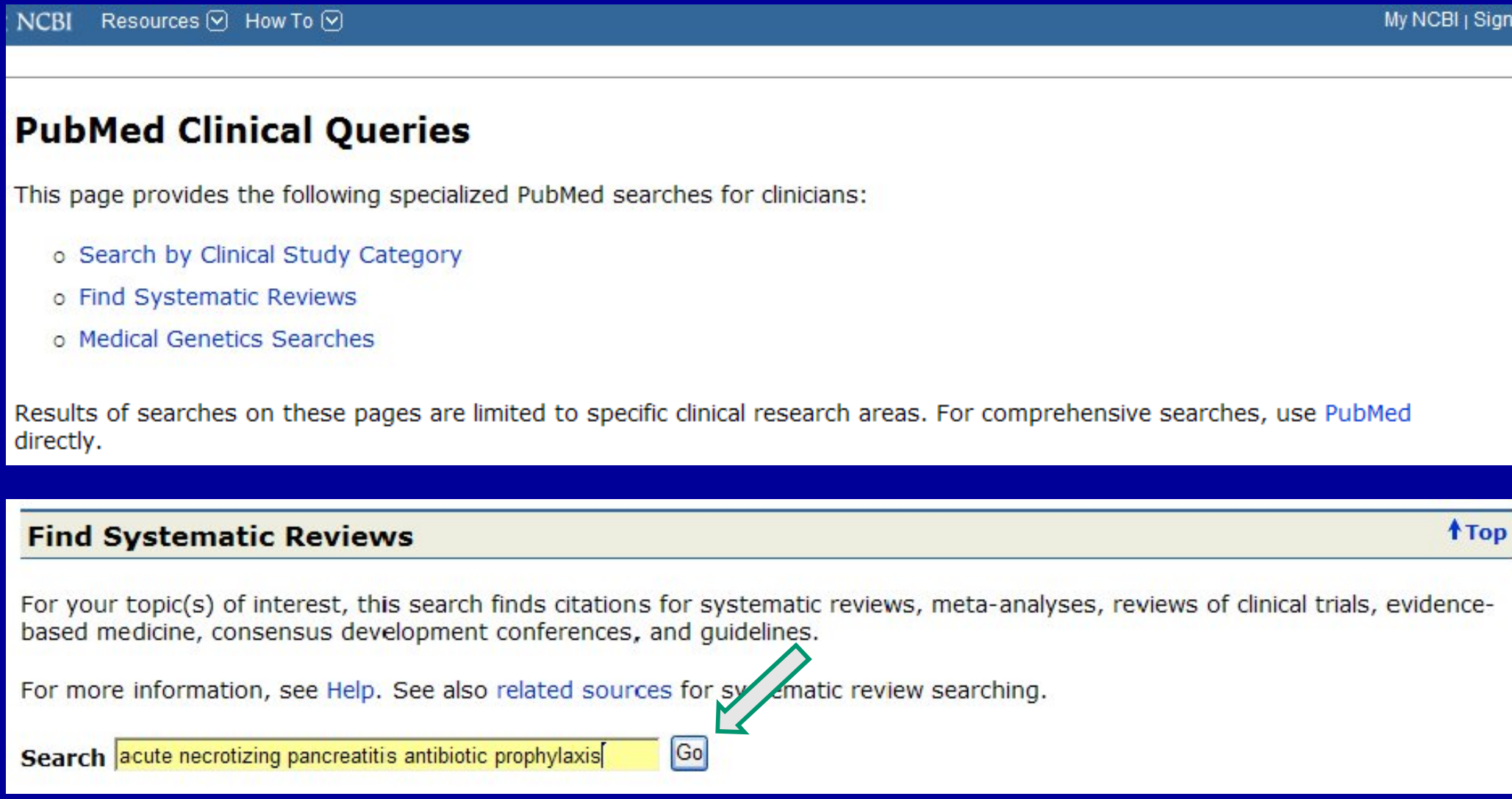
❷Acquire

PubMed translation of query into search terms

PICO	Element	Search terms for PubMed
P	Acute necrotizing pancreatitis	"acute necrotizing pancreatitis" [MeSH]
I	Prophylactic antibiotics	"antibiotic prophylaxis" [MeSH term]
C	Placebo No treatment	"placebo" [MeSH term]
O	Infected necrosis Mortality	"infection" [MeSH term] "necrosis" [MeSH term] "mortality" [MeSH term]
Other	Meta-analysis	SR in PubMed Clinical Queries

* **MeSH**: **Me**dical **S**ubject **H**eadings in PubMed

PubMed Clinical Queries



PubMed.gov
U.S. National Library of Medicine
National Institutes of Health

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(acute necrotizing pancreatitis antibiotic prophylaxis) AND systematic[sb] | Search | Clear

Display Settings: Summary, 20 per page, Sorted by Recently Added | Send to:

Results: 19

Antibiotic prophylaxis is not protective in severe acute pancreatitis: a systematic review and meta-analysis.
4. Jafri NS, Mahid SS, Idstein SR, Hornung CA, Galandiuk S.
Am J Surg. 2009 Jun;197(6):806-13. Epub 2009 Feb 13. Review.
PMID: 19217608 [PubMed - indexed for MEDLINE]
Related articles

Prophylactic antibiotics in necrotizing pancreatitis: a meta-analysis.
5. Hart PA, Bechtold ML, Marshall JB, Choudhary A, Puli SR, Roy PK.
South Med J. 2008 Nov;101(11):1126-31.
PMID: 19088522 [PubMed - indexed for MEDLINE]
Related articles

Prophylactic antibiotic treatment in acute necrotizing pancreatitis: results from a meta-analysis.
6. Xu T, Cai Q.
Scand J Gastroenterol. 2008;43(10):1249-58.
PMID: 18609129 [PubMed - indexed for MEDLINE]
Related articles

Prophylactic antibiotics cannot reduce infected pancreatic necrosis and mortality in acute necrotizing pancreatitis: evidence from a meta-analysis of randomized controlled trials.
8. Bai Y, Gao J, Zou DW, Li ZS.
Am J Gastroenterol. 2008 Jan;103(1):104-10. Epub 2007 Oct 9. Review.
PMID: 17925000 [PubMed - indexed for MEDLINE]
Related articles

Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis.
10. Villatoro E, Bassi C, Larvin M.
Cochrane Database Syst Rev. 2006 Oct 18;(4):CD002941. Review.
PMID: 17054156 [PubMed - indexed for MEDLINE]
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American Journal of Gastroenterology

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ISSN 0002-9270
doi: 10.1111/j.1572-0241.2007.01575.x

Prophylactic Antibiotics Cannot Reduce Infected Pancreatic Necrosis and Mortality in Acute Necrotizing Pancreatitis: Evidence From a Meta-Analysis of Randomized Controlled Trials

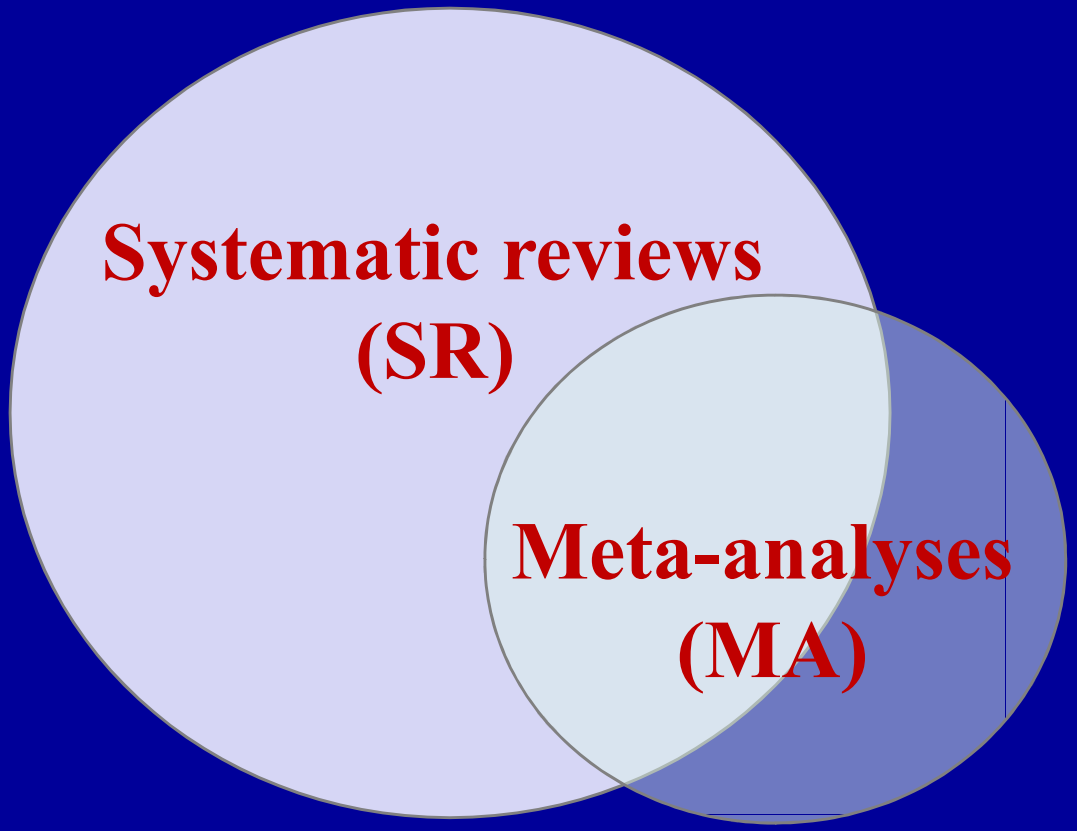
Yu Bai, M.D., Jun Gao, M.D., Duo-wu Zou, M.D., and Zhao-shen Li, M.D.
Department of Gastroenterology, Changhai Hospital, Second Military Medical University, Shanghai, China

(Am J Gastroenterol 2008;103:104–110)

Steps of EBM

❸ Appraise

Systematic review & meta-analysis



MA may, or may not, include a SR

Egger M et all. Systematic reviews in health care: Meta-analysis in context. BMJ Publishing Group, London, 2nd edition, 2001.

Definition of meta-analysis

"Statistical analysis that combines or integrates the results of several independent clinical trials considered by the analyst to be combinable"

Proceedings of biopharmaceutical section of American statistical association. 1988 ; 2 : 28 – 33.

Rationale for a meta-analysis

By combining the samples of individual studies, the overall sample size is increased, thereby improving the statistical power of the analysis as well as precision of estimates of treatment effects

Steps of meta-analysis

Researchers should write in advance a detailed protocol

1. Formulation of the problem to be addressed
2. Data collection
3. Data recording
4. Data analysis
5. Reporting the results (**Forest plot**)

❶ Formulation of the addressed problem

PICO

Study design: RCTs

P	Patient	Severe AP with CT-proven necrosis
I	Intervention	Prophylactic antibiotics
C	Comparaison	Placebo or no treatment
O	Outcome	Infected pancreatic necrosis -Mortality

❶ Formulation of the addressed problem

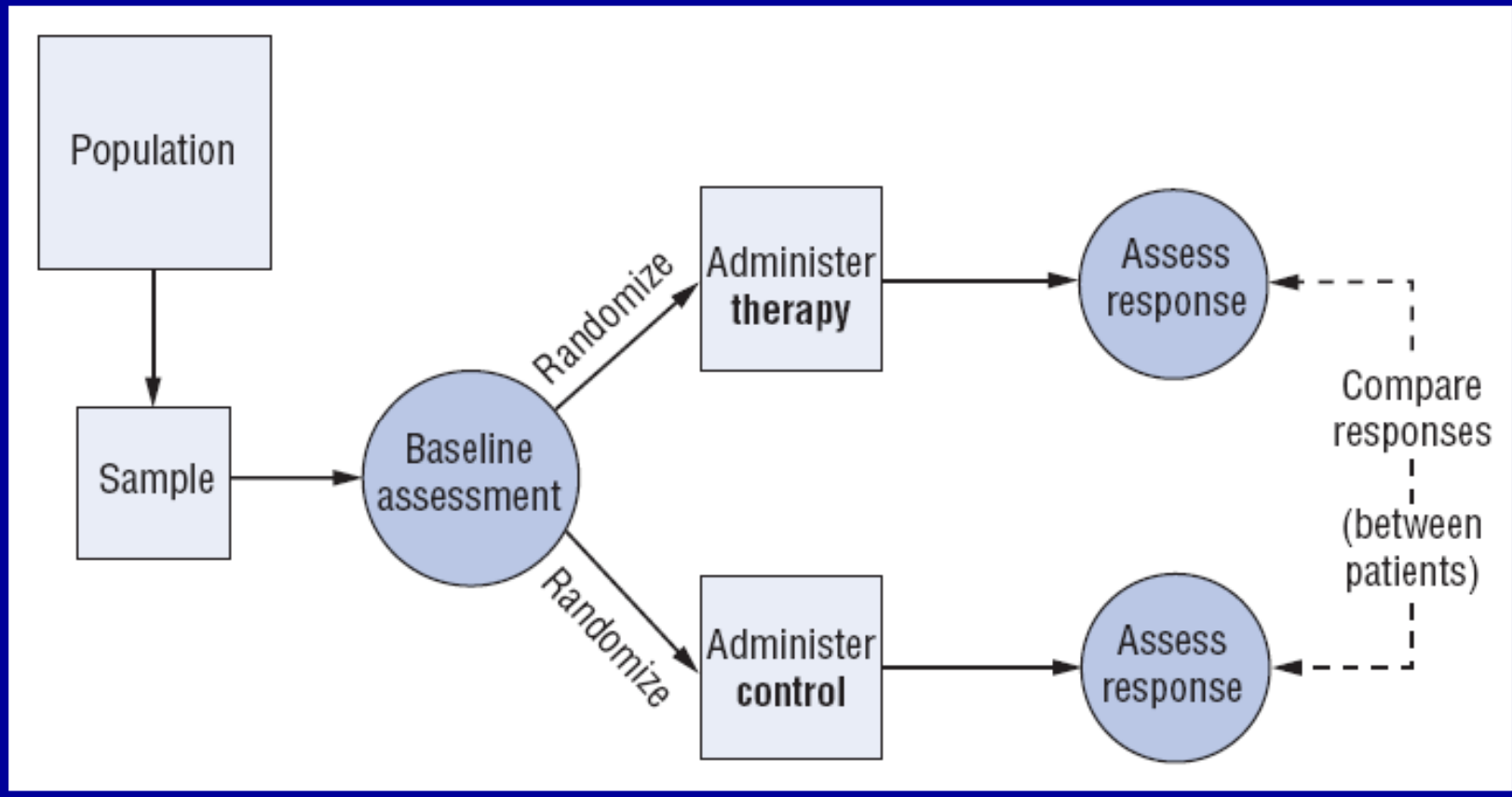
Specify inclusion & exclusion criteria

- **Controlled trials**
- **Randomization** of patients

- Intention to treat principle (**ITT**)
- Preferably **blinded**
- Outcome assessment: **p** – **RR** – **OR** – **CIs** – **NNT**

Guyatt G, et al. User's guide to the medical literature.
Essentials of evidence based clinical practice. Mc Graw Hill, 2nd ed, 2008.

Basic structure of a RCT / Parallel trial

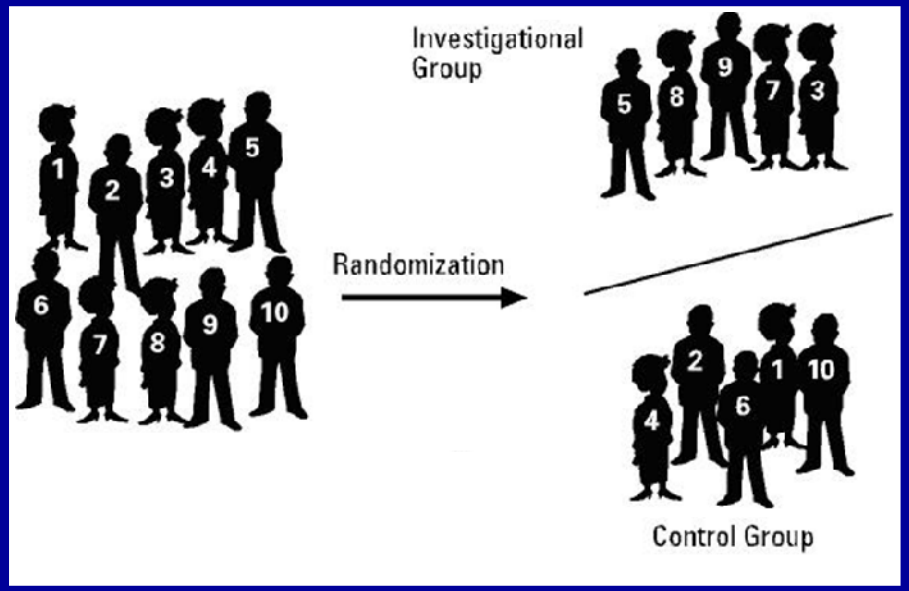


Most frequently used design

Petrie A, Sabin C. Medical statistics at a glance. Blackwell Publishing, 2nd edition, 2005.

Randomization

- **Simple randomization** → **Inacceptable**
- **Random table**
- **Block randomization**
- **Stratified randomization**
- **Minimization method**
- **Unequal randomization**
- **Allocation concealment** → **Preferred**



Intention to treat analysis

Quality control rather than analytic tool

- Strategy in conduct & analysis of RCT ensuring that all patients allocated to treatment or control groups are analyzed together as representing that treatment arm whether or not they received the prescribed treatment or completed the study

Randomized participants = Analyzed participants

McGovern D, Summerskill W, Valori R, Levi M. Key topics in EBM. BIOS Scientific Publishers, 1st ed, Oxford, 2001.

Blinding or Masking

Blinding can be implemented in at least 6 levels in RCTs

- **Participants**
- **Investigators who administer interventions**
- **Investigators taking care of the participants**
- **Investigators assessing the outcomes**
- **Data analyst**
- **Investigators who write results of the trial**

Usually the same

❷ Data collection

Finding all studies (Is there an existing SR?)

- **Electronic search**

Initial search	**PubMed – Cochrane Review**
	Others databases: **EMBASE**, **CINAHL**
Further search	References of relevant reviews
	Find terms you didn't use (**MeSH***)
Search again	Snowballing

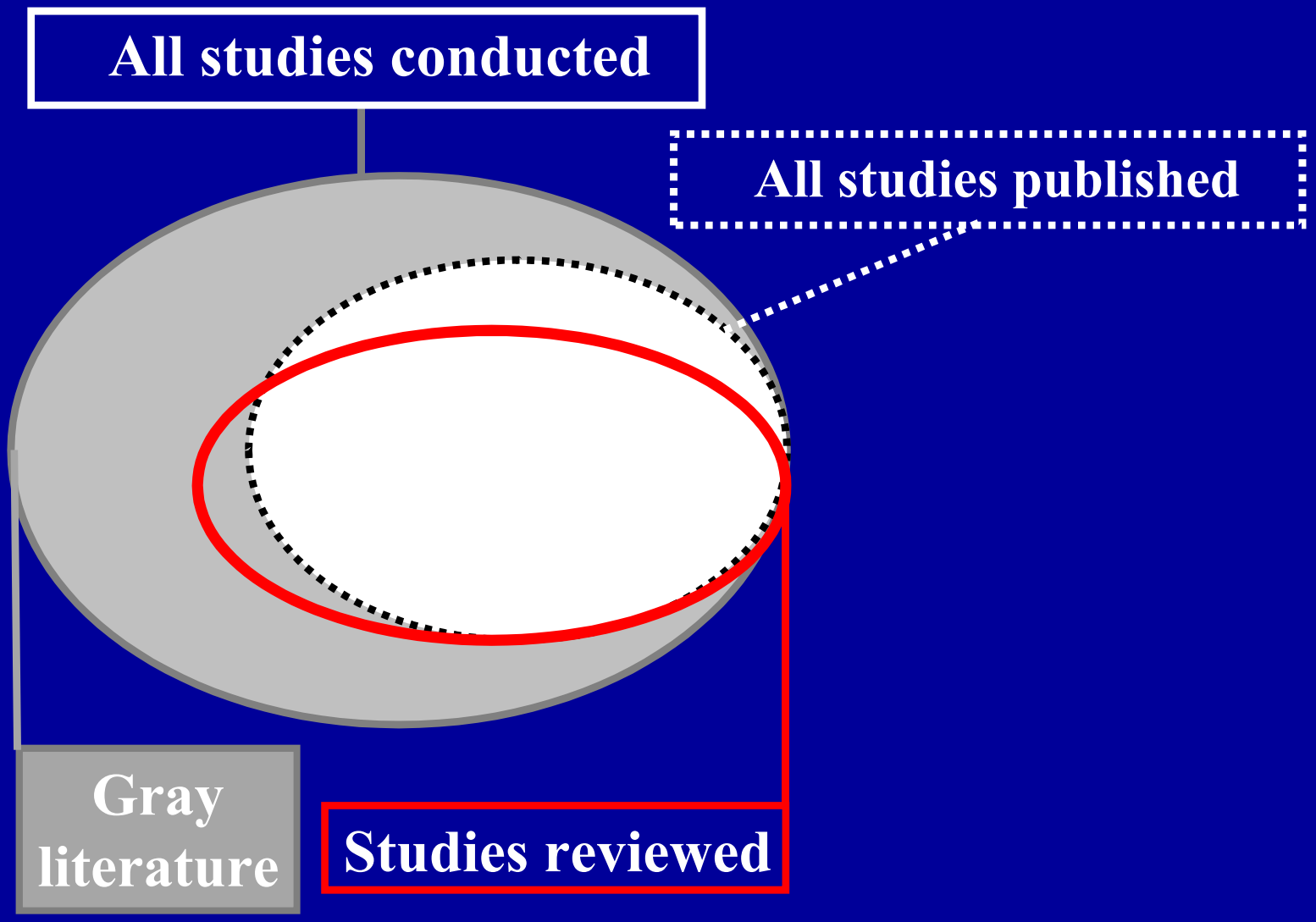
- **Supplementary search**

Hand search

Write to researchers

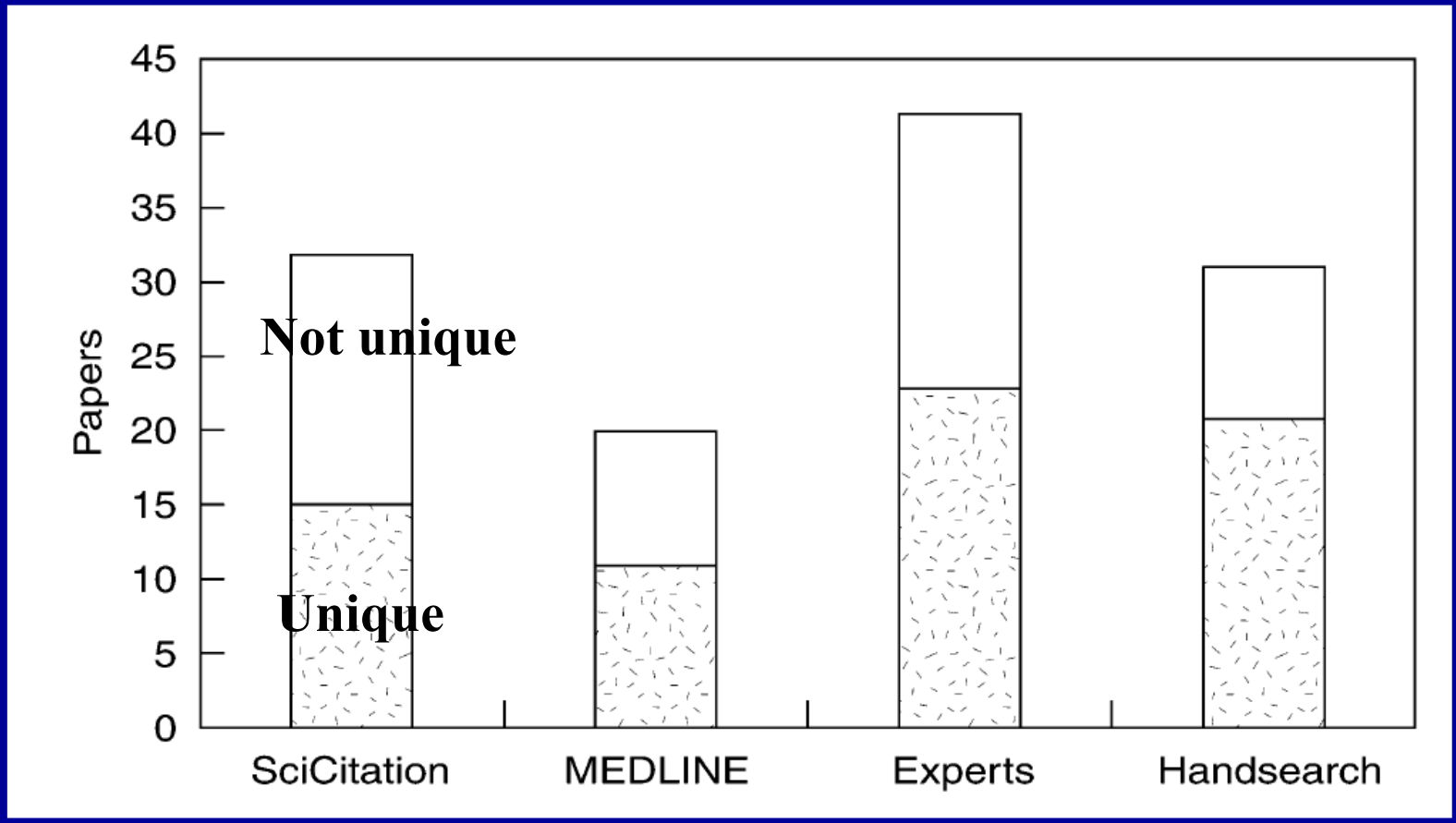
* **MeSH**: **Me**dical **S**ubject **H**eadings in MEDLINE

Studies included in meta-analysis



Why using multiple sources?

Papers identified in a SR of near patient testing



Glasziou P et al. Systematic reviews in health care: a practical guide. Cambridge University Press, 1st edition, 2001.

❷ Data collection

Prophylactic antibiotics in pancreatic necrosis

- **Electronic databases**
  - MEDLINE
  - EMBASE
  - CCTR
  - Cochrane Library
  - Science Citation Index
- **Hand search**
  - References from published trials
  - Major conference abstracts

CCTR: **C**ochrane **C**ontrolled **T**rials **R**egister

Bai Y et al. Am J Gastroenterol 2008 ; 103 : 104 – 110.

❸ Data recording

- 2 **independent observers** extract the data
- Quality of the studies may be rated with specially designed **checklist** or scales
- **Blinding** observers to names of authors, institutions, names of journals, funding & acknowledgments

Existing tools to assess trial quality

- Several components grouped in

  Scales Each item scored numerically
  Overall quality score is generated

  Checklists Components evaluated separately
  No numerical scores

- Systematic search of literature in 1995 identified
  25 scales & **9 checklists** for assessing trial quality*

* Moher D et all. Controlled clinical trials 1995 ; 16 : 62 – 73.

❸ Data recording

Prophylactic antibiotics in pancreatic necrosis

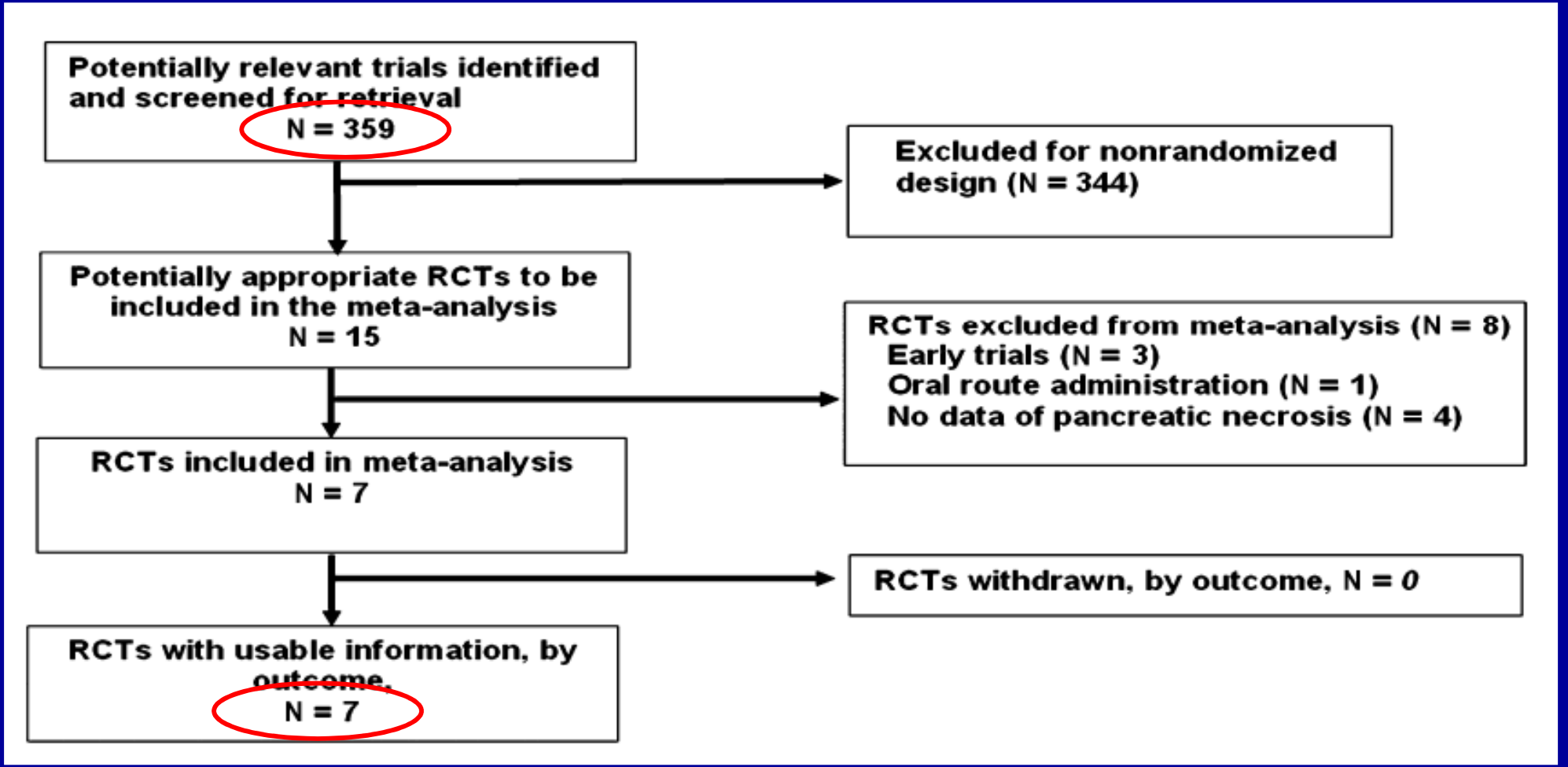
- Quality assessment performed **independently** by 2 authors using empirical evidence [1-2]
- Disagreement resolved by discussion between 2 reviewers

- **Low risk of bias** → Generation of allocation sequence
  - Allocation concealment
  - Blinding
- **High risk of bias** — 1 or more component inadequate

[1] Schulz KF et al. JAMA 1995 ; 273 : 408 – 12.
[2] Moher D et al. Lancet 1998 ; 352 : 609 – 13.

Antibiotic prophylactic in pancreatic necrosis

Flow diagram



Bai Y et al. Am J Gastroenterol 2008 ; 103 : 104 – 110.

Characteristics of RCTs included in MA

Author	Year	Setting	Total No	Blinding	Risk of Bias	Dosage and Duration
Pederzoli	1993	Multicenter	74	Single	High	Imipenem 0.5 g IV 8 hourly
Sainio	1995	Single center	60	Single	High	Cefuroxime 1.5 g IV 8 hourly
Schwarz	1997	Single center	26	Single	High	Ofloxacin 0.2 g b.i.d. IV & metronidazole 0.5 g b.i.d. IV
Nordback	2001	Single center	39	Single	High	Imipenem 1 g IV 8 hourly
Isenmann	2004	Multicenter	76	Double	Low	Ciprofloxacin 0.4 g b.i.d. IV & metronidazole 0.5 g b.i.d. IV
Dellinger	2007	Multicenter	100	Double	Low	Meropenem 0.5 g IV 8 hourly
Rokke	2007	Multicenter	73	No	High	Imipenem 0.5 g IV 8 hourly

467 patients included in 7 trials

Bai Yu & al. Am J Gastroenterol 2008 ; 103 : 104 – 110.

❹ Data analysis

2 stage statistical process of MA

- **Treatment effect for each study**

p value (**p**)

Relative Risk (**RR**) or Odds Ratio (**OR**)

Confidence Intervals (**CIs**)

Number Needed to Treat (**NNT**)

- **Overall treatment effect**

Calculated as weighted average of individual statistics

Statistical power of MA is often very high

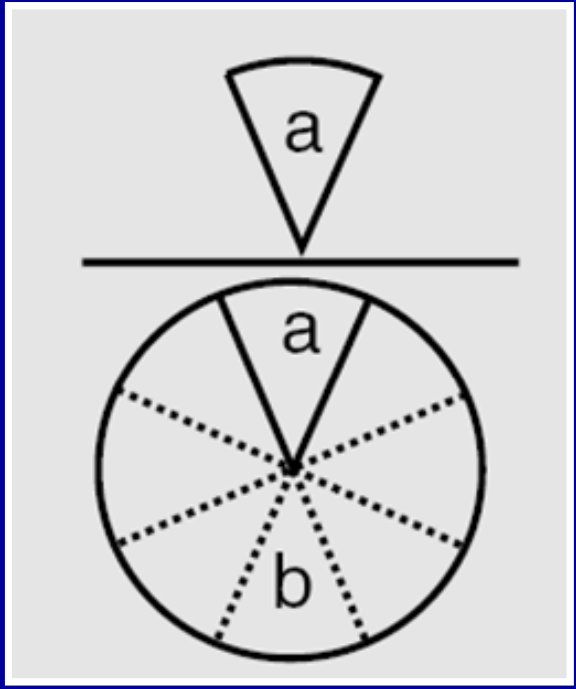
Probability value (p value)

- **p > 0.05 Statistically insignificant**
- **p < 0.05 Statistically significant**

Statistically significant → **Doesn't mean** → **Clinically significant**

Risk & Odds

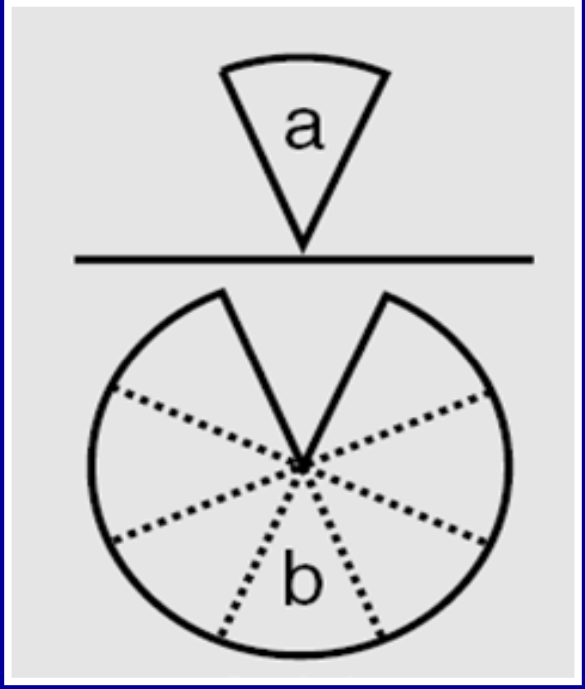
Risk



$$\text{Risk} = \frac{\mathbf{a}}{\mathbf{a + b}}$$

RR: risk patients/risk controls

Odds



$$\text{Odds} = \frac{\mathbf{a}}{\mathbf{b}}$$

OR: odds patients/odds controls

Interpretation of RR & OR

OR or RR should be accompanied by CI

RR or OR > 1

Increased likelihood of outcome in treatment group

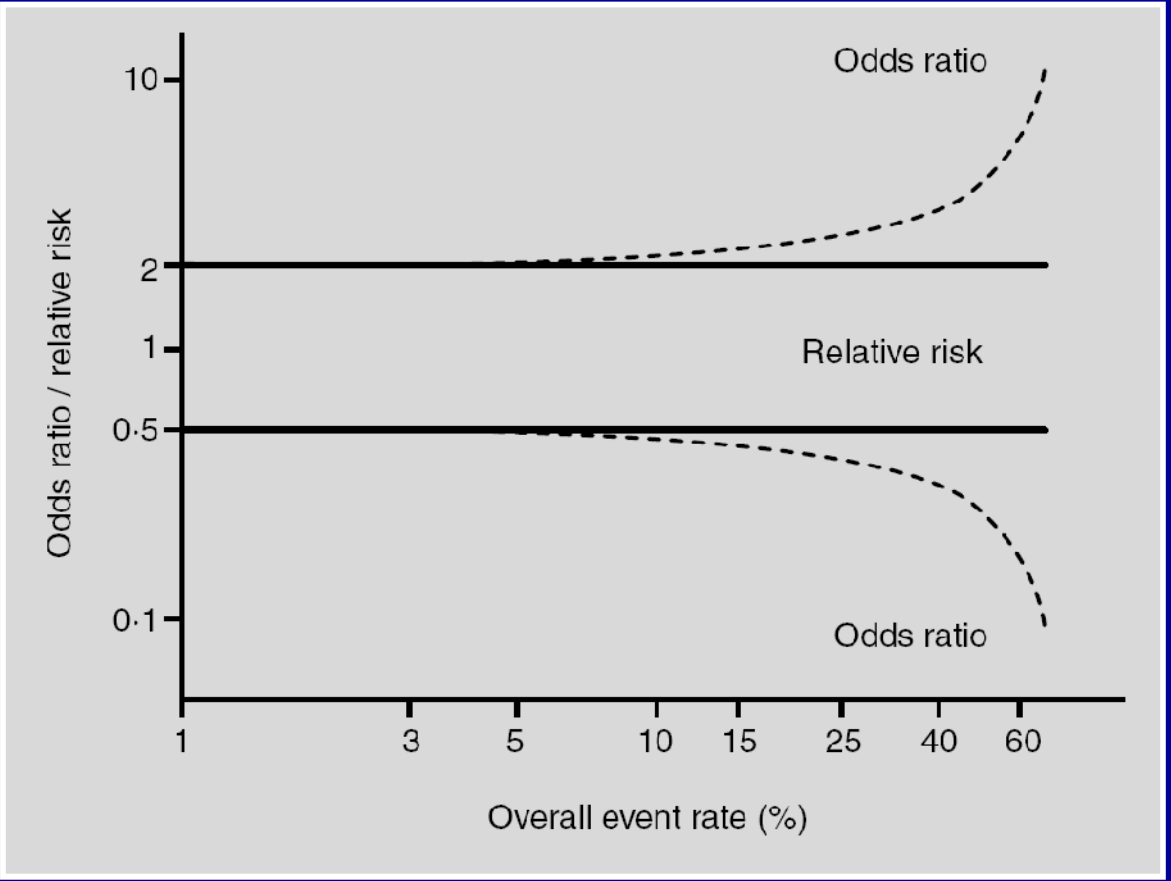
RR or OR < 1

Decreased likelihood of outcome in treatment group

RR or OR = 1

No difference of outcome between tt & control group

Odds ratio or relative risk?



OR will be close to RR if endpoint occurs infrequently (<15%)

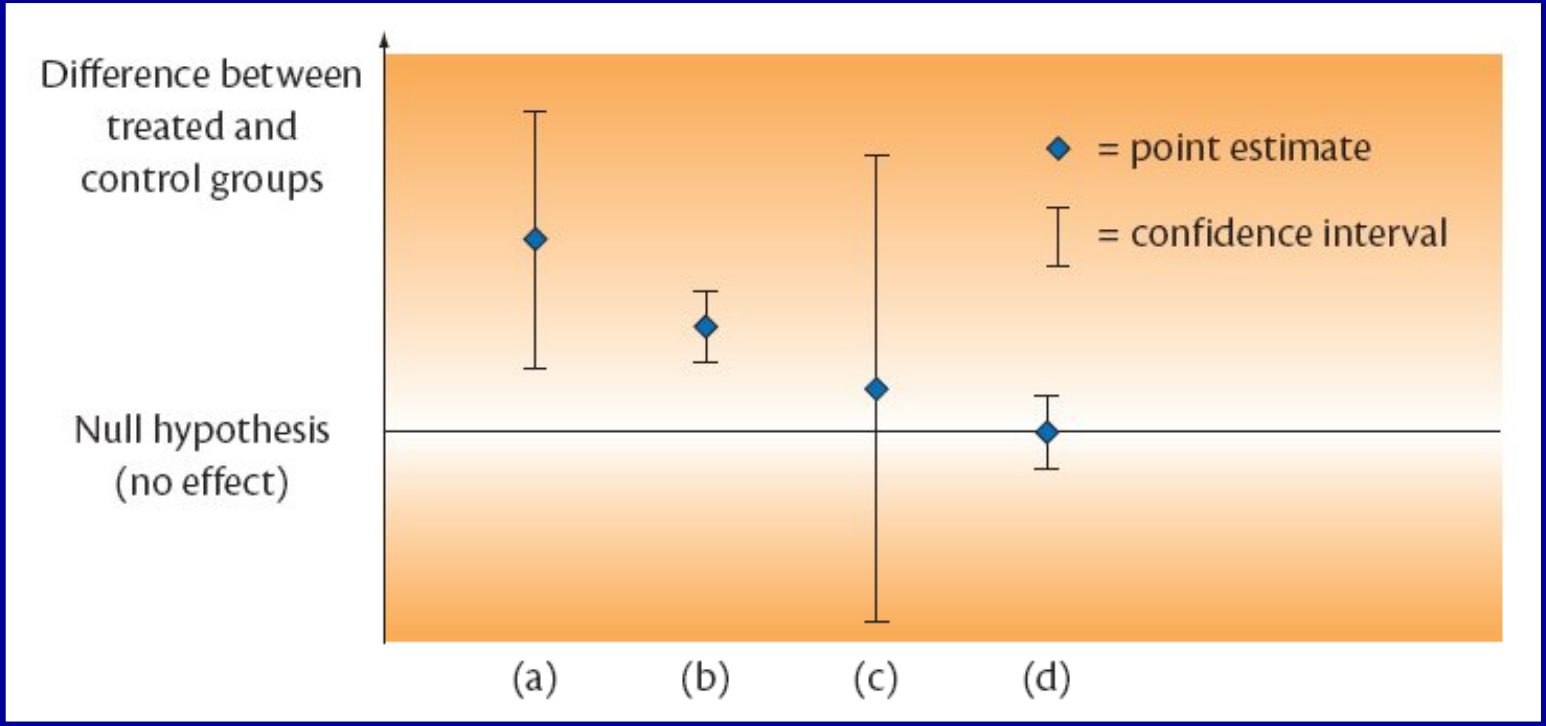
If outcome is more common, OR will differ increasingly from RR

Egger M et all. Systematic reviews in health care: Meta-analysis in context. BMJ Publishing Group, London, 2nd edition, 2001.

Confidence intervals

Value	95 % CI are commonly used 90 or 99% CI are sometimes used
Width of CI	Indicates precision of the estimate Wider the interval, less the precision
CI includes 1	No statistically significant difference
CI doesn't include 1	Statistically significant difference

Statistical significance & CI



(a) Statistically significant , low precision
(b) Statistically significant, high precision
(c) Not statistically significant, low precision
(d) Not statistically significant, high precision

Glasziou P et al. Evidence based practice workbook. Blackwell, 2nd edition, 2007.

Number Needed to Treat (NNT)

- **Relative risk (RR)**

  Risk in treatment group / risk in control group

- **Absolute risk reduction (ARR)**

  Risk in control group – risk in treatment group

- **NNT** (expressed in clinically relevant way)

  1 /ARR

Statistical methods/overall treatment effect

Larger trials have more influence than smaller ones

Fixed effects model [1]

Random effects model [2]

Bayesian models[3] Controversial

Fixed & random effects

No single correct method

[1] Prog Cardiovasc Dis 1985 ; 17 : 335 – 71.

[2] Stat Med 1992 ; 11 : 141 – 58.

[3] BMJ 1996 ; 313 : 603 – 7.

❹ Data analysis

Prophylactic antibiotics in pancreatic necrosis

- **Treatment effect for each study**

  p value (**p**)
  Relative risk (**RR**)
  95% confidence intervals (**CIs**)

- **Overall treatment effect**

  Random effects model only
  Inherited heterogeneity between the studies
  More conservative estimate of effect by using wider CIs

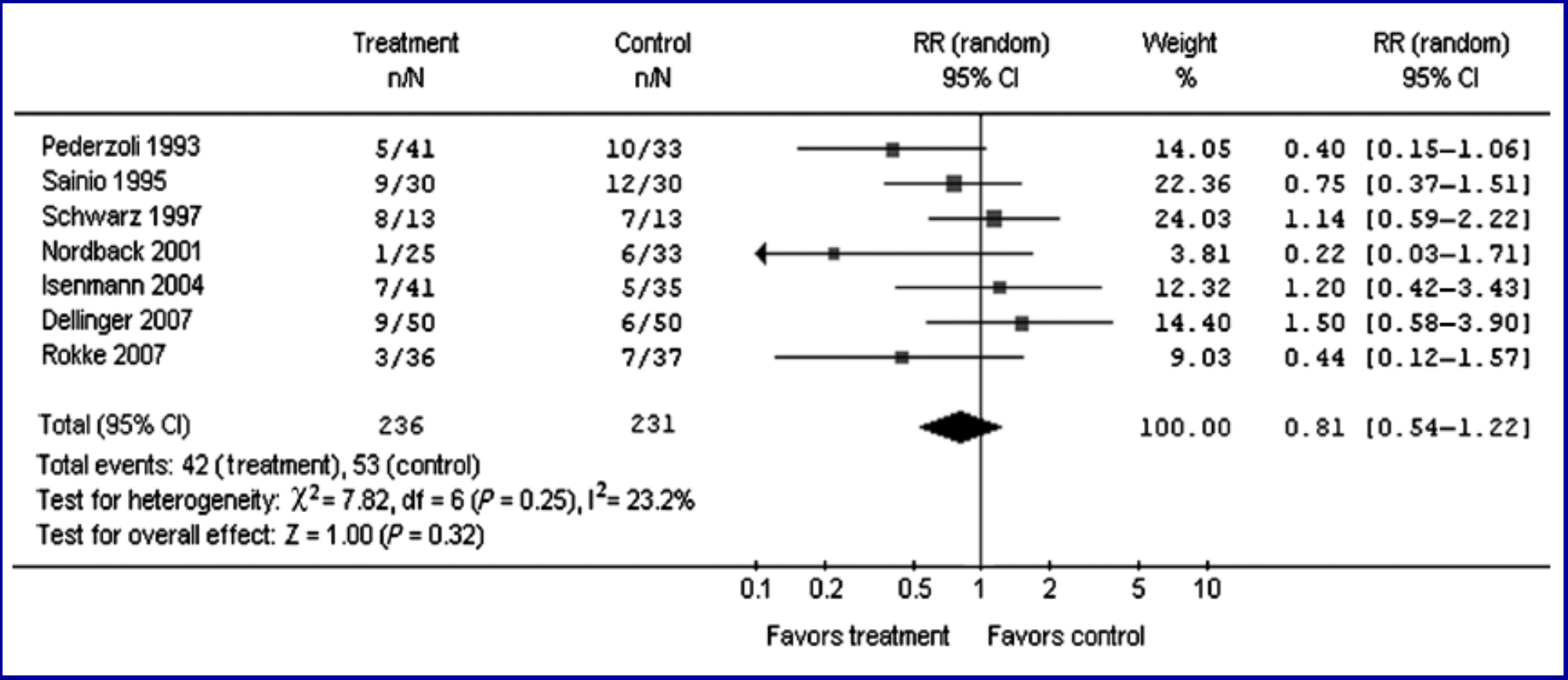
Bai Yu & al. Am J Gastroenterol 2008 ; 103 : 104 – 110.

❺ Reporting the results

The typical graph for displaying results of a meta-analysis is called a ‘‘forest plot’’

Antibiotic prophylaxis & pancreatic necrosis

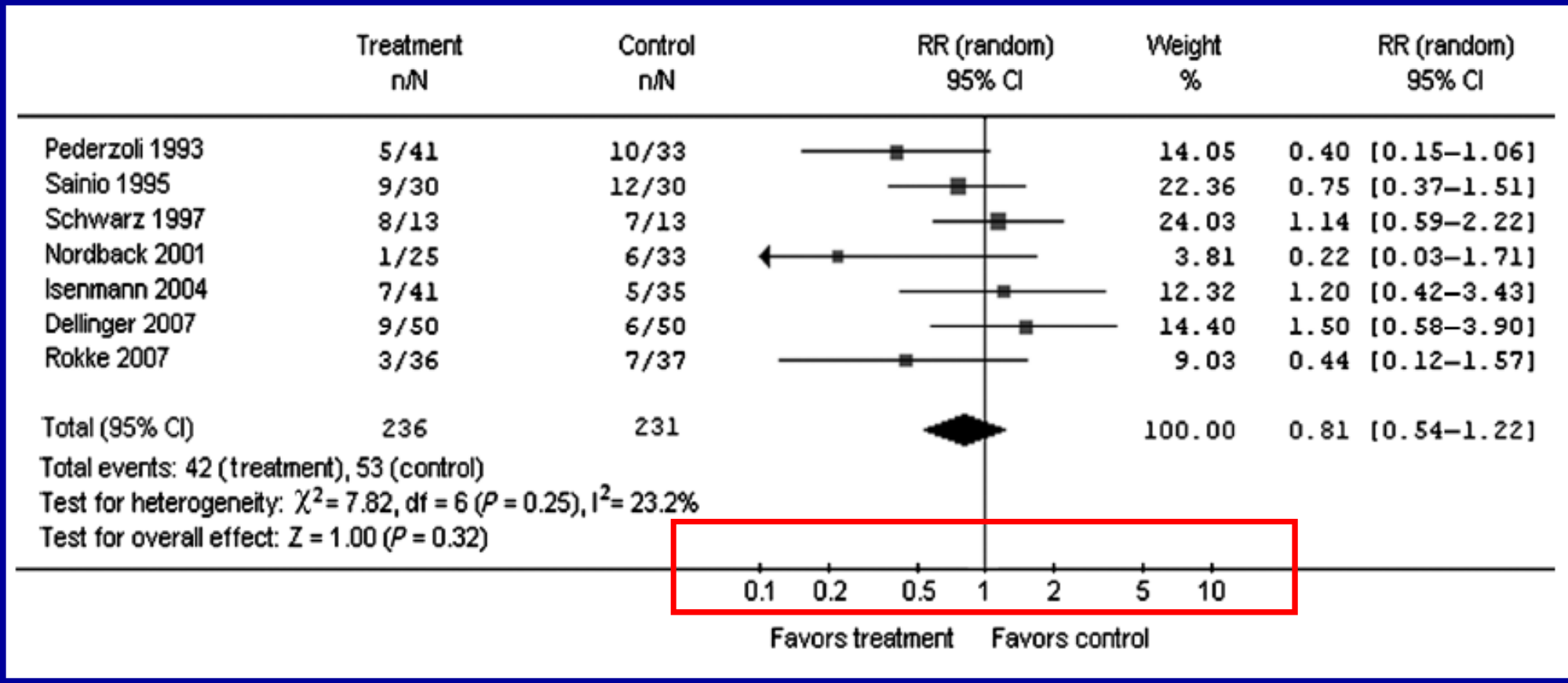
Forest plot



Bai Y et al. Am J Gastroenterol 2008 ; 103 : 104 – 110.

Antibiotic prophylaxis & pancreatic necrosis

Horizontal line

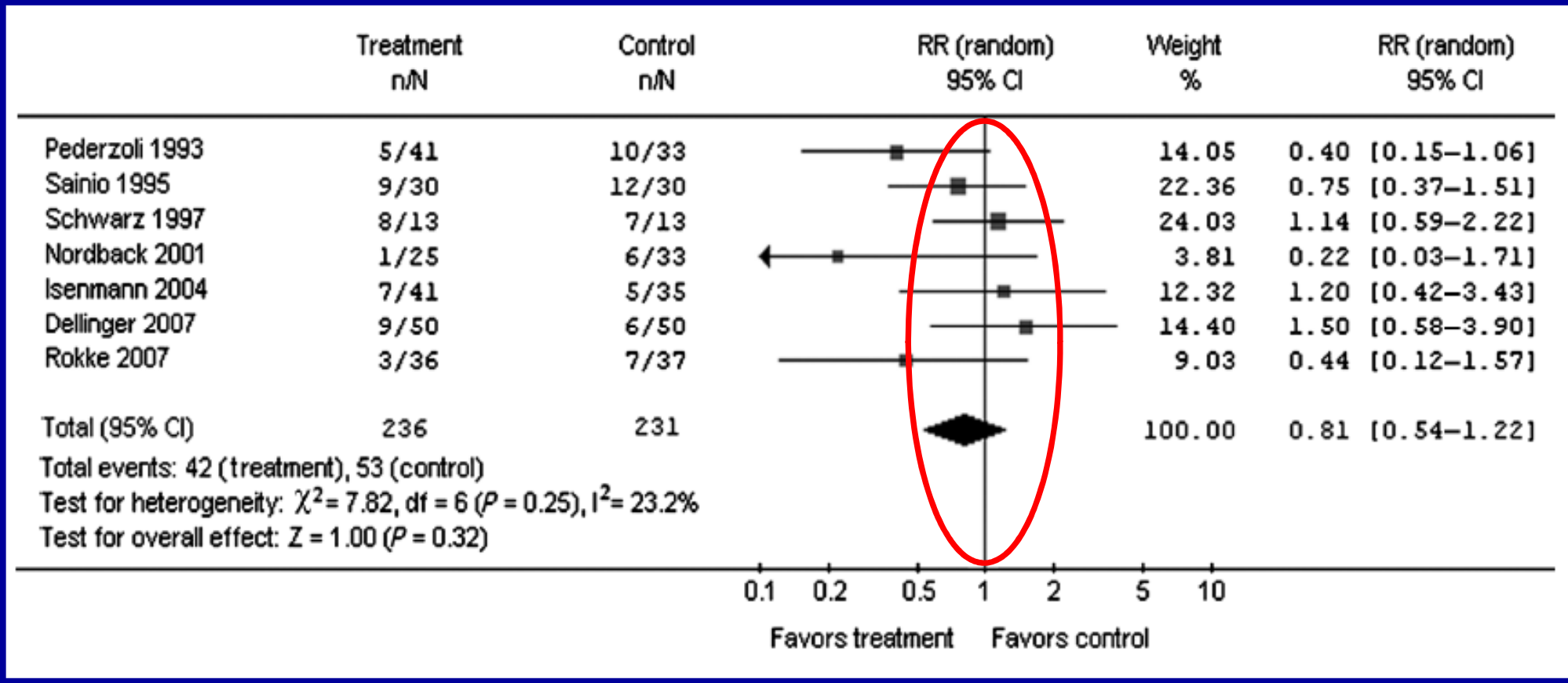


Scale measuring the treatment effect

Bai Y et al. Am J Gastroenterol 2008 ; 103 : 104 – 110.

Antibiotic prophylaxis & pancreatic necrosis

Vertical line or line of no effect

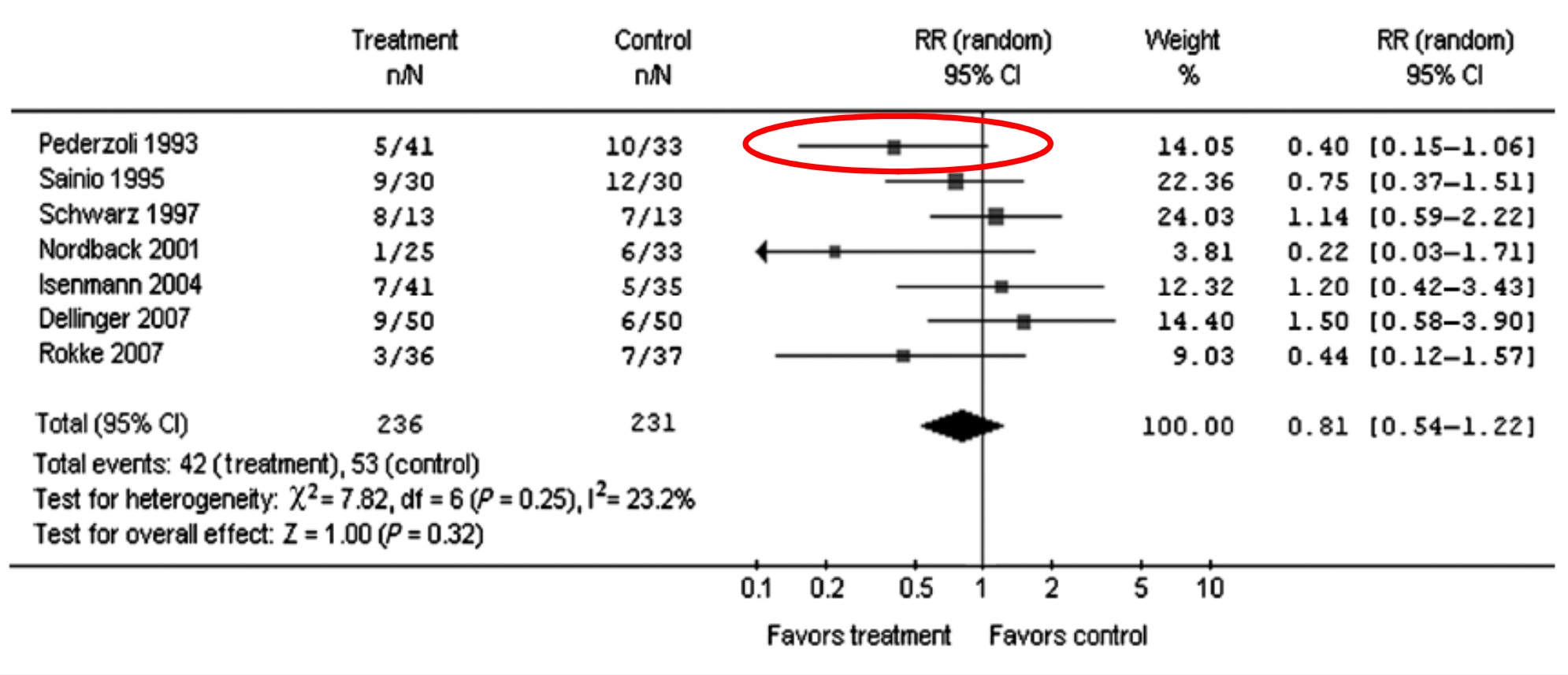


Treatment & control groups have the same effect

Bai Y et al. Am J Gastroenterol 2008 ; 103 : 104 – 110.

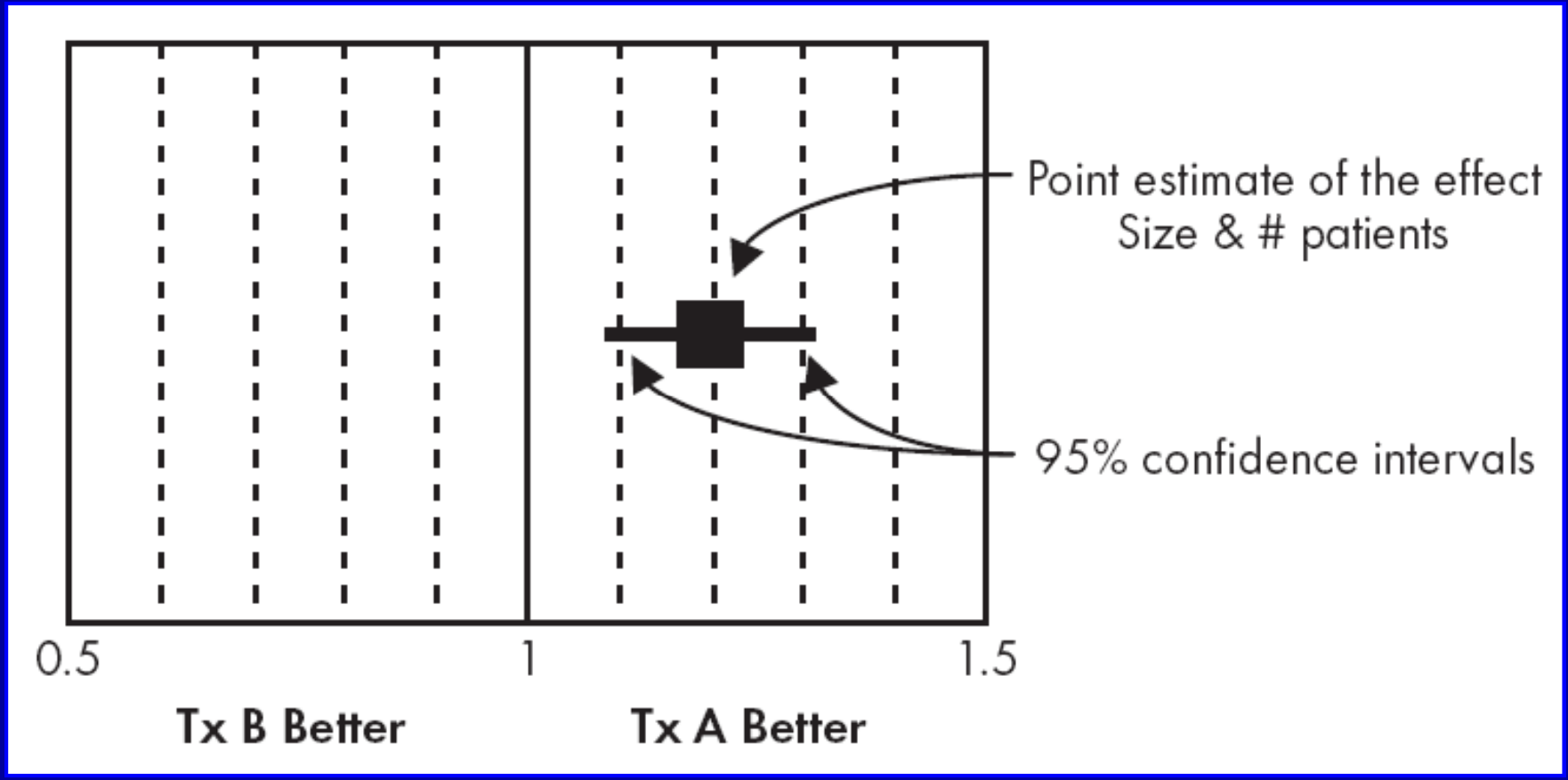
Antibiotic prophylaxis & pancreatic necrosis

Point estimate & CIs for each study



Bai Y et al. Am J Gastroenterol 2008 ; 103 : 104 – 110.

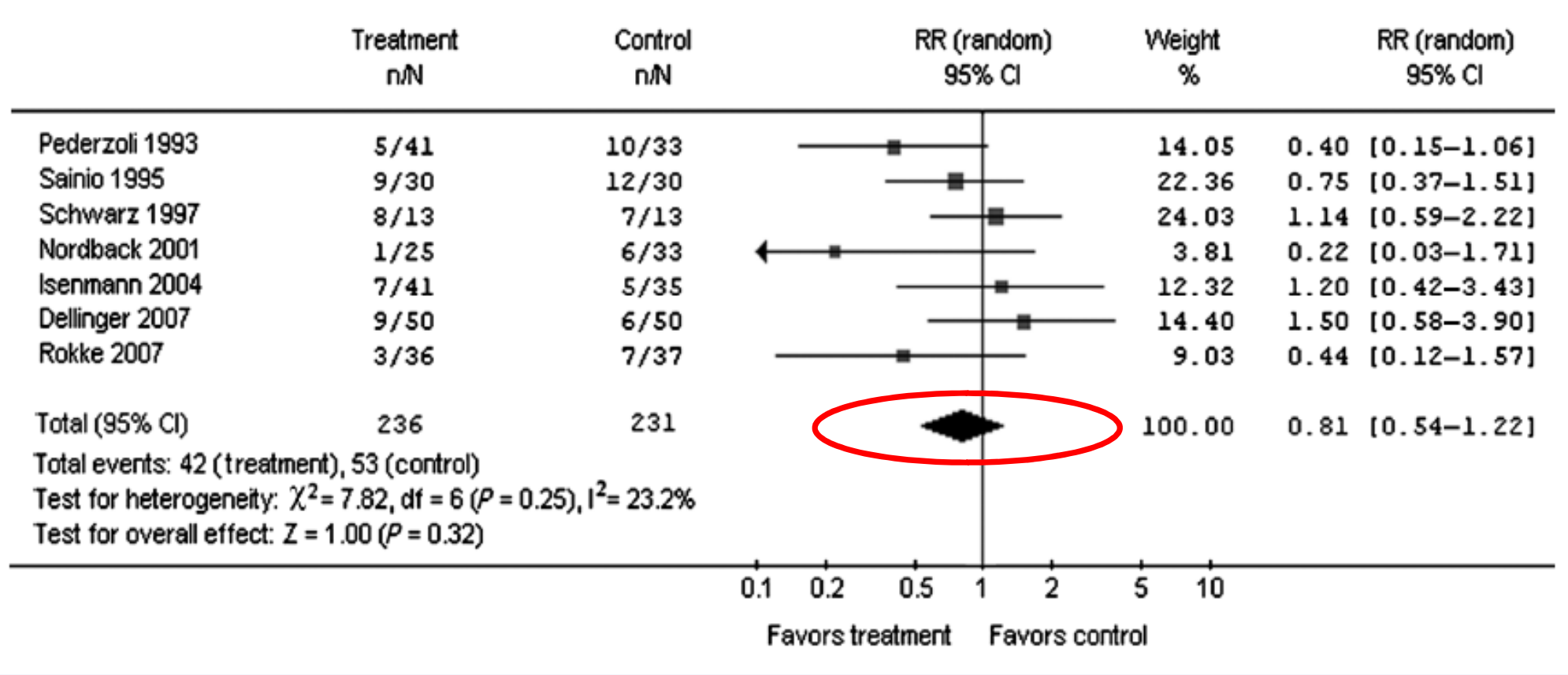
Point estimate (RR or OR) & CI



Gallin JI, Ognibene FP. Principles & practice of clinical research. A Press, 2nd ed, 2005.

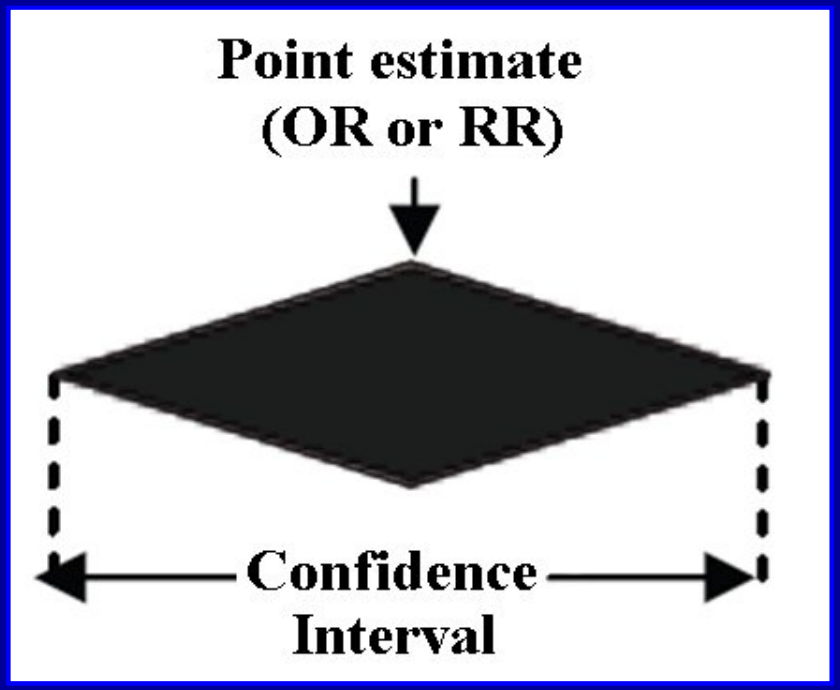
Antibiotic prophylaxis & pancreatic necrosis

Diamond



Bai Y et al. Am J Gastroenterol 2008 ; 103 : 104 – 110.

The diamond



Shows combined point estimate (OR or RR)

& CI for the meta-analysis

Perera R, Heneghan C, Badenoch D. Statistics Toolkit.
Blackwell Publishing Ltd, Oxford, 1st edition, 2008.

Diamond in meta-analysis

Diamond on Left of the line of no effect

Less episodes of outcome of interest in treatment group

Diamond on Right of the line of no effect

Mo**R**e episodes of outcome in treatment group

Diamond touches the line of no effect

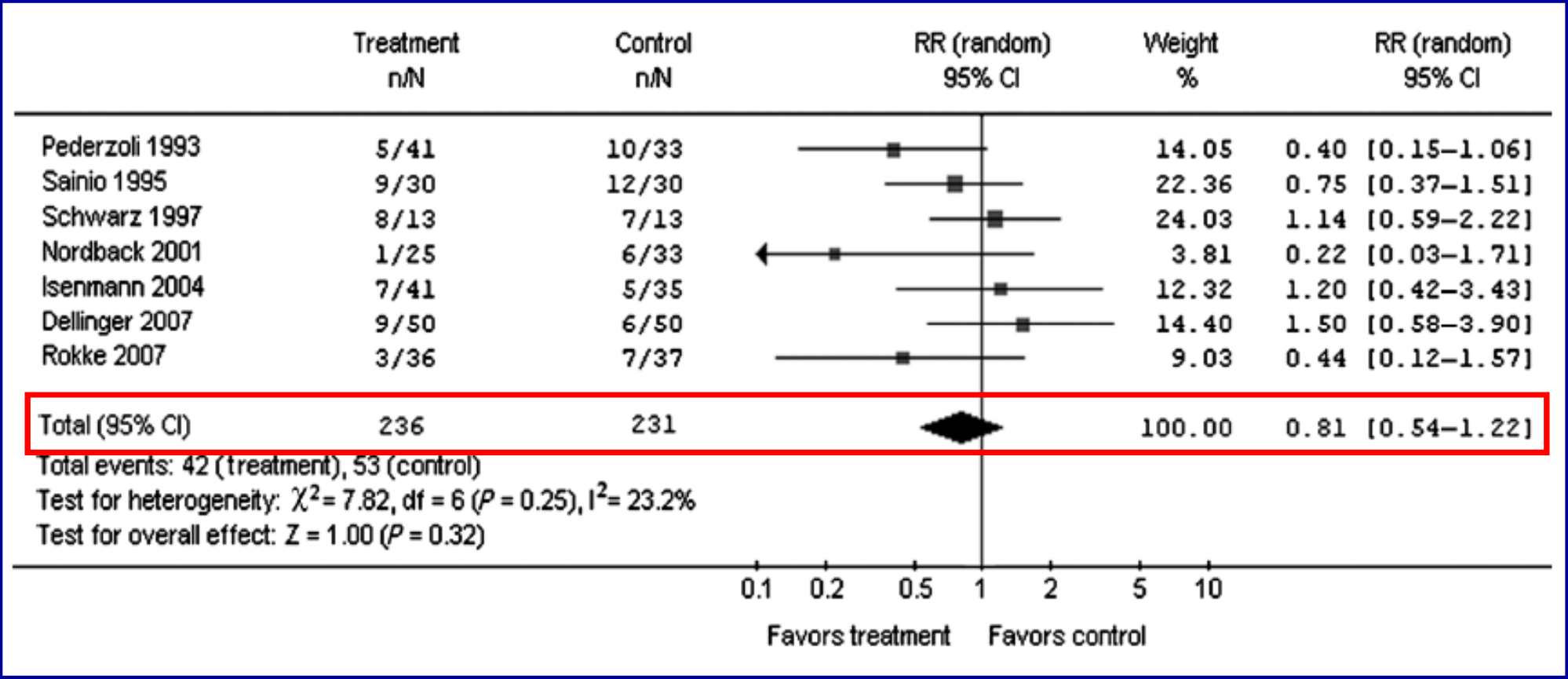
No statistically significant difference between groups

Diamond does not touch the line of no effect

Difference between two groups statistically significant

Antibiotic prophylaxis & pancreatic necrosis

The diamond

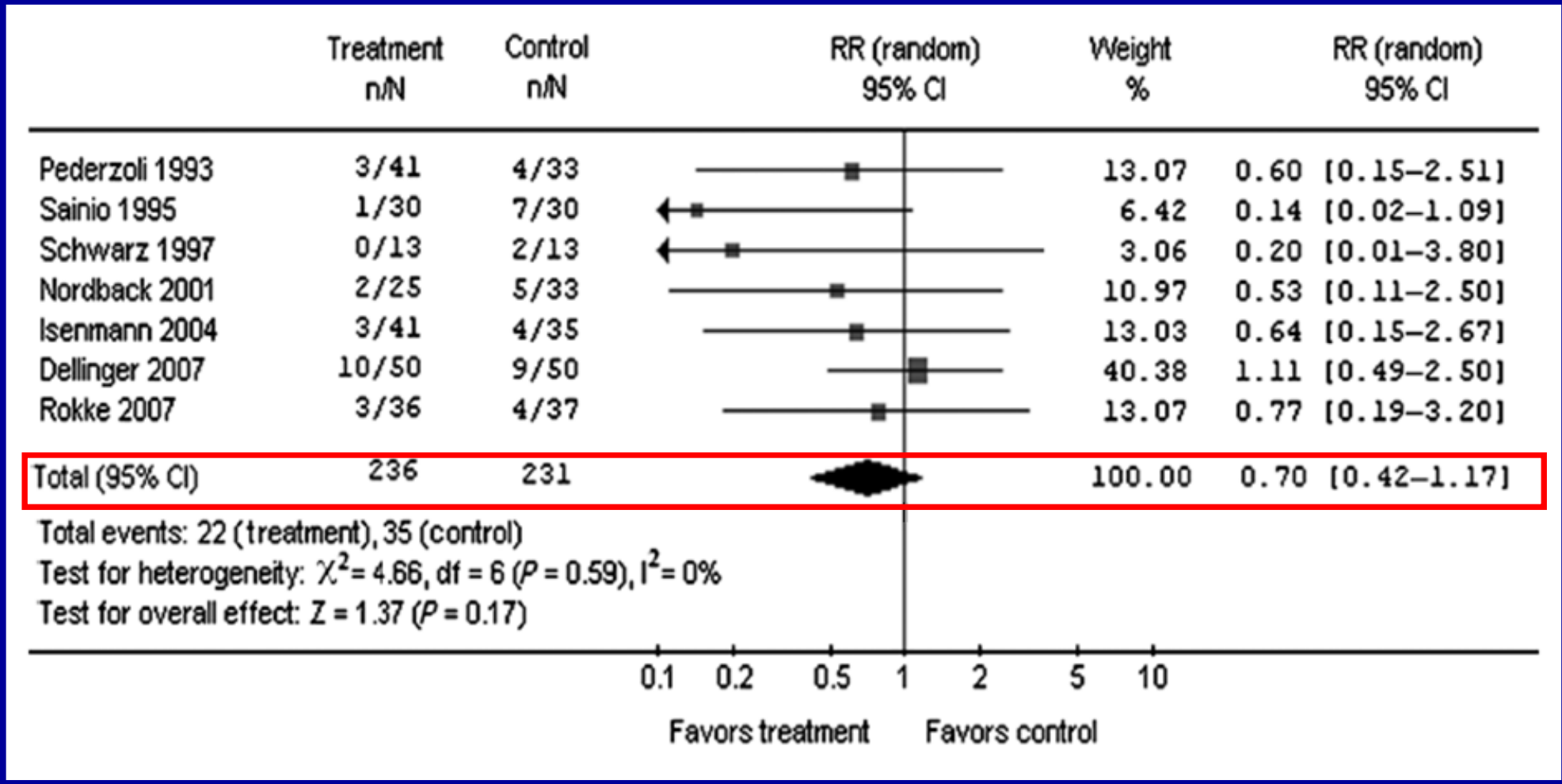


Shows the overall result of MA

Bai Y et al. Am J Gastroenterol 2008 ; 103 : 104 – 110.

Antibiotic prophylactic effect on mortality

The diamond



Bai Y et al. Am J Gastroenterol 2008 ; 103 : 104 – 110.

Interpretation of forest plot

Names on left	First authors of primary studies
Black squares	RR or OR of individual studies
Black square size	Weight of each trial in MA
Horizontal lines	95% confidence intervals
Vertical line	Line of no effect (OR or RR = 1)
Diamond	Overall treatment effect
Diamond Center	Combined treatment effect
Tips of diamond	95% CI

Meta-analytic analyses are prone to bias

& need to be interpreted with caution

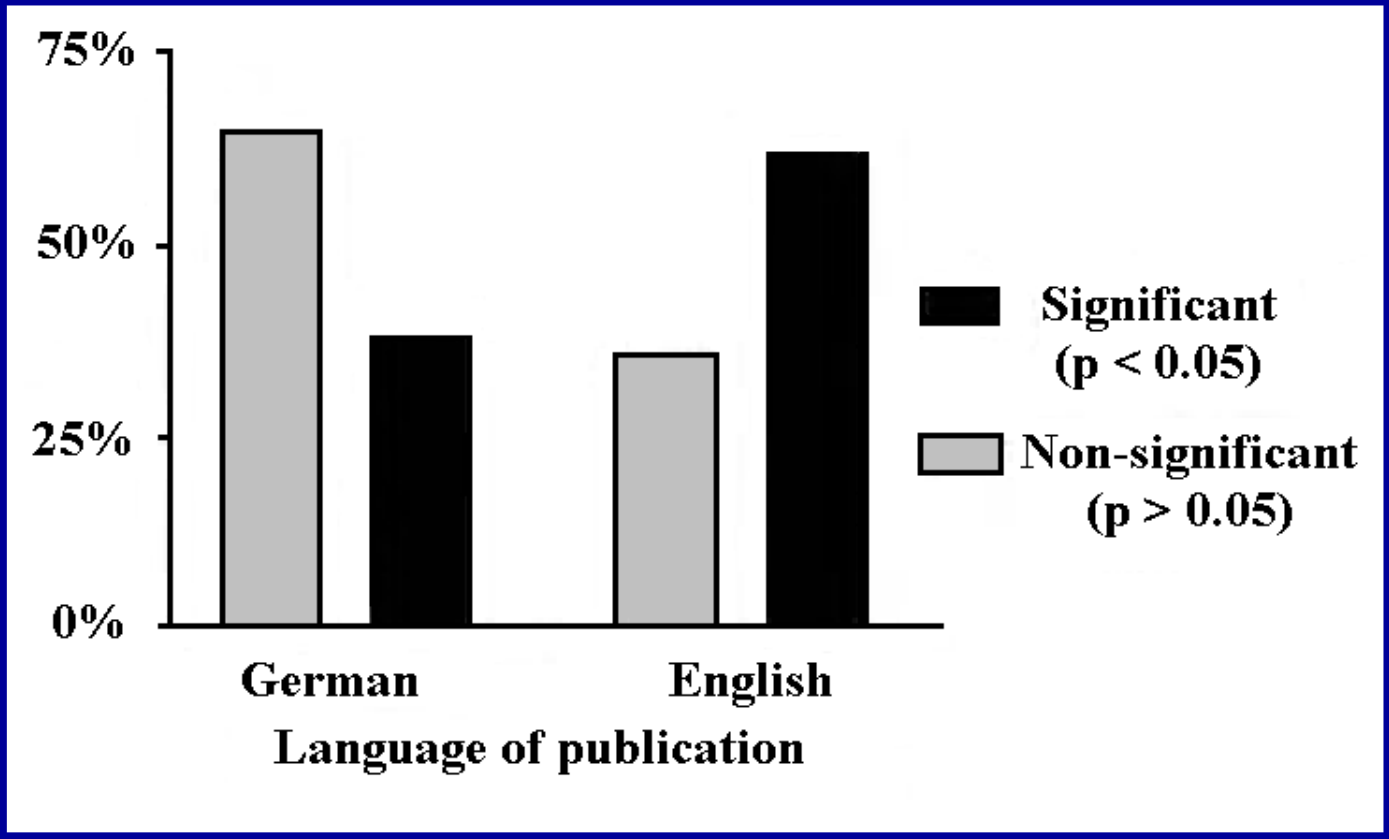
Bias: difference between study results & truth

Bias in meta-analysis (1)

- **Publication bias:** studies never published
  - Studies with no beneficial effect of treatment
  - Studies sponsored by pharmaceutical industry
  - Studies from a single centre versus multiple centers
- **English language bias:**
  - Positive findings published in a international journal
  - Negative findings published in a local journal
- **Database bias:**
  - Journals not indexed in major databases

Language bias

40 pairs of trials published by the same author



Controlled trials with statistically significant results was higher among reports published in English

Egger M et all. Lancet 1997 ; 350 : 326 – 9.

Bias in meta-analysis (2)

- **Multiple publication bias**

  Studies with significant results lead to multiple publications

- **Bias in provision of data**

  Additional data not reported in print needed for MA

- **Biased inclusion criteria**

  Selective inclusion of studies with positive findings

  Exclusion of studies with negative findings

Explaining heterogeneity

In language of meta-analysis

- **Homogeneity** means results of each individual trial are compatible with the results of any of the others

- **Heterogeneity** means results of each individual trial are incompatible with results of any of the others

Do the pieces fit together?

Simon SD. Statistical evidence in medical trials: What do the data really tell us? Oxford University Press, Oxford, 1st edition, 2006

How to measure heterogeneity in MA?

- **Qualitative**

  Forest plot **Visual evidence of heterogeneity**

  Funnel plot **Visual evidence of heterogeneity**

- **Quantitative**

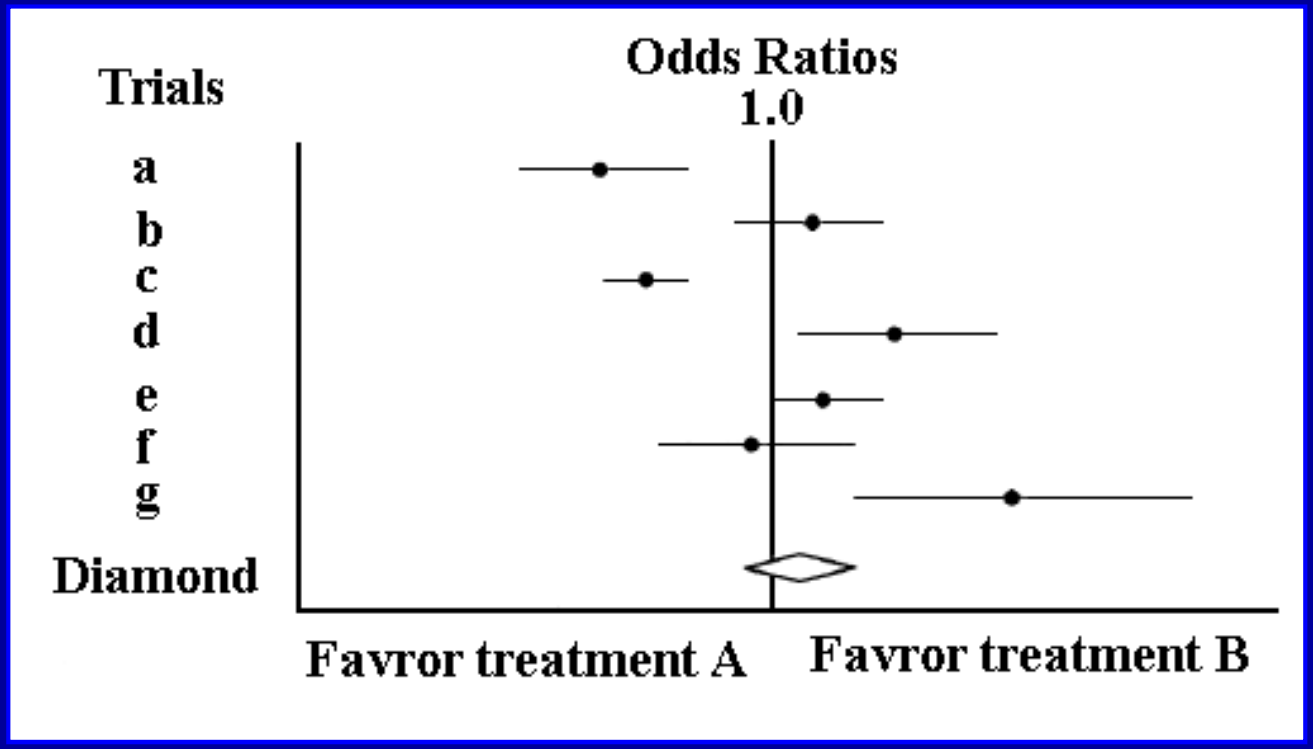
  X-squared

  I-squared **Based on Cochran's Q**

Simon SD. Statistical evidence in medical trials: What do the data really tell us? Oxford University Press, Oxford, 1st edition, 2006

Heterogeneity & forest plot

Hypothetical MA



Some trials with lower C.I. above upper C.I. of other trials

Some lines do not overlap

McGovern D, Summerskill W, Valori R, Levi M. Key topics in EBM.
BIOS Scientific Publishers, 1st Edition, Oxford, 2001.

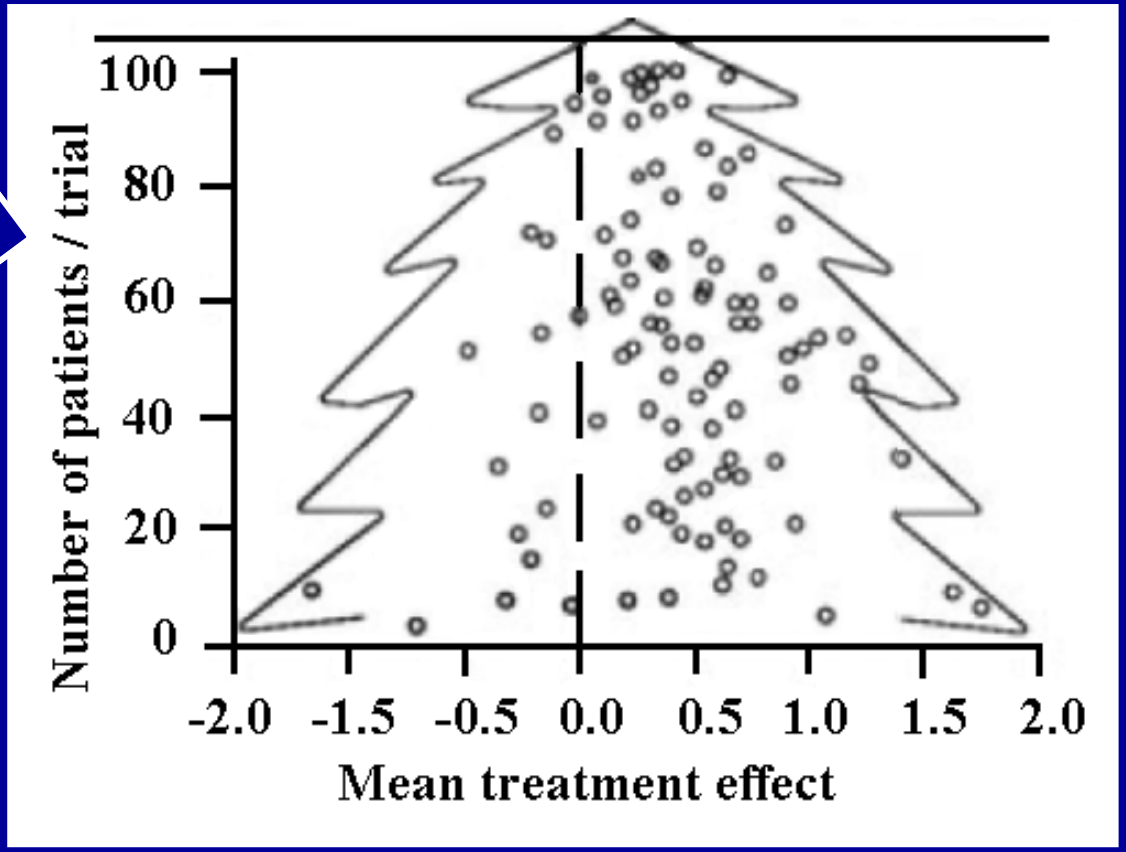
Funnel plots

Bias detected by simple graphical test

- **Plot for each trial** RR or OR on x axis
  Sample size on y axis
- **Absence of bias**
  Plot should resemble **inverted funnel** or **Christmas tree**
- **Presence of bias**
  Plot shows asymmetrical & skewed shape

Ideal funnel plot

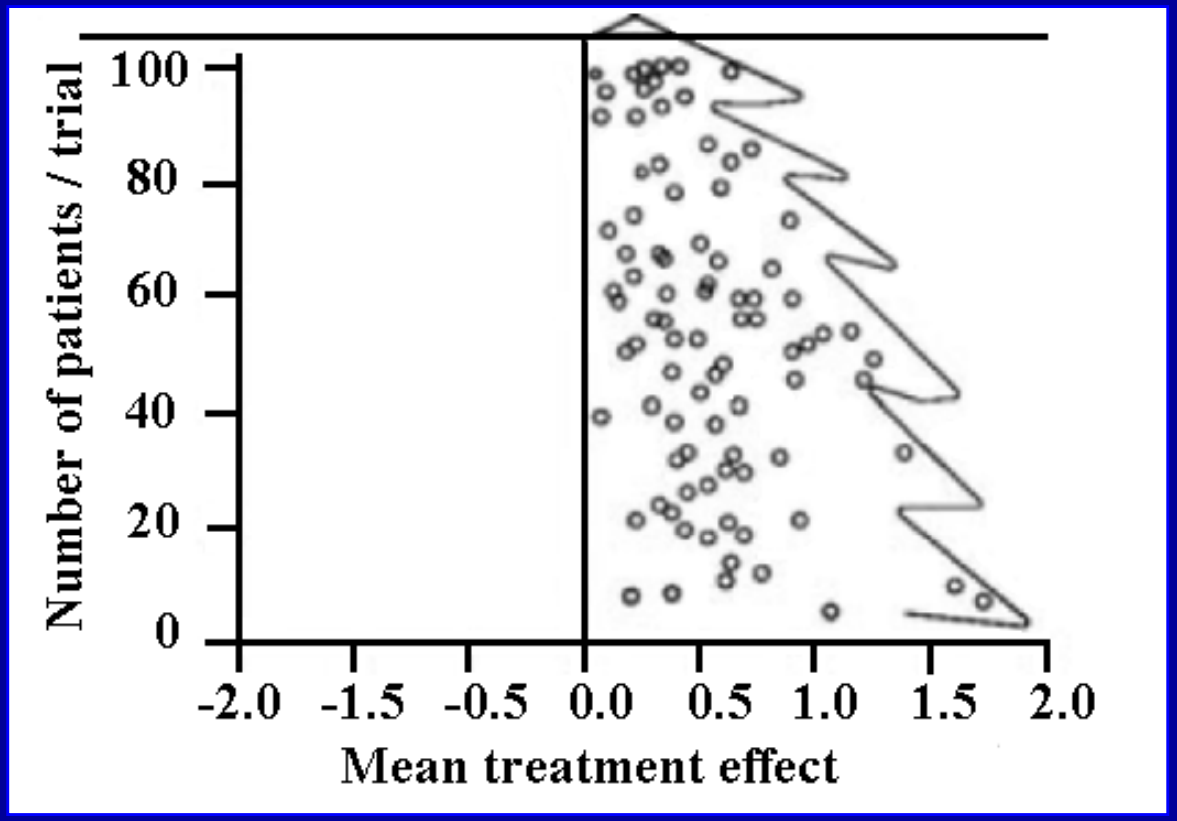
Christmas tree



The smaller the trial, the larger the distribution of results

Cleophas TJ et all. Statistics applied to clinical trials.
Springer, The Netherlands , 3rd edition, 2006.

Cut Christmas tree



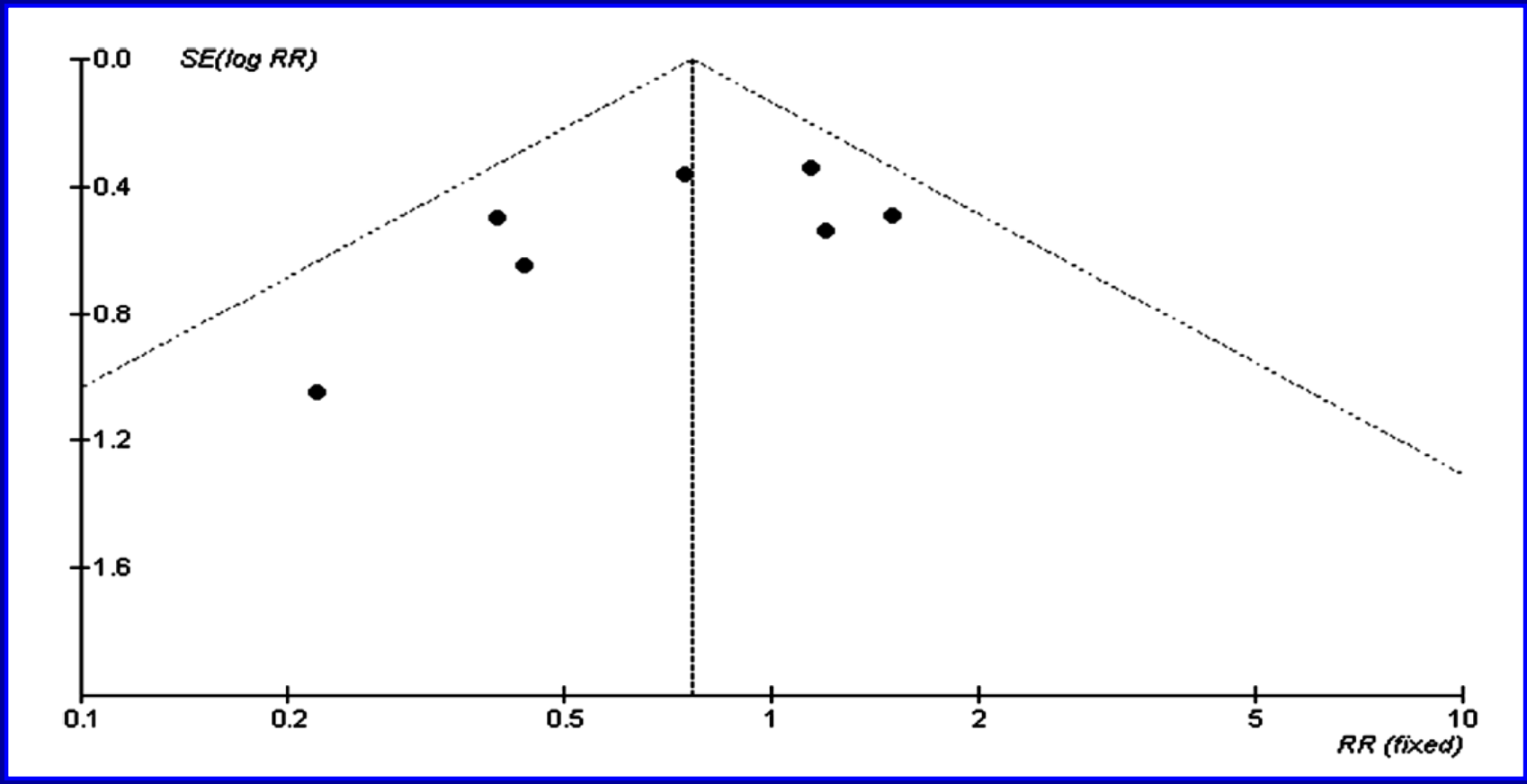
Negative trials not published (missing)

Suspicion of considerable publication bias in this MA

Cleophas TJ et all. Statistics applied to clinical trials. Springer, The Netherlands , 3rd edition, 2006.

Funnel plot

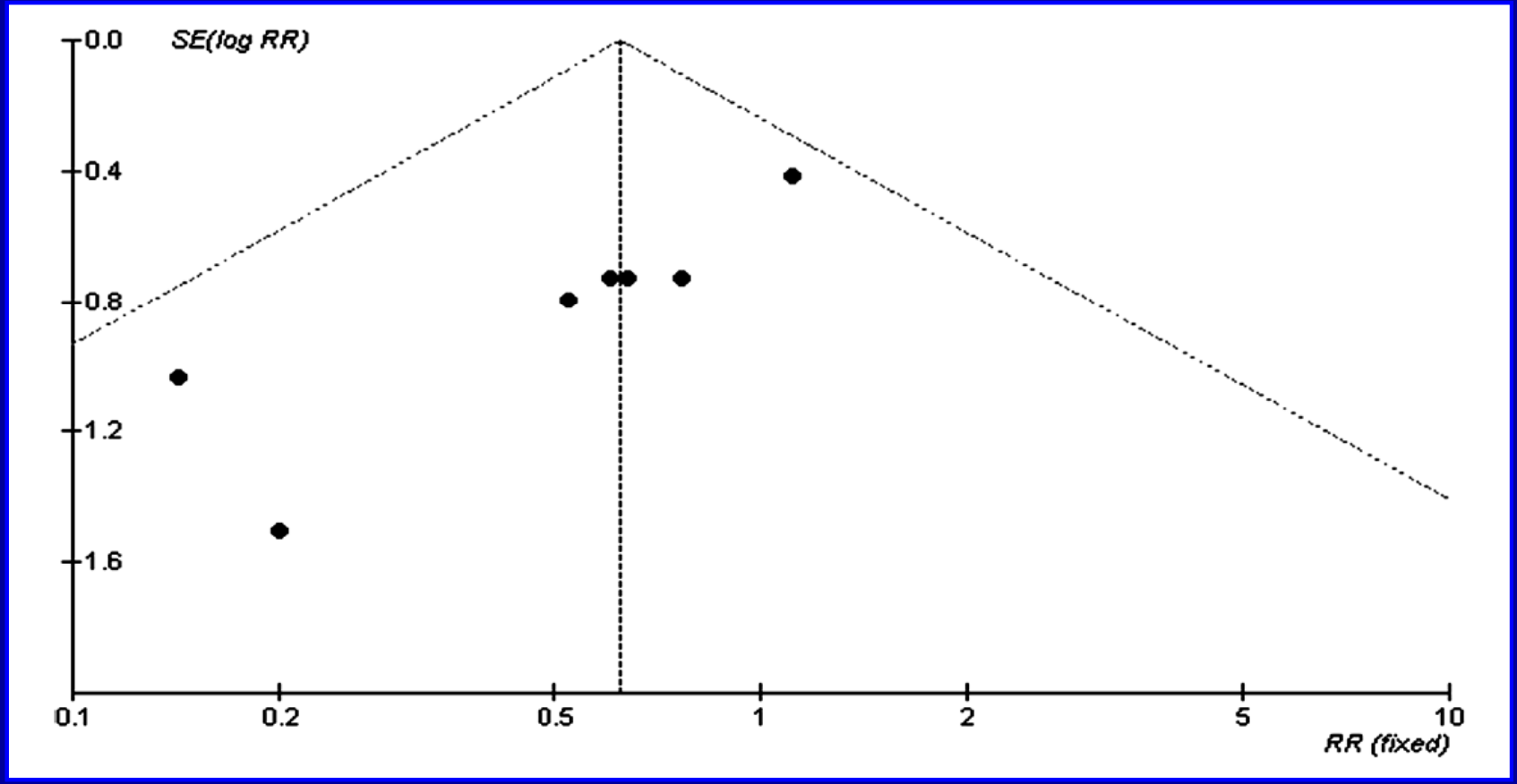
Publication bias of antibiotics for infected necrosis



Bai Y et al. Am J Gastroenterol 2008 ; 103 : 104 – 110.

Funnel plot

Publication bias of trials of antibiotics for mortality



Bai Y et al. Am J Gastroenterol 2008 ; 103 : 104 – 110.

Quantitative measure of heterogeneity

Many prefer not to use quantitative measure

- **X-squared:**

Degree of freedom (df)	Number of trials in MA – 1
$X^2 \approx df$	No heterogeneity
X^2 much greater than df	Serious heterogeneity

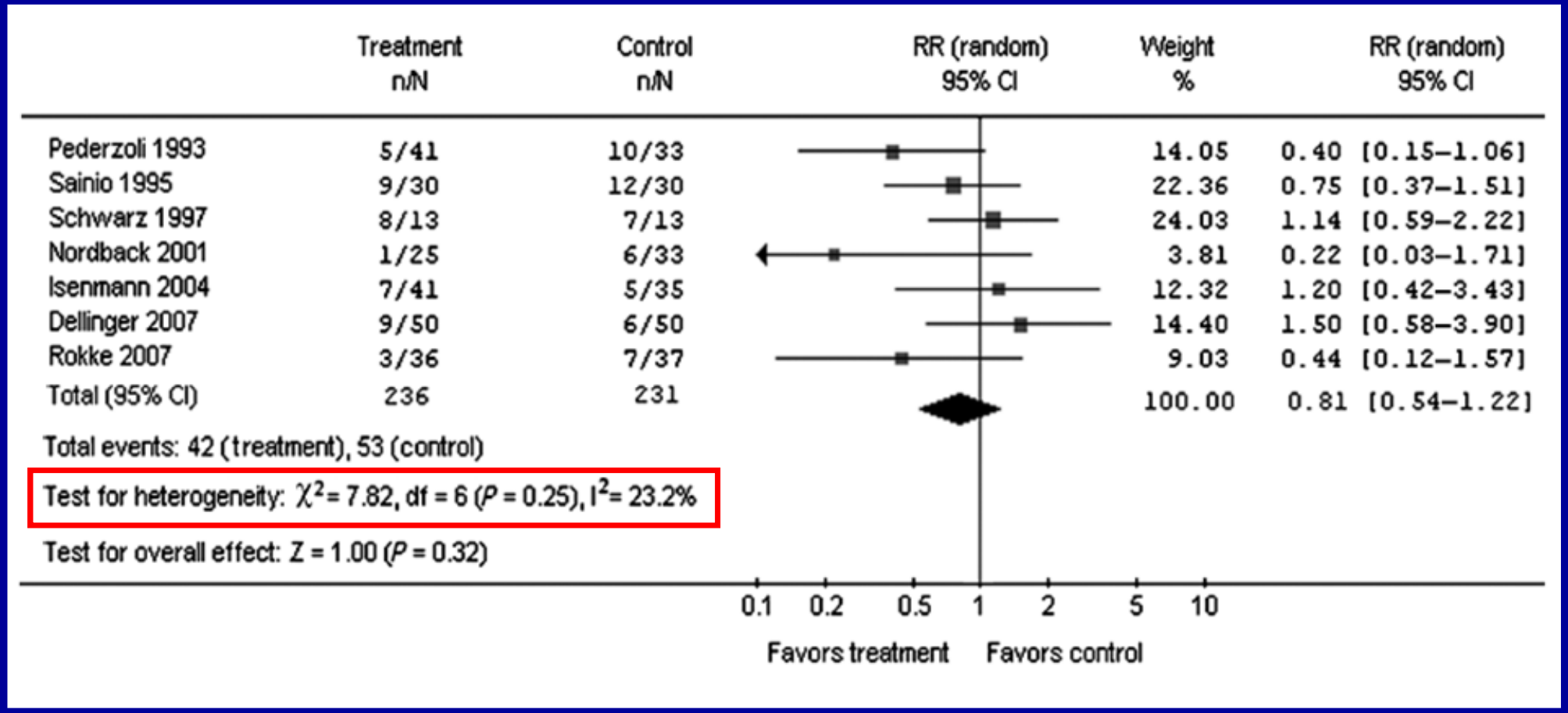
- **I-squared** (0 – 100%)

< 25%	No heterogeneity
50% – 75%	Serious heterogeneity

Simon SD. Statistical evidence in medical trials: What do the data really tell us? Oxford University Press, Oxford, 1st edition, 2006

Antibiotic prophylaxis & pancreatic necrosis

Heterogeneity



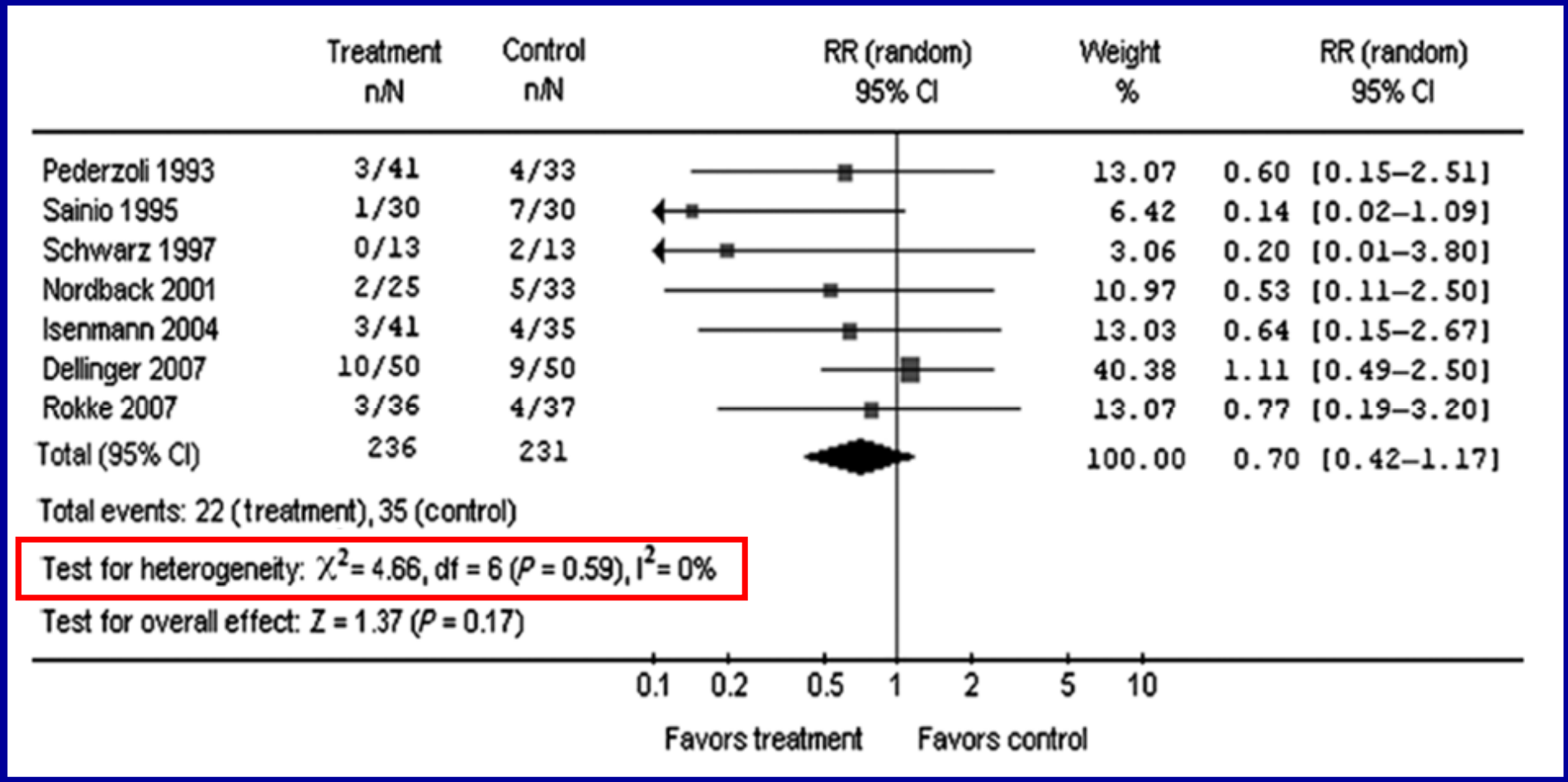
$X^2 = 7.82$ (df 6 – No heterogeneity)

$I^2 = 23.2\%$ (No or little heterogeneity)

Bai Y et al. Am J Gastroenterol 2008 ; 103 : 104 – 110.

Antibiotic prophylactic effect on mortality

Heterogeneity

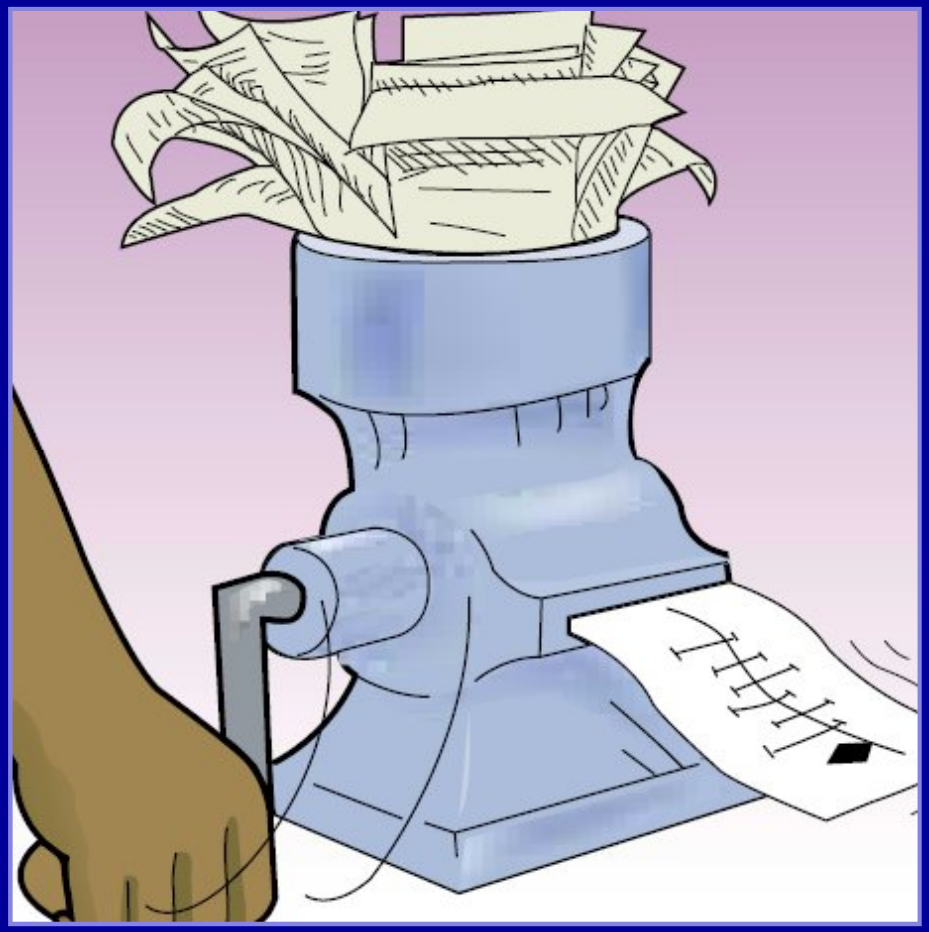


$X^2 = 4.66$ (df 6 – No heterogeneity)

$I^2 = 0$ % (No or little heterogeneity)

Bai Y et al. Am J Gastroenterol 2008 ; 103 : 104 – 110.

Appraising & applying meta-analysis



Heneghan C, Badenoch D. EBM toolkit. BMJ Books, London, 1st edition 2002.

Questions for appraising MA – 1

❶ Clearly **focused question**	**Focused question**
❷ Identification of **all relevant studies**	**Good search**
❸ Inclusion the **right type of study**	Yes (**RCTs**)
❹ Assessment **quality of all studies**	Yes but no blinding
❺ Reasonable to **combine** study results	Yes (**good X^2 & I^2**)

Critical Appraisal Skills Programme. Appraisal Tools. Oxford, UK.
http://www.phru.nhs.uk/casp/appraisa.htm (accessed 10 Dec 2004).

Questions for appraising MA – 2

❻ **Result presentation & main result**	**RR (95% CI)** **No difference**
❼ **Precision** of the results	No (**wide 95% CI**)
❽ Results **applied** to local population	**Mainly alcoholic**
❾ All **important outcomes** considered	**Antibiotic SE?**
❿ **Change practice** as result of MA	**No?**

Critical Appraisal Skills Programme. Appraisal Tools. Oxford, UK.
http://www.phru.nhs.uk/casp/appraisa.htm (accessed 10 Dec 2004).

Steps of EBM

❺ Assess

Prophylactic antibiotics in pancreatic necrosis

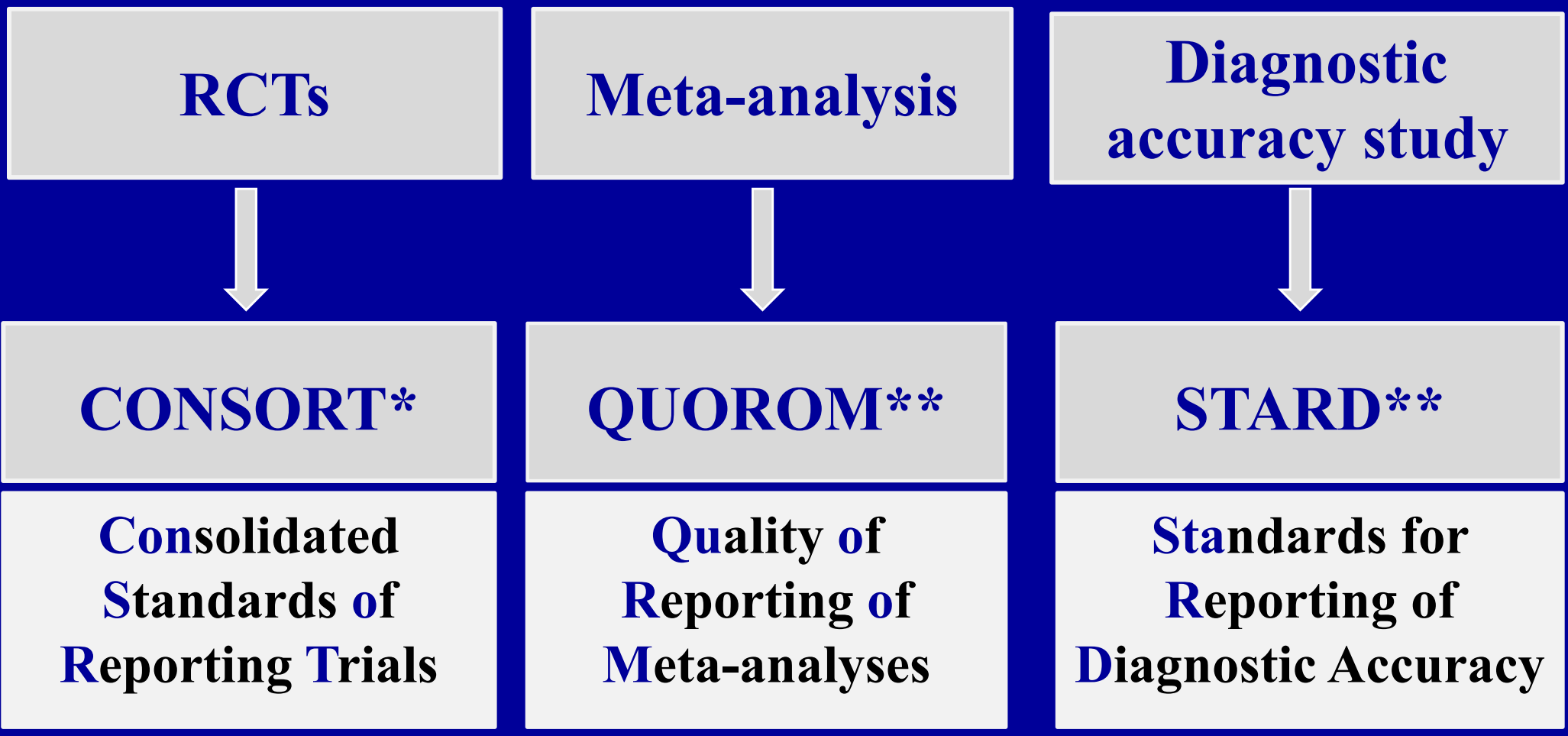
Limitations of this MA

- **Timing** of initiation of antibiotics
- **Subgroup analysis** Age
  Etiology of pancreatitis
  Presence of organ failure
- **Wide 95% CI** Infected necrosis 0.81 (0.54 –1.22)
  Mortality 0.70 (0.42 – 1.17)

Further large scale better design RCTs are needed

Bai Y et al. Am J Gastroenterol 2008 ; 103 : 104 – 110.

Improving quality of reports



* Altman DG et al. Ann Intern Med 2001 ; 134 : 663 - 94.

** Moher D et al. Lancet 1999 ; 354 : 1896 - 900.

*** Bossuyt PM et all. BMJ 2003; 326 : 41 – 44.

QUOROM* statement

Targeted authors of MA rather than readers

- **Experts** 30 experts (epidemiologists, clinicians, editors, statisticians, researchers)
- **Date** Oct 2–3, 1996 (Chicago – USA)
- **Aim** Improve quality of reporting MA & may be SR
- **Results** **Flow diagram:** progress through stages of MA
  Checklist: 21 headings & subheadings

*** Quorom: Quality of Reporting of Meta-analyses**

Moher D et al. Lancet 1999 ; 354 : 1896 - 900.

The QUOROM checklist

Heading	Subheading	Descriptor	Reported Page No
Title		Identify report as MA or SR of RCTs	
Abstract	Objectives Data sources Review methods Results Conclusion	Use a **structured format** Clinical question explicitly **Databases (list)** & other information sources Selection criteria, validity assessment, data synthesis Characteristics of RCTs, point estimates, CI Main results	
Introduction		Clinical problem, rationales for intervention & review	
Methods	Searching Selection Validity assessment Data abstraction Study characteristics Data synthesis	Information sources in detail, precise restrictions Inclusion & exclusion criteria Criteria & process used (**masked conditions**, ..) Process used (completed independently, in duplicate) Study design, intervention, outcome & heterogeneity Measures of effect (**RR**), method of combining results (**statistical testing** & **CI**), missing data; **statistical heterogeneity**, assessment of **publication bias**	
Results	Trial flow Study characteristics Data synthesis	Profile summarizing **trial flow** Data for each trial (age, sample size, dose, follow-up) Agreement, summary results, effect sizes & CI in ITT	
Discussion		Key findings, internal & external validity, **biases**, …	

How much work is a meta-analysis?

- Analysis of 37 MA by Allen & Olkin of **MetaWorks***
- **Hours** Average **1139** (216 – 2518)
- **Breakdown**

588	Protocol, searching, & retrieval
44	Statistical analysis
206	Report writing
201	Administration

- Total time depends on number of citations

* Company based in Massachusetts (USA) specializes in doing SR

Allen, I.E. Olkin, I. JAMA 1999; 282 : 634 – 5.

“Doing a meta-analysis is easy, doing one well is hard”

Ingram Olkin

Importance of meta-analysis

- **For some clinicians**

  MA is seen as exercises in "mega-silliness"

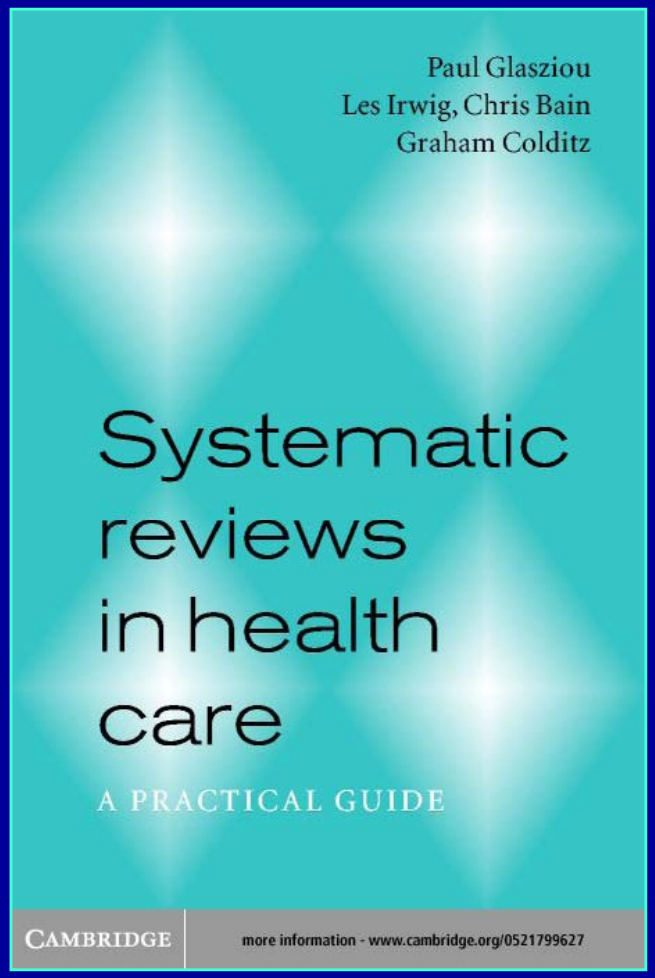
- **For other clinicians**

  MA left no place for narrative review article

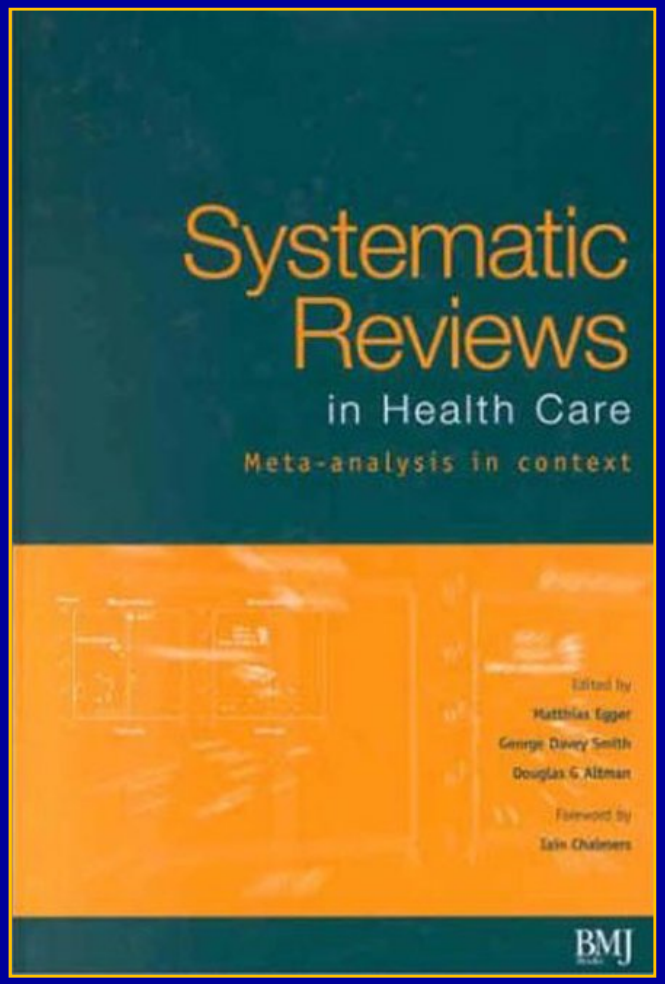
- **The truth**

  Is likely to lie somewhere between these 2 extremes

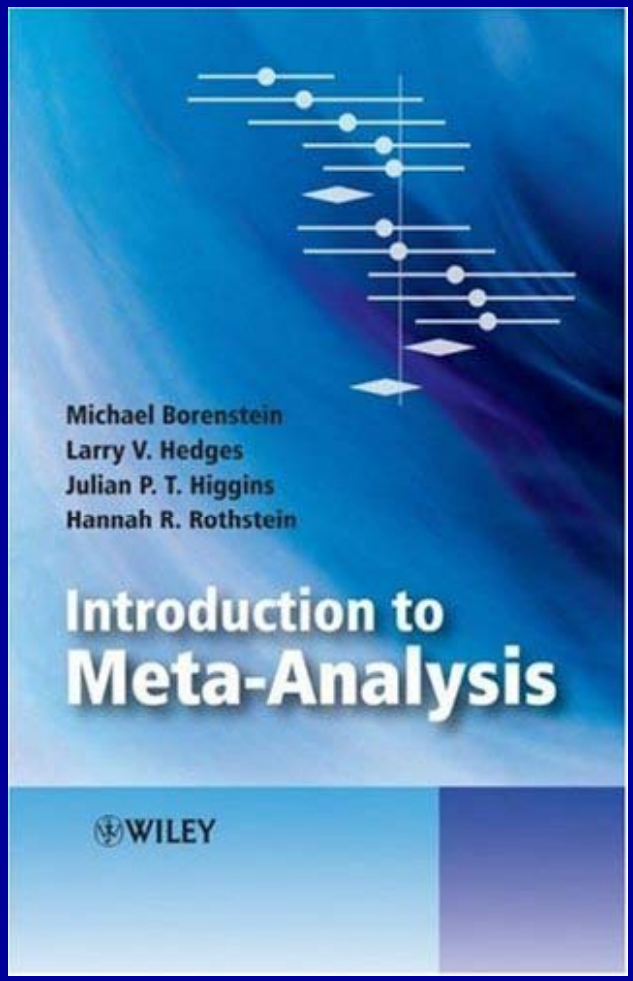
References



Cambridge Press
2001

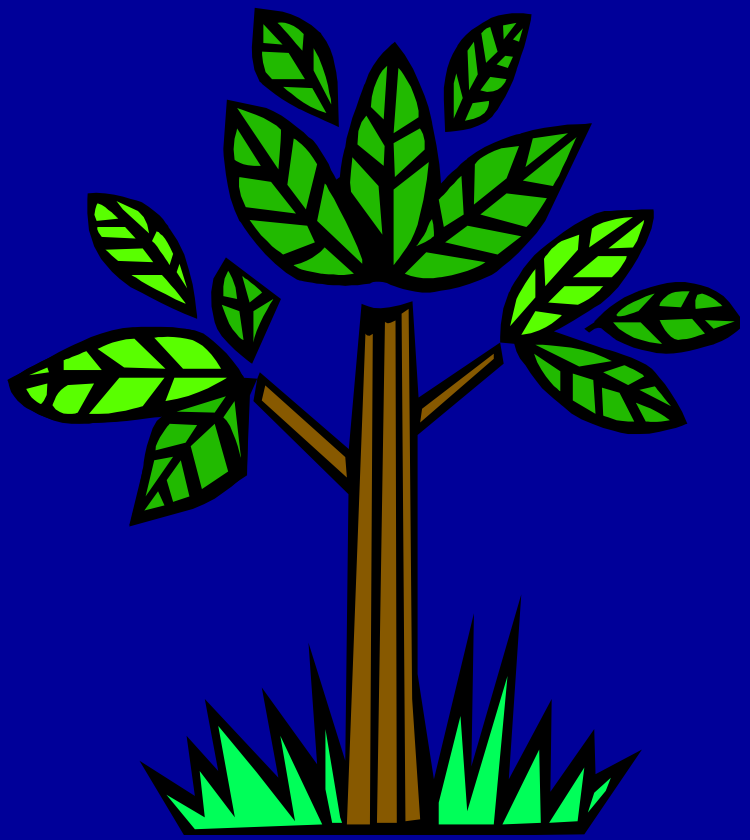


BMJ Publishing Group
2001



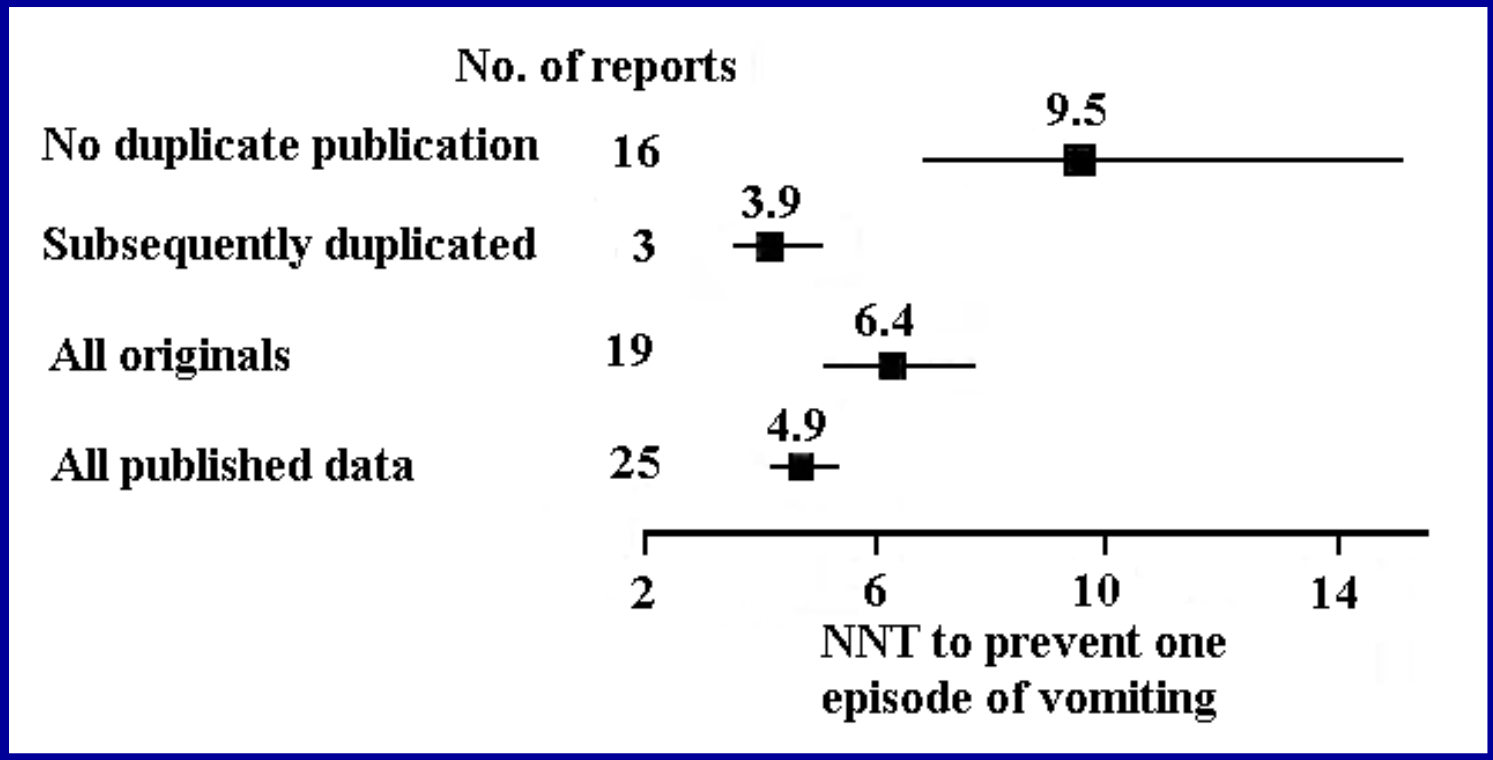
John Wiley & Sons
2009

Thank You



Multiple publication bias

Odansetron to prevent postoperative nausea &vomiting

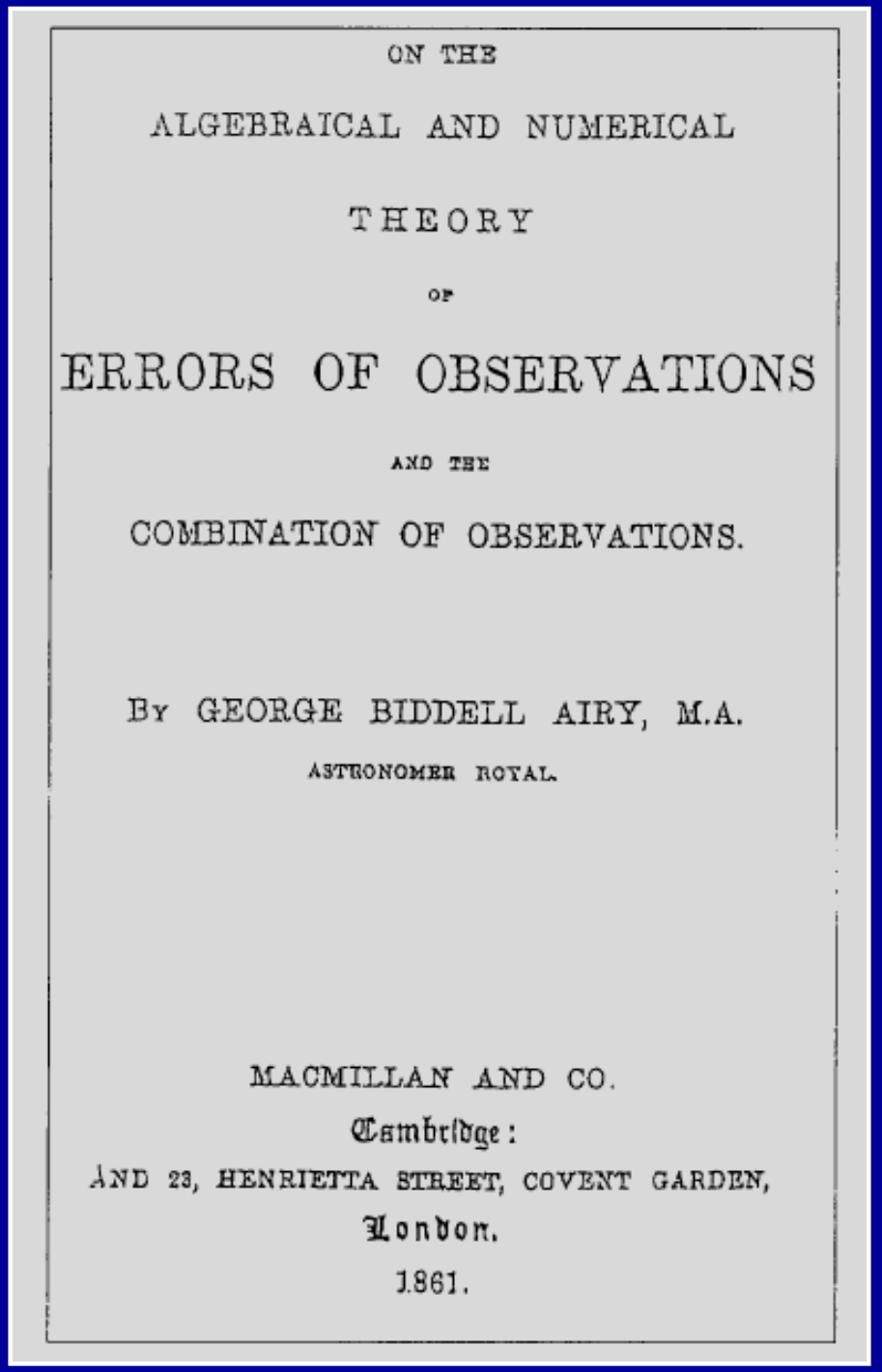


Data from 3 large multicentre trials duplicated in 6 further reports

Inclusion of duplicated data ⇨ overestimation of treatment effect

Tramèr MR et al. BMJ 1997 ; 315 :635 – 40.

Title page of what may be seen as the first “textbook” of MA, published in 1861



ON THE

ALGEBRAICAL AND NUMERICAL

THEORY

OF

ERRORS OF OBSERVATIONS

AND THE

COMBINATION OF OBSERVATIONS.

By GEORGE BIDDELL AIRY, M.A.

ASTRONOMER ROYAL.

MACMILLAN AND CO.

Cambridge:

AND 23, HENRIETTA STREET, COVENT GARDEN,

London.

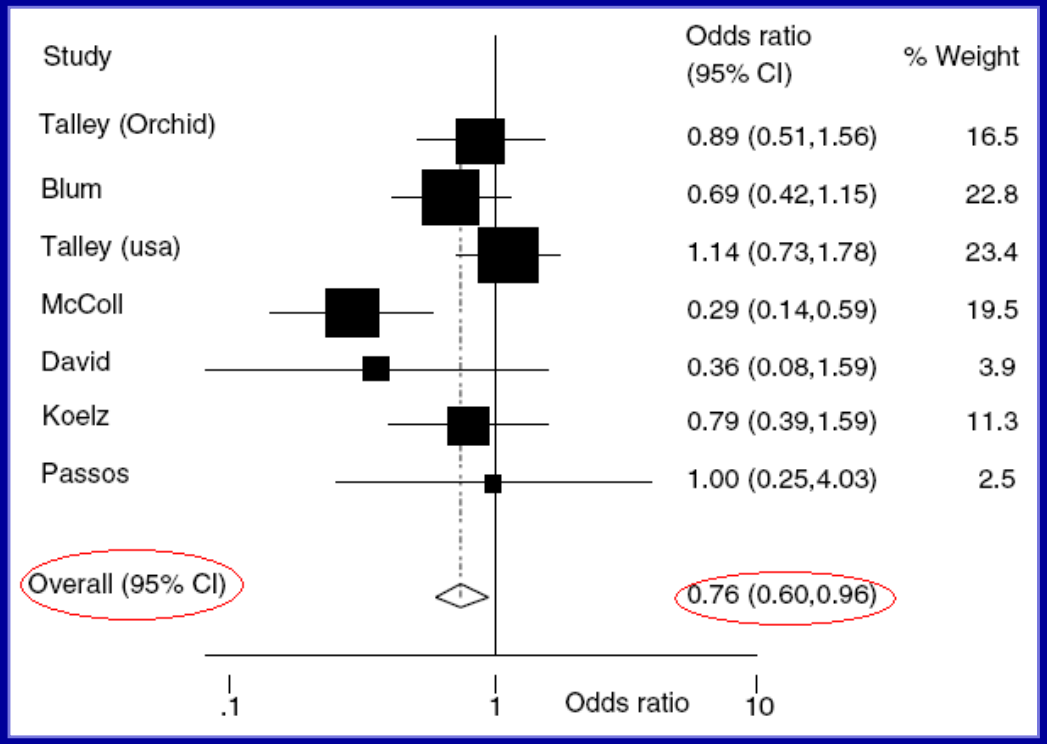
1861.

Egger M et all. Systematic reviews in health care. BMJ Publishing Group, 2001.

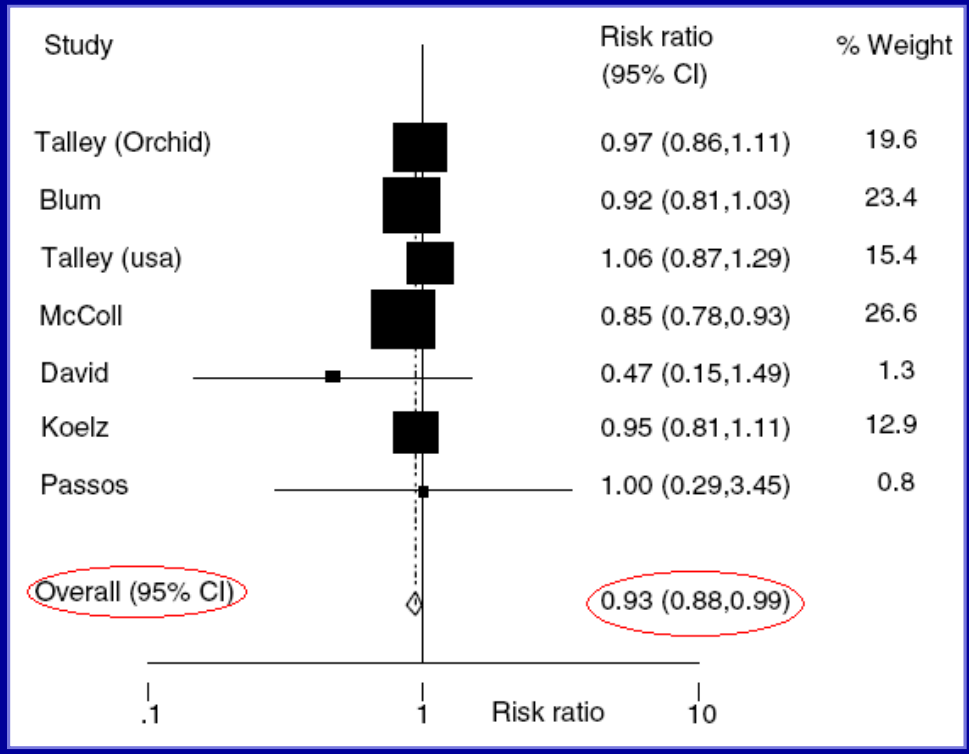
Relative Risk or Odds Ratio?

HP eradication in nonulcer dyspepsia

Using OR



Using RR



Significant heterogeneity

Reduced heterogeneity

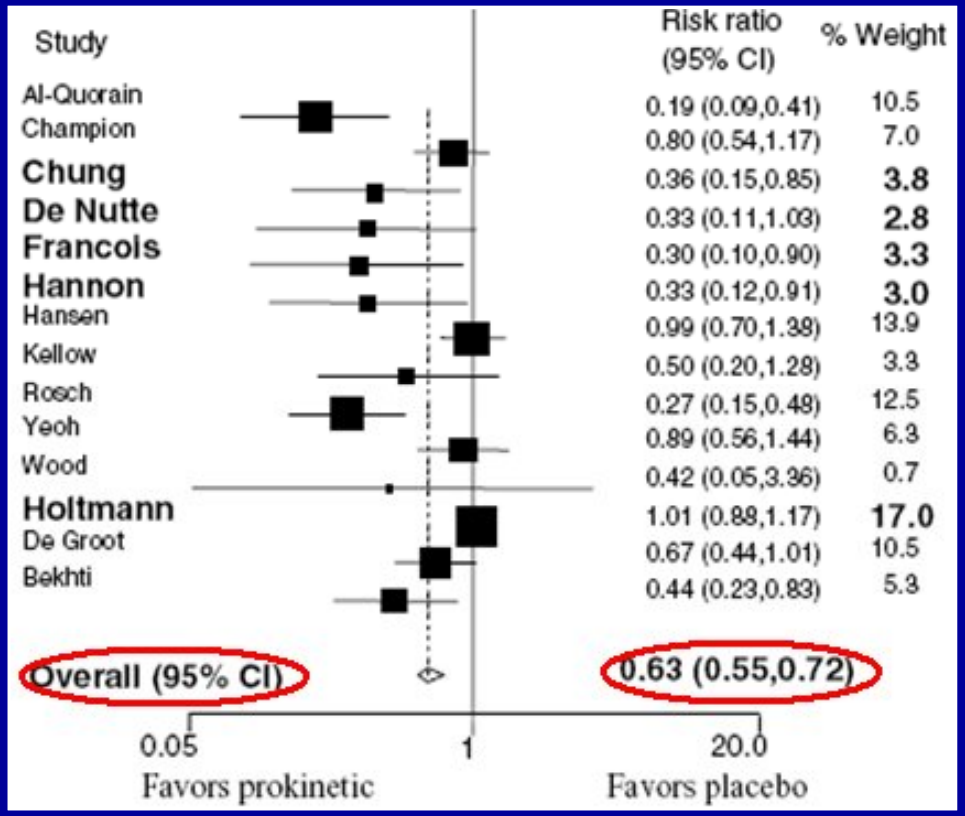
It is useful to analyze data in both OR & RR

Moayyedi P. Am J Gastroenterol 2004; : 2297-2301.

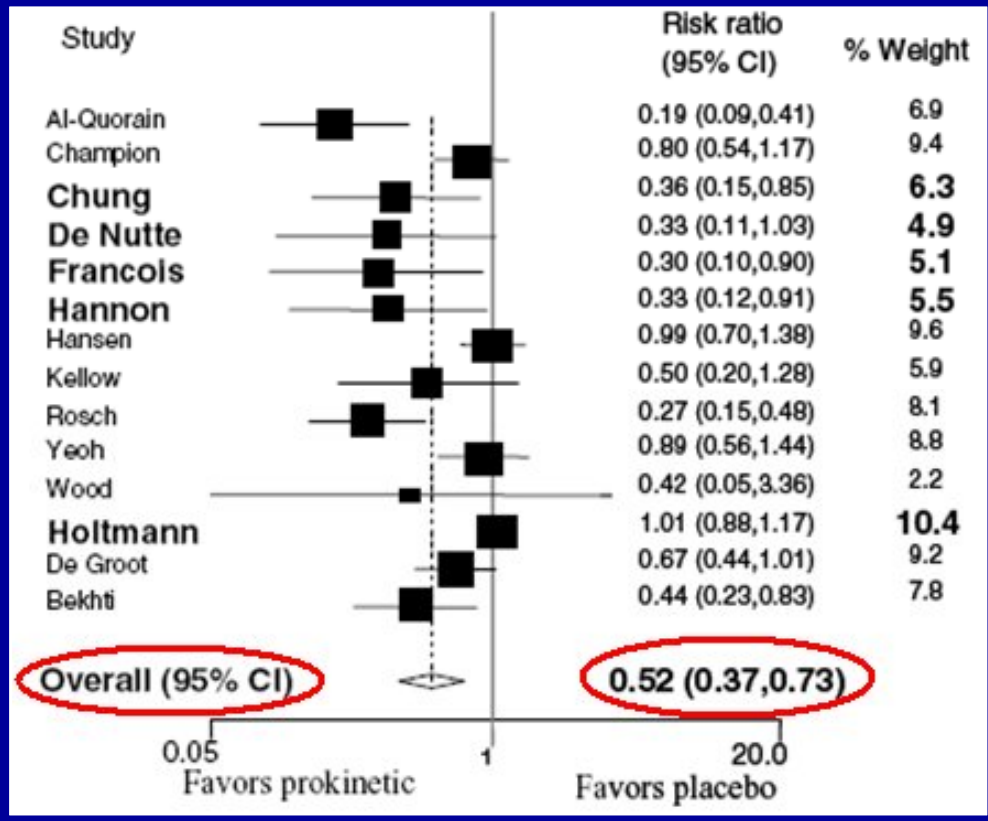
Random or fixed effect modelS?

Prokinetics in nonulcer dyspepsia

Fixed effects model



Random effects model



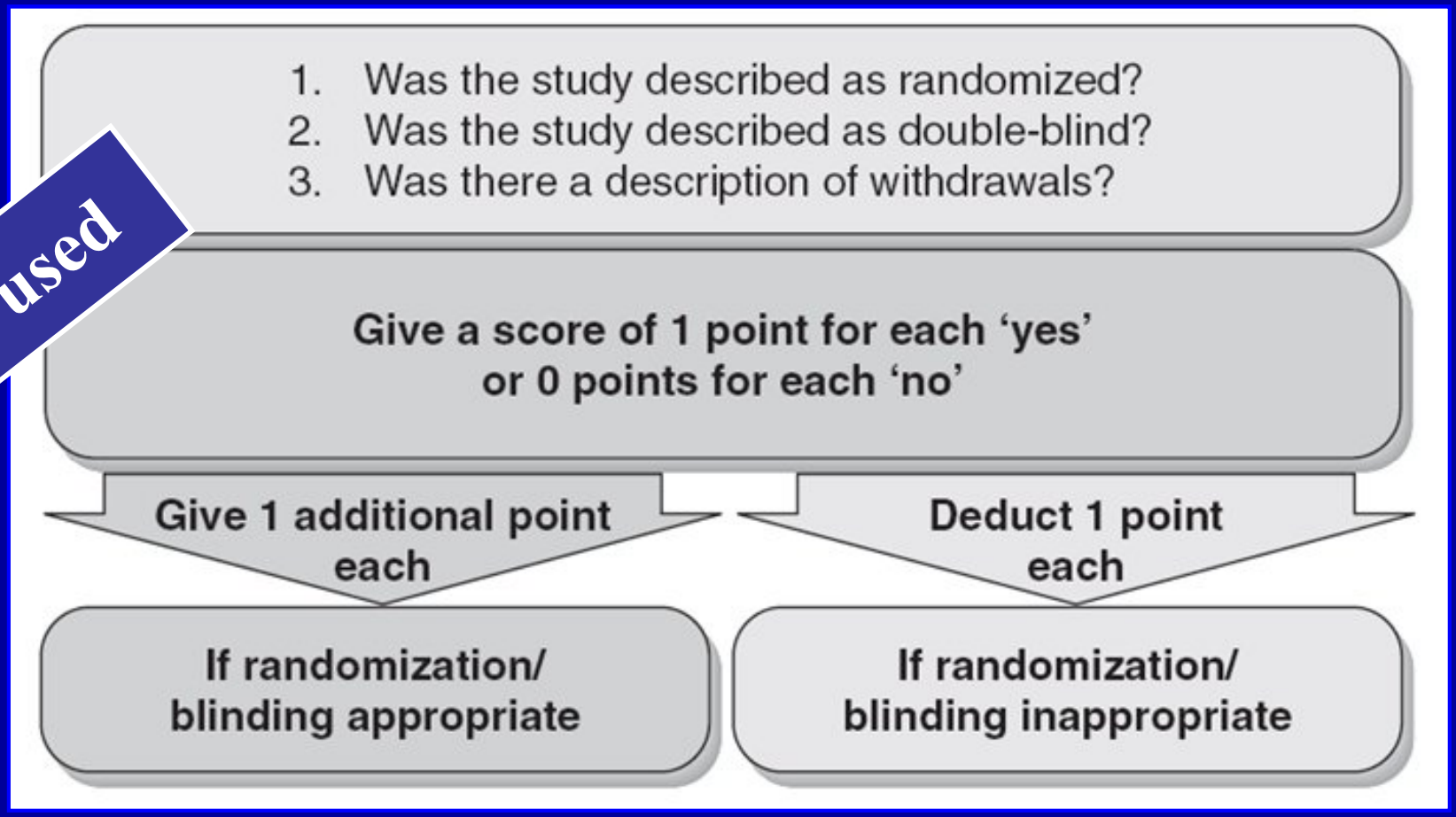
Small trials given more weight than large trials in random effects

Increase estimated overall effect size & widen the 95% CI

Moayyedi P. Am J Gastroenterol 2004; : 2297-2301.

The Jadad scale

Widely used



Scores: 0 - 5 points – Poor quality if $\leq$ 2 points

Jadad AR, Enkin MW. Randomized control trials.
Blackwell Publishing, 2nd Ed, 2007.

Appraising a RCT (checklist) – 1

Are the results valid?	
At start of trial	❶ Were the patients **randomized**? ❷ Was the randomization **concealed**? ❸ Similar prognostic factors in 2 groups?
During trial	❹ Was trial **blinded** & to what extent?
At end of trial	❺ Was **follow-up** complete? ❻ Was **ITT** principle applied? ❼ Was the trial **stopped early**?

Guyatt G, et al. User's guide to the medical literature.
Essentials of evidence based clinical practice. Mc Graw Hill, 2nd ed, 2008.

Appraising a RCT (checklist) – 2

What are the results?

8- How **large** was the treatment effect?

9- How **precise** was estimate of treatment effect?

How can I apply the results to patient care?

10- Were the study patients **similar** to my patient?

11- Were all patient-**important outcomes** considered?

12- Are the likely treatment benefits worth **harm & cost**?

Guyatt G, et al. User's guide to the medical literature.
Essentials of evidence based clinical practice. Mc Graw Hill, 2nd ed, 2008.