

Systematic reviews and meta-analysis

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Division of infectious diseases

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Systematic review definition

- The compilation of all available data
- Addressing a specific question
- Following a pre-defined protocol
- All steps are replicable
- Data can be summarized through meta-analysis or not

Definitions

- **Systematic review**: the compilation of all available data on a specific question, following a pre-defined protocol in which all steps are replicable
- **Meta-analysis**: the statistical procedure summarizing quantitative data from the individual studies

Scope of systematic reviews

- Systematic reviews address practical questions of our clinical practice
- What are our practical questions on hospitalized CAP



The curious physician

Admitting a patient with suspected CAP

- The benefit of hospital admission
- Risk factors for *S. aureus* CAP
- What is the benefit of obtaining a blood culture?
- Does normal CRP rule out pneumonia?
- Optimal antibiotic treatment
- Adjunctive steroids
- Effects of antipyretics
- Effects of bed rest
- Will probiotics prevent CDAD?
- Optimal duration of antibiotic treatment
- Risk factors for death

Practical questions - I

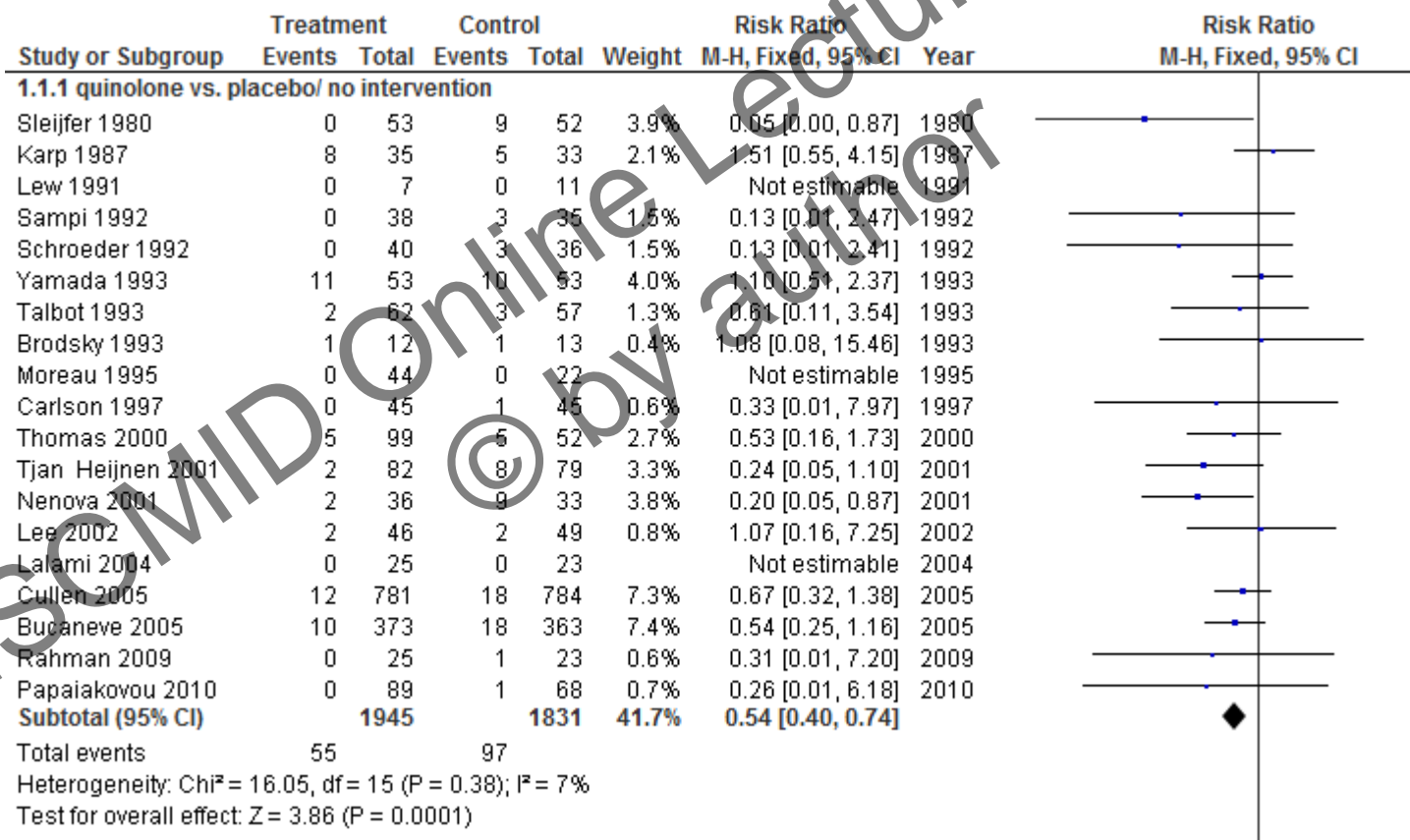
- Is this treatment effective?
 - Drug A vs. placebo or no treatment
- What is the preferred treatment?
 - Drug A vs. drug B
- What management strategy is better?
 - Strategy A vs. strategy B

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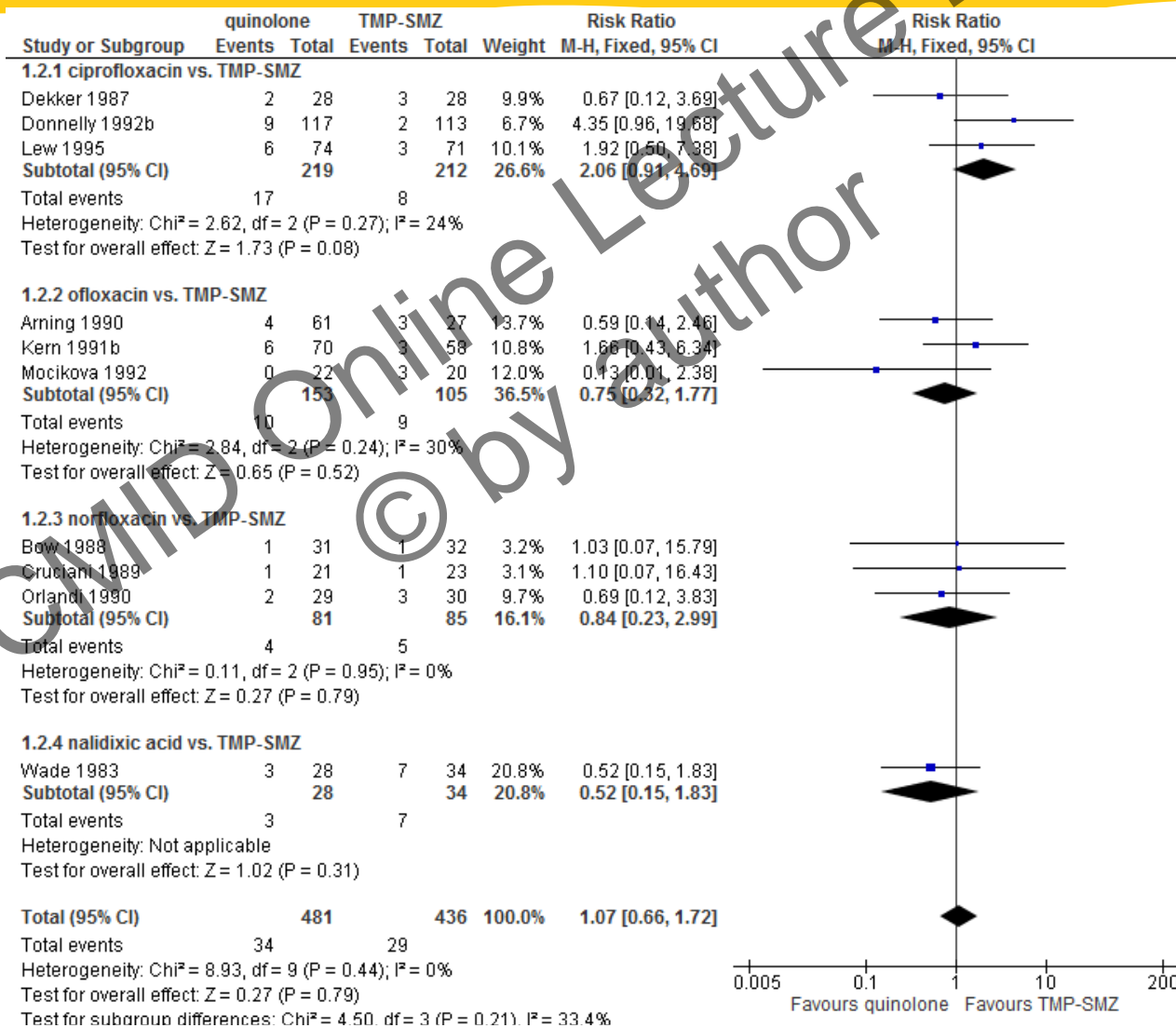
Scope of SR/MA: interventional

- Focus on a very specific question
 - A vs. placebo/ no treatment (efficacy)
 - A vs. B (effectiveness)
- Most common type of systematic review
- Most informative systematic reviews
- All MA software designed to handle intervention reviews

Drug A vs. placebo/ no treatment



Drug A vs. drug B



Systematic vs. narrative review

Systematic

- Focus on single question
- Defined search strategy aiming for all available evidence
- Commonly includes MA
- Risk of bias assessment
- Not open to interpretation

Narrative

- Broad scope
- Not always defined
- Commonly not summarized quantitatively
- None
- Personal opinion appreciated

Practical questions - II

- Test A - is a positive result diagnostic of the disease
- Test A - does a negative result rule out the disease
 - Sensitivity and specificity of test A
- Which test should I choose?
 - Sens/ spec test A vs. sens/spec test B

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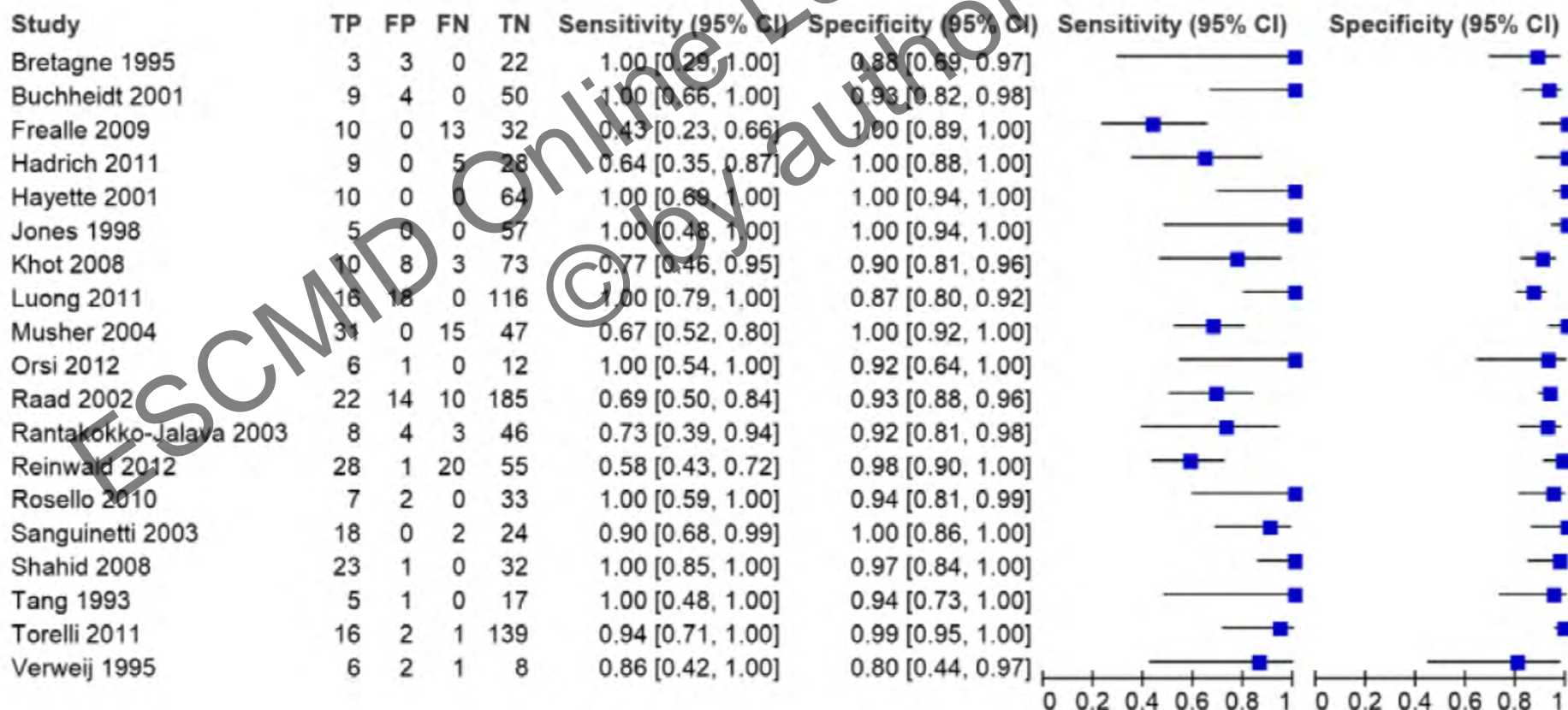
Scope of SR/MA: diagnostic

- Summarize diagnostic performance of a specific test
- Compare between tests
- Methodology evolving
- Results commonly not very informative because of large heterogeneity

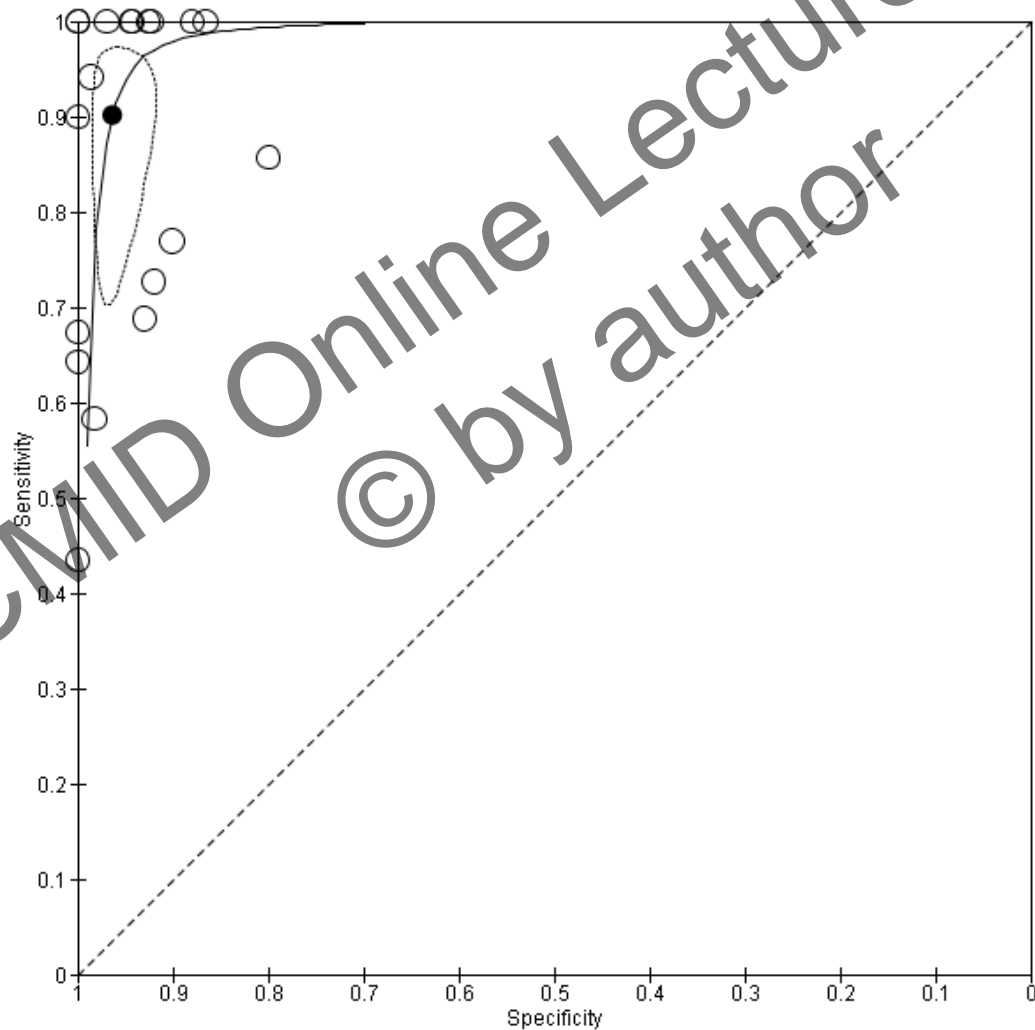
Diagnostic SR/ MA

PCR in deep sputum for diagnosis of invasive pulmonary aspergillosis

PCR for proven/probable



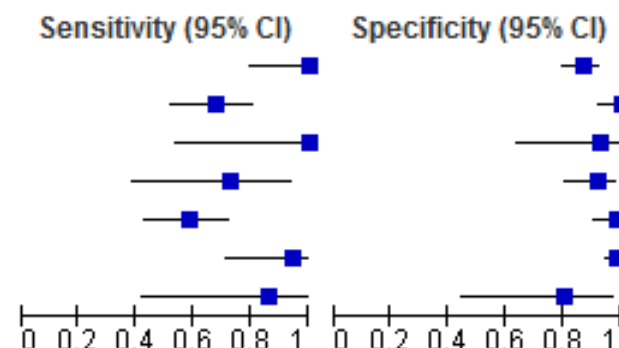
Diagnostic SR/ MA



Test 1 vs. test 2

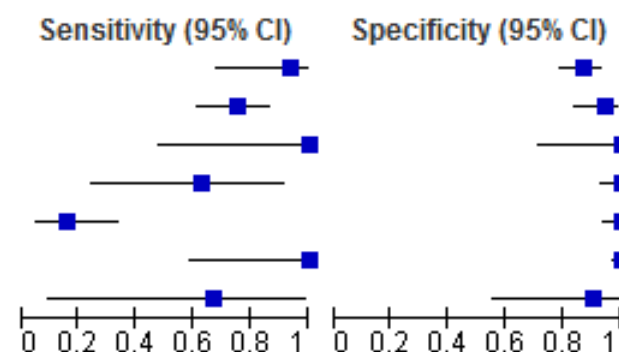
PCR for proven/ probable

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Luong 2011	16	18	0	116	1.00 [0.79, 1.00]	0.87 [0.80, 0.92]
Musher 2004	31	0	15	47	0.67 [0.52, 0.80]	1.00 [0.92, 1.00]
Orsi 2012	6	1	0	12	1.00 [0.54, 1.00]	0.93 [0.64, 1.00]
Rantakokko-Jalava 2003	8	4	3	46	0.73 [0.39, 0.94]	0.92 [0.81, 0.98]
Reinwald 2012	28	1	20	55	0.58 [0.43, 0.72]	0.98 [0.90, 1.00]
Torelli 2011	16	2	1	139	0.94 [0.71, 1.00]	0.99 [0.95, 1.00]
Verweij 1995	6	2	1	8	0.86 [0.42, 1.00]	0.80 [0.44, 0.97]

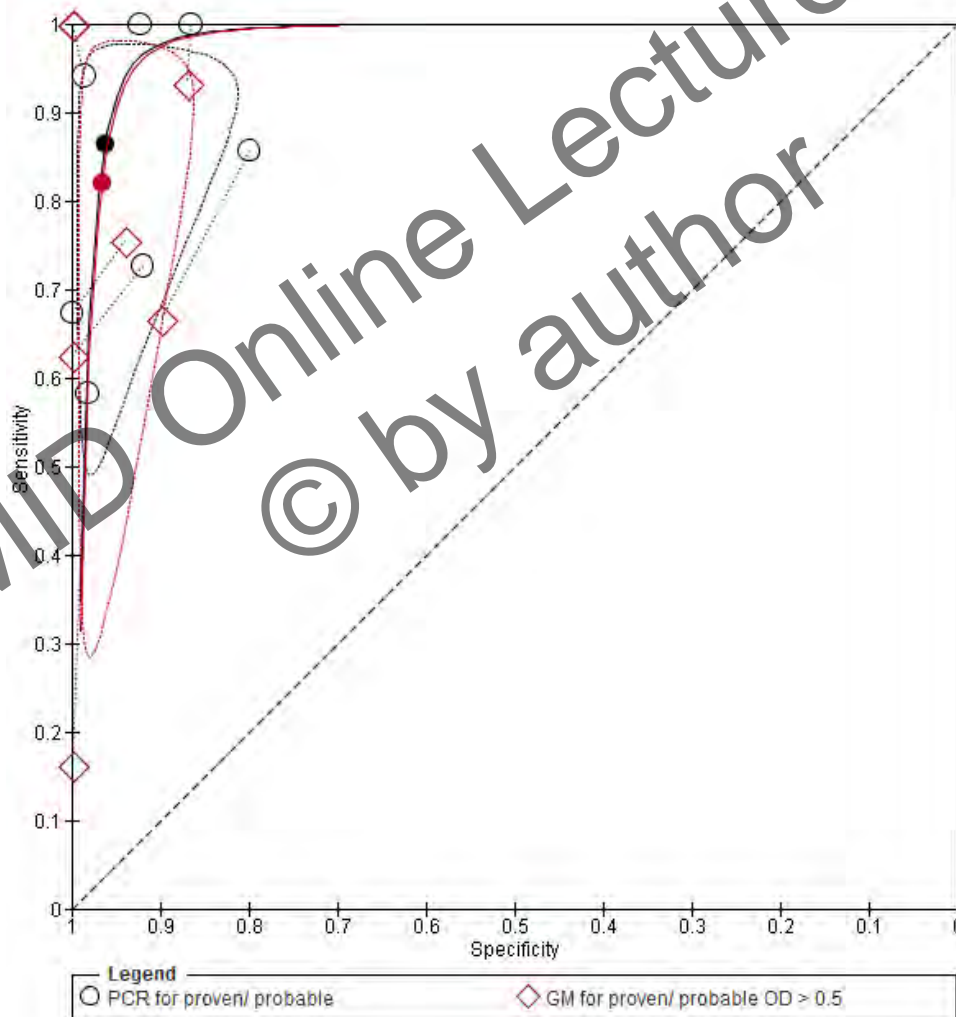


GM for proven/ probable OD > 0.5

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Luong 2011	14	14	1	93	0.93 [0.68, 1.00]	0.87 [0.79, 0.93]
Musher 2004	37	3	12	47	0.76 [0.61, 0.87]	0.94 [0.83, 0.99]
Orsi 2012	5	0	0	11	1.00 [0.48, 1.00]	1.00 [0.72, 1.00]
Rantakokko-Jalava 2003	5	0	3	50	0.63 [0.24, 0.91]	1.00 [0.93, 1.00]
Reinwald 2012	5	0	26	56	0.16 [0.05, 0.34]	1.00 [0.94, 1.00]
Torelli 2011	7	0	0	141	1.00 [0.59, 1.00]	1.00 [0.97, 1.00]
Verweij 1995	2	1	1	9	0.67 [0.09, 0.99]	0.90 [0.55, 1.00]



Test 1 vs. test 2



Practical questions - III

- Incidence of disease
- Prevalence of condition
- Outcome of disease
- Risk factor for disease
- Risk factor for adverse outcome of disease

Scope of SR/MA:

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The curious physician

Admitting a patient with suspected CAP

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- Optimal duration of antibiotic treatment
- Risk factors for death

Conditions favoring SR/ MA

- There is no clear answer to my question
- Preferably my question is relevant elsewhere
- Studies were performed addressing my formulated question
 - Preferably randomized controlled trials in intervention reviews
- There is no existing systematic review

Intervention reviews

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Corticosteroids for pneumonia

I. Inclusion criteria

Inclusion criteria: types of studies

- Addresses the study methodology to be included in the systematic review
- Most robust intervention reviews include only randomized controlled trials
- If good reasons exist, possible variations
 - Placebo-controlled trials only
 - Cluster-randomized trials
 - Pseudorandomized trials

Corticosteroids for pneumonia

- Types of studies: RCTs

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Inclusion criteria: participants

- Who will be included
 - Age limits
 - Disease condition - definitions, severity, stage of illness
 - Treatment conditions other than intervention assessed

Who would you exclude?

Corticosteroids for pneumonia

- Types of studies: RCTs
- Types of participants: adults and children with radiographically-diagnosed pneumonia acquired in the community or healthcare setting, of any severity, and treated with antibiotics
 - Excluded: neonates; pneumonia due to or secondary to influenza

Inclusion criteria: interventions

- Define interventions
- Define comparisons
- Define restrictions on types of drugs, dosing, timing, schedule and duration
- Definitions commonly liberal compared to those of a RCT

Corticosteroids for pneumonia

- **Types of studies:** RCTs
- **Types of participants:** adults and children (neonates excluded) with radiographically-diagnosed pneumonia acquired in the community or healthcare setting, of any severity, and treated with antibiotics
- **Types of interventions:** corticosteroids administered orally or intravenously, at any dose, for any duration, starting within 48 hours of start of antibiotic treatment
- **Types of comparisons:** corticosteroids vs. placebo or no treatment

Inclusion criteria: outcomes

- The privilege of a systematic reviewer is in the selection of the outcomes
 - Select the outcome/s most relevant to the patient
- Define primary outcome, preferably single
 - Should incorporate benefit and harm of the intervention
 - Well-measurable
- Define secondary outcomes, including adverse events

Steroids for pneumonia

- The privilege of a systematic reviewer is in the selection of the outcomes
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 - Should incorporate benefit and harm of the intervention
 - Well-measurable
- Define secondary outcomes, including adverse events

Corticosteroids for pneumonia

- **Primary outcome:** All cause mortality at day 30. If 30 day mortality will not be reported we will use mortality at another fixed point in time and if unavailable in-hospital mortality
- **Secondary outcomes:**
 - Early clinical failure: The study's definitions of clinical failure will be accepted providing that they address hemodynamic and respiratory status. The outcome must be collected between day 5-7
 - Late clinical failure: collected between day 14-30
 - Respiratory failure on day 14
 - Duration of hospital stay
 - Superinfections

Corticosteroids for pneumonia

- **Adverse events:**

- Hyperglycemia defined as any measurement of glucose >200 mg/dl
- Cardiac arrhythmias
- Clostridium-difficile-associated diarrhea

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Outcomes as inclusion criteria?

- Defining outcomes as inclusion criteria allows for meta-analysis
- A systematic review need not define outcomes as mandatory for inclusion
 - In this case the study will be included in the SR but not in the MA
- In any case, do not preclude study inclusion by outcome on the first round
 - Outcomes may be found only in full text after careful reading
 - Outcomes can be obtained from the authors

Corticosteroids for pneumonia

II. Search strategy

Search strategy principles

- Aims to identify all published and unpublished studies fulfilling inclusion criteria
- Without language or date restrictions

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Defining the review search strategy

- Define databases to be searched
- Define dates of search per database
- Define search string for each database
 - Search includes PICO/ PIC
- A search specialist assistance recommended when designing the search strategy

Search sources

- Databases: PubMed, Embase, LILACs, Chinese databases, The Cochrane Library
- Relevant conference proceedings
- Trial registry databases
- References of all included studies
- Optionally, contact with authors; references of reviews and previous SRs; websites of pharmaceutical companies manufacturing the intervention drugs

PubMed search string

- (steroids OR corticosteroids OR Glucocorticoids[MESH] OR prednisone OR hydrocortisone OR methylprednisolone OR methylprednisolone) AND
- (pneumonia[MESH] OR pneumonitis OR lower respiratory tract infection) AND
- Cochrane filter for RCTs

Cochrane Highly Sensitive Search Strategy for identifying randomized trials in PubMed

- #1 randomized controlled trial [pt]
- #2 controlled clinical trial [pt]
- #3 randomized [tiab]
- #4 placebo [tiab]
- #5 drug therapy [sh]
- #6 randomly [tiab]
- #7 trial [tiab]
- #8 groups [tiab]
- #9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
- #10 animals [mh] NOT humans [mh]
- #9 NOT #10

Corticosteroids for pneumonia

III. Risk of bias assessment

Risk of bias assessment

Allocation generation

The methods of creating a completely random sequence of treatment allocation

Low-risk	High-risk
Computer generated	Alternation
Coin toss	BY hospital room number

Risk of bias assessment

Allocation concealment

A mechanism that prevents foreknowledge of treatment assignment prior to inclusion of patients in the trial, to prevent selection bias

Low-risk	High-risk
Central procedure	No mechanism
Sealed opaque envelopes	Open table or list

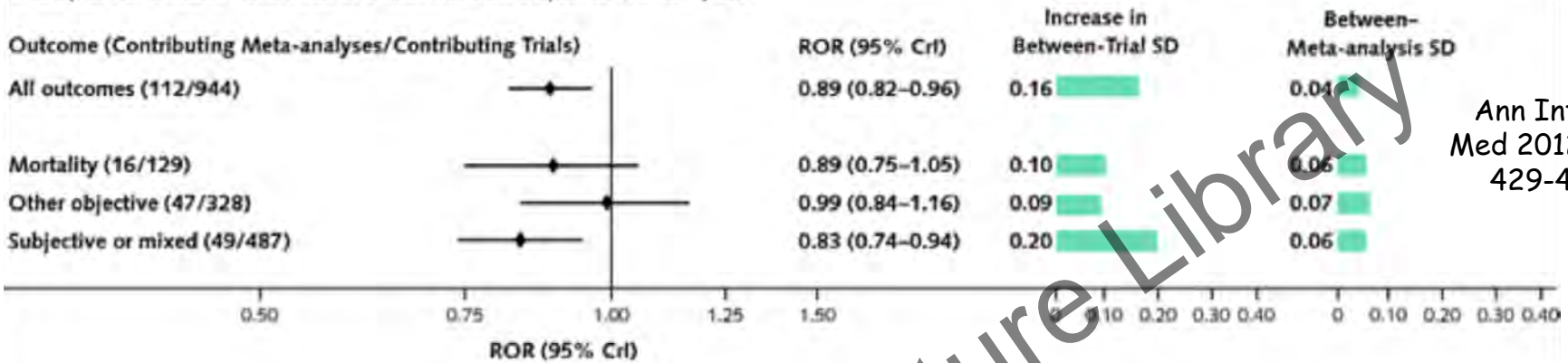
Risk of bias assessment

Blinding

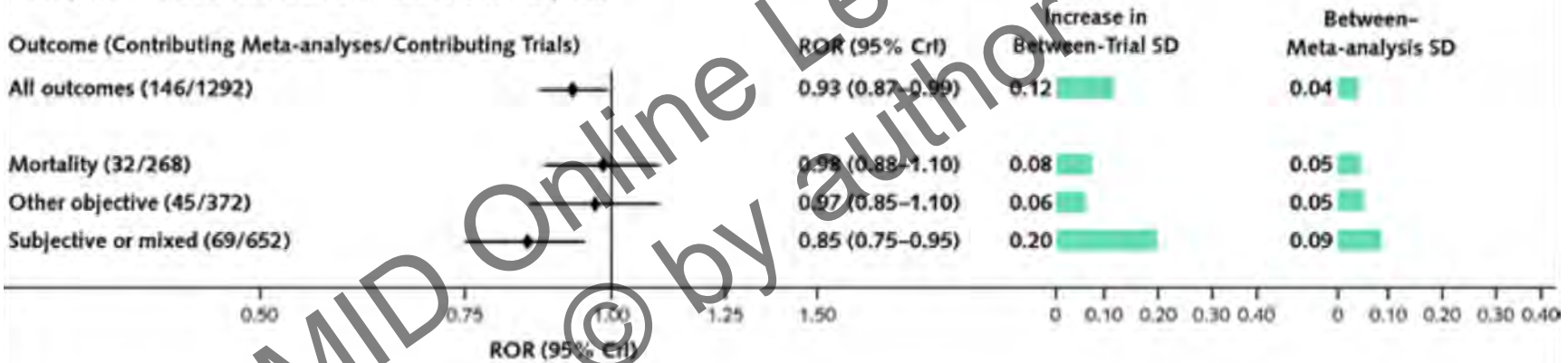
Masking of treatment assignments during the trial from patients, healthcare providers, outcome assessors

Low risk	High risk
Double blinding	Open trial
	Poor blinding

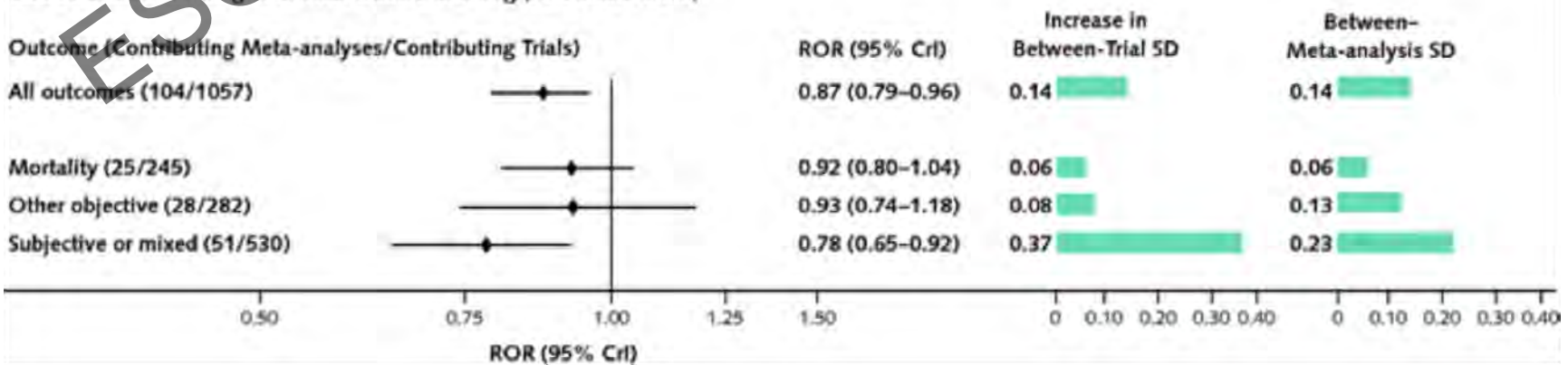
Inadequate or Unclear Generation of Randomization Sequence (vs. Adequate)



Inadequate or Unclear Allocation Concealment (vs. Adequate)



Lack of Double-Blinding or Unclear Double-Blinding (vs. Double-Blind)



Ann Intern
Med 2012;157:
429-438

Risk of bias assessment

Incomplete outcome data

Missing outcome data, due to attrition (drop-out) during the study or exclusions from the analysis

- Define threshold for % dropouts valid
- Document intention-to-treat assumptions

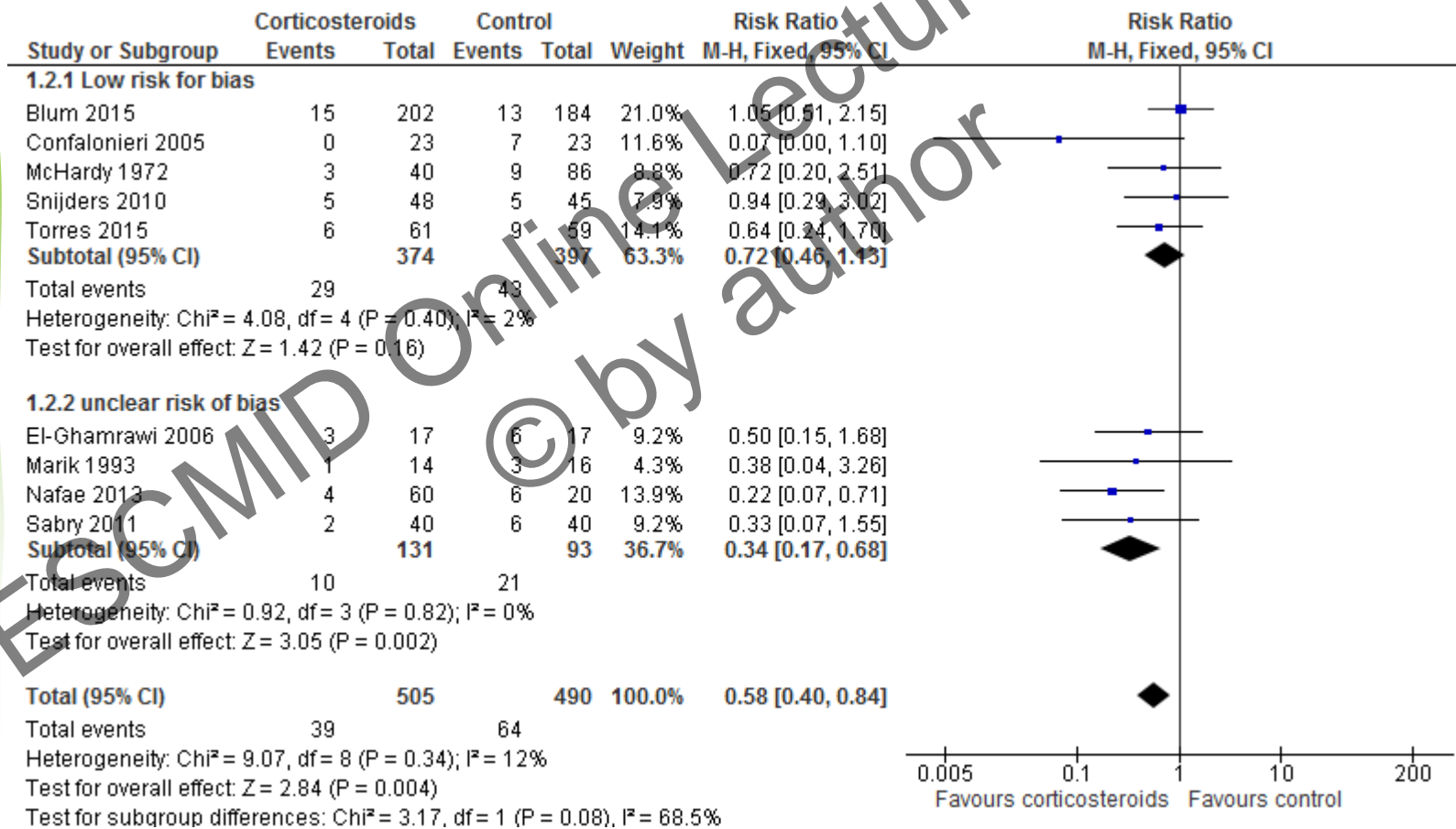
Risk of bias assessment

Selective reporting

selection of a subset of the original variables recorded, on the basis of the results, for inclusion in publication of trials

- Preferably compare publication to study protocol/ registry
- Address both outcome definition and timing

Use of risk of bias in SR/MA?



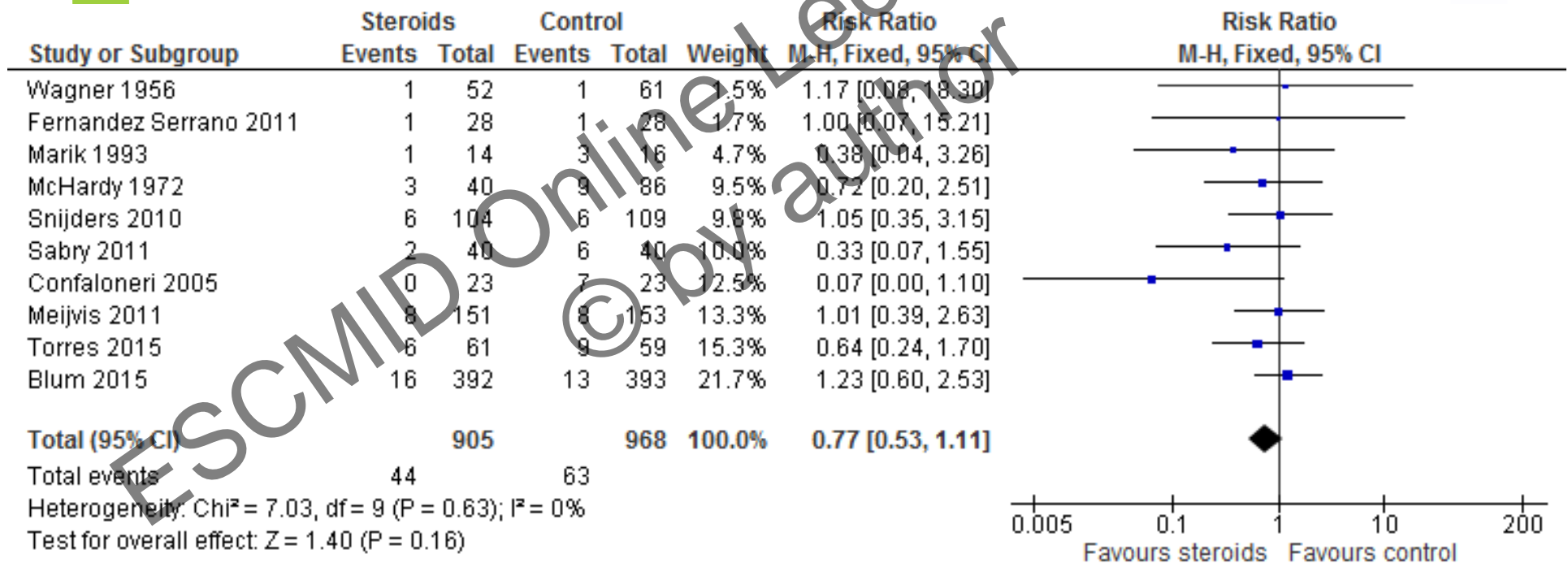
Corticosteroids for pneumonia

IV. Data analysis

Routine

- Measures of treatment effects in primary studies
 - Typically, measures of treatment effects are recalculated in SRs
 - Define for dichotomous and continuous outcomes
- Meta-analysis methods
 - Typically copy-paste...

Steroids for pneumonia: all-cause mortality



Corticosteroids for pneumonia

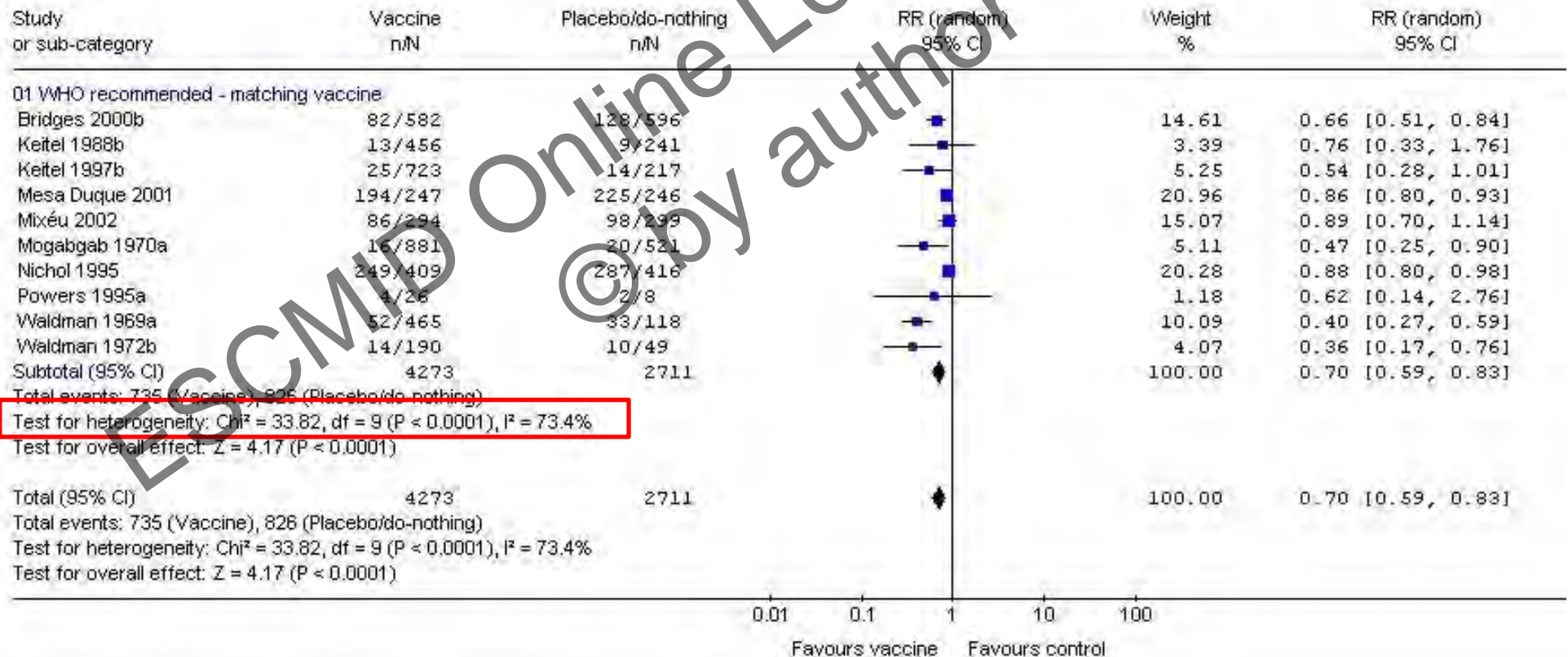
IV. Heterogeneity assessment and investigation

Heterogeneity in meta-analysis

- Clinical heterogeneity
 - Almost always present
 - Assessed and appraised using clinical expertise
- Statistical heterogeneity
 - Chi square test assesses whether observed differences in results are compatible with chance alone
 - I-square test describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance)

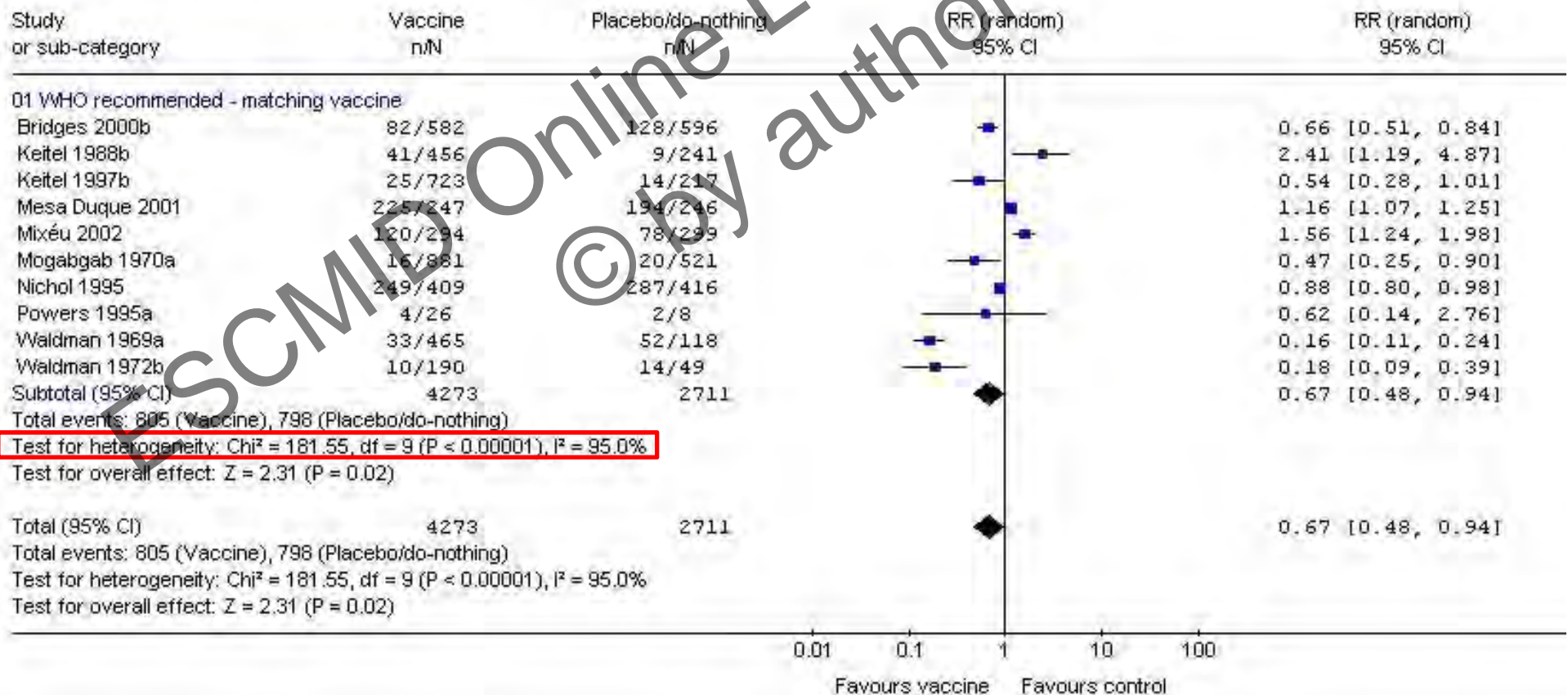
Influenza vaccine vs placebo to prevent flu-like illness

Review: Vaccines for preventing influenza in healthy adults (PR comments > Authors)
 Comparison: 01 Inactivated parenteral vaccine versus placebo or do-nothing
 Outcome: 01 Influenza-like illness



Influenza vaccine vs placebo to prevent flu-like illness (simulation)

Review: Vaccines for preventing influenza in healthy adults (PR comments > Authors)
 Comparison: 01 Inactivated parenteral vaccine versus placebo or do-nothing
 Outcome: 01 Influenza-like illness



Clinical heterogeneity?

- Different pneumonia severity at baseline
- Different steroid doses
- Outcomes measured at different time points

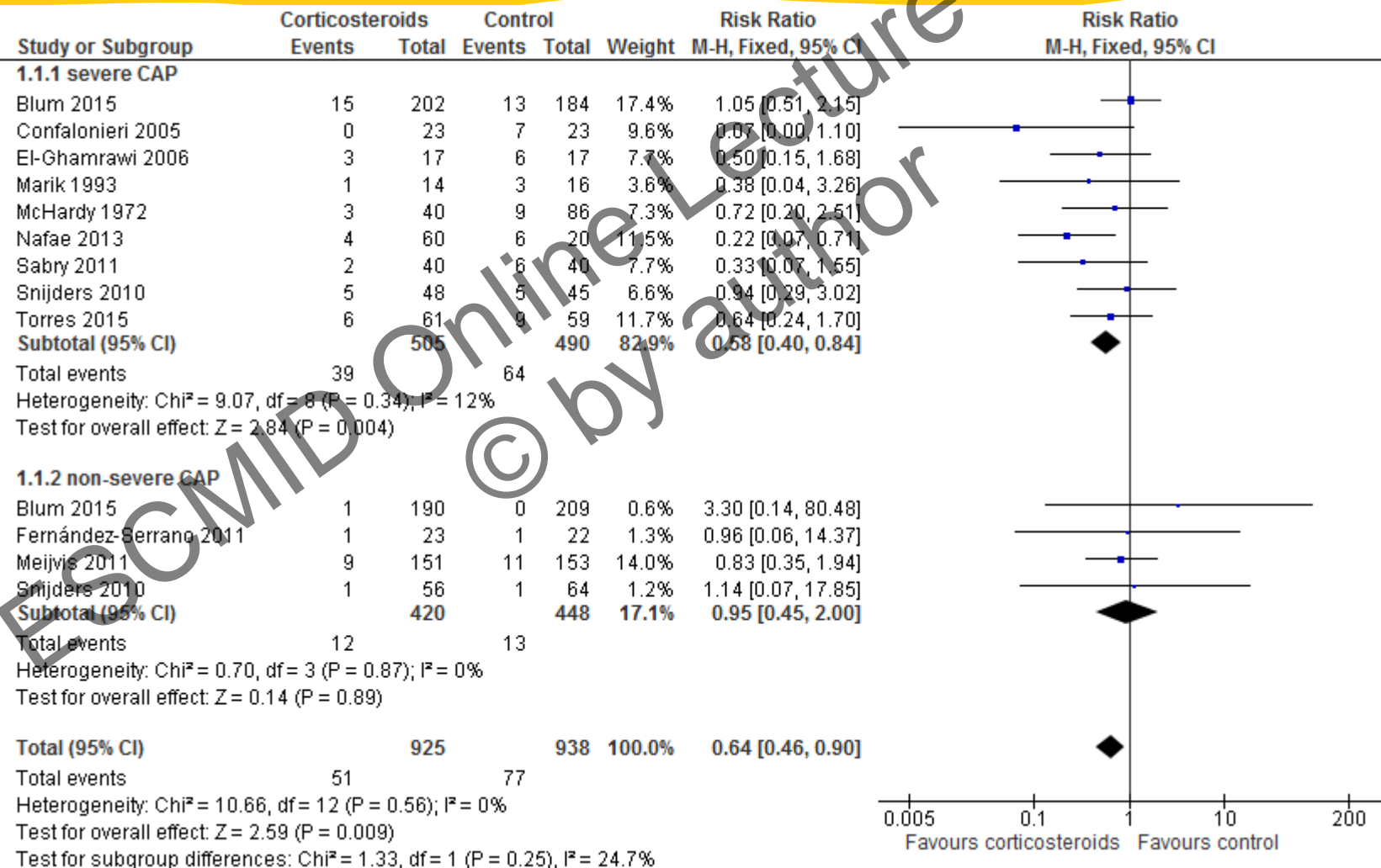
Heterogeneity investigation

- Predefine variables hypothesized to underlie heterogeneity
- Base hypotheses on understanding of the disease/ intervention and on the literature review
- Limit analyses to 3-4 variables investigated
- Define the outcomes for heterogeneity investigation

Corticosteroids for pneumonia: heterogeneity investigation

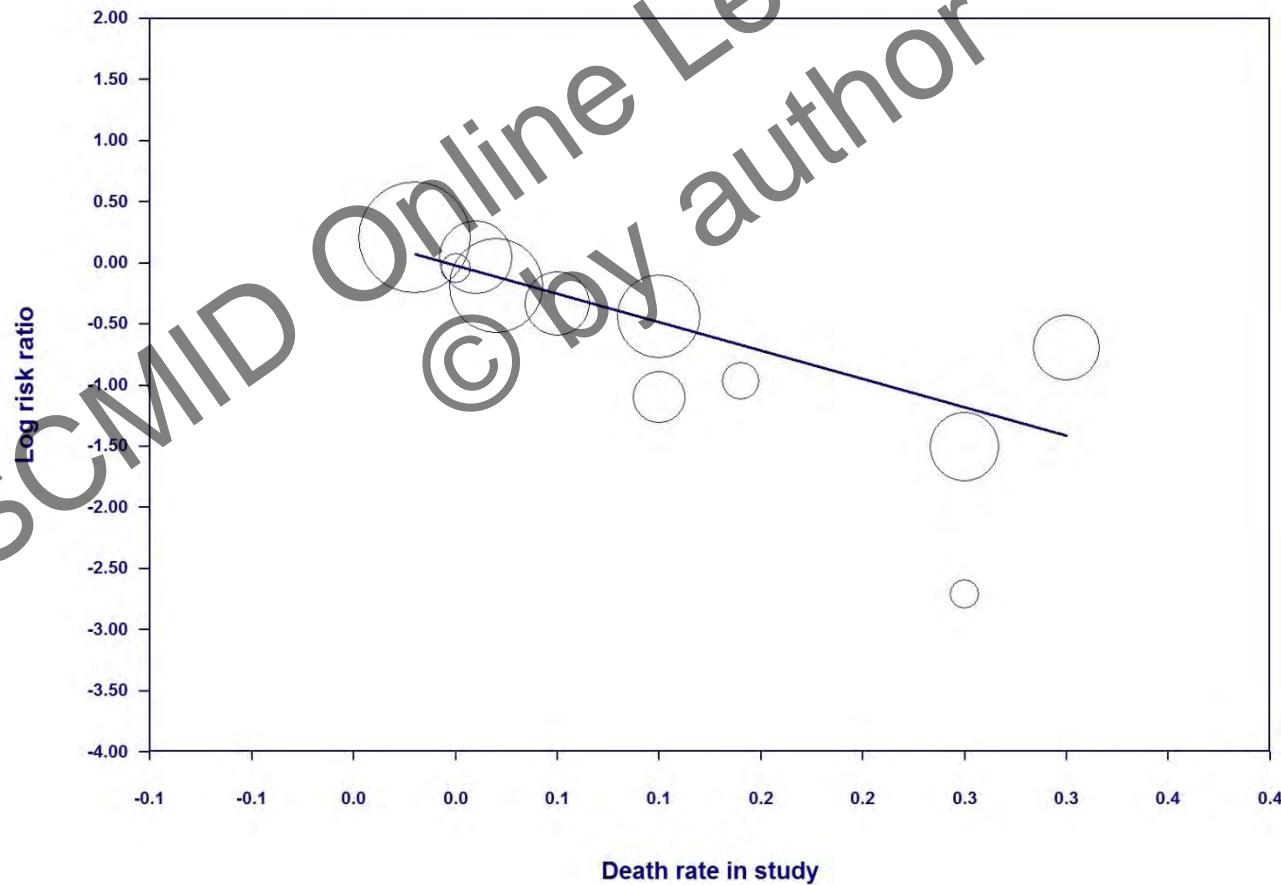
- Subgroup analyses will be performed for the primary outcome and early clinical failure
 - Severe vs. non-severe pneumonia, where severe pneumonia will be defined when the control arm mortality rate will be $> 9\%$ ($PSI \geq IV$)
 - Patients with chronic lung disease at baseline vs. None (or percentage of patients with chronic lung diseases in study)
 - Children vs. Adults

Subgroup analysis: pneumonia severity



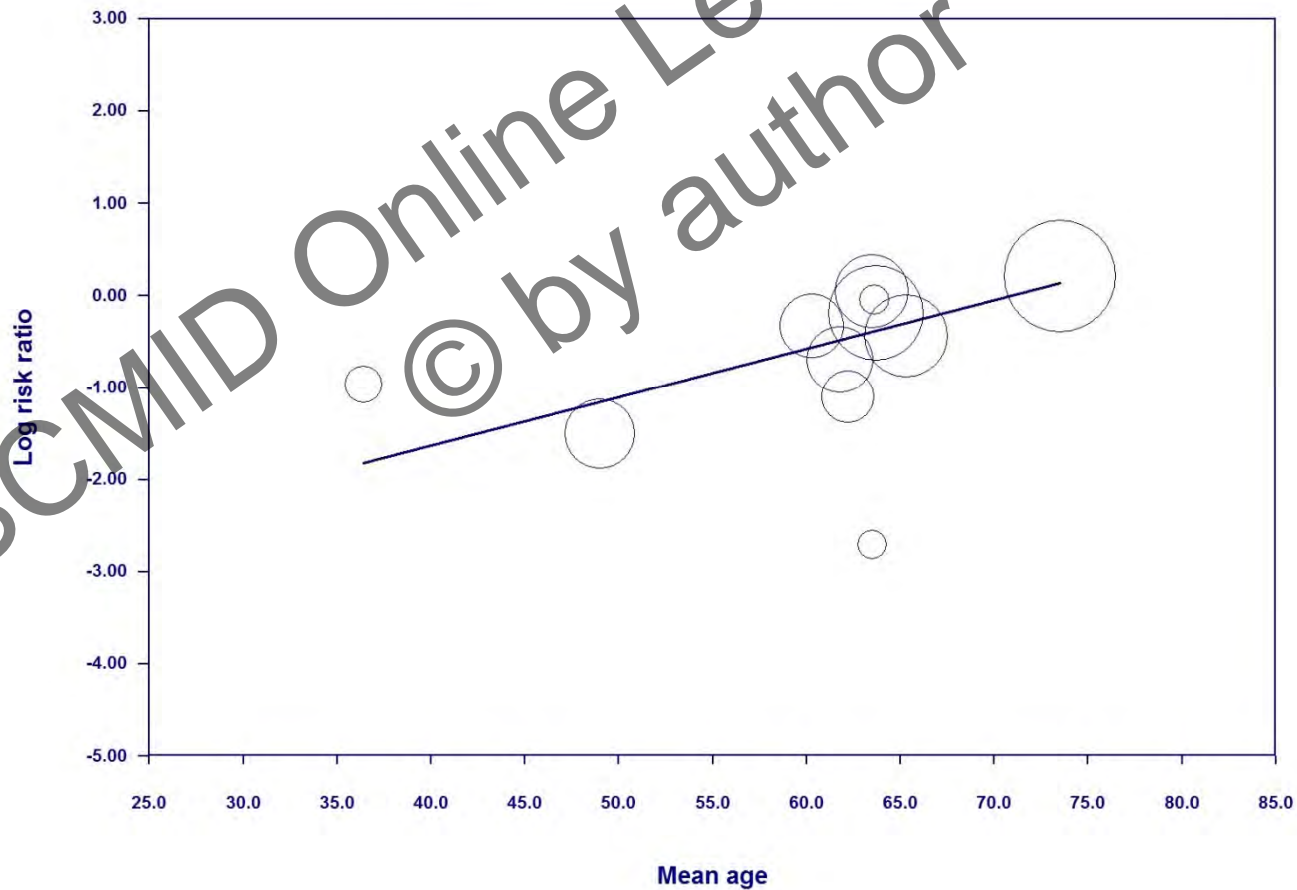
Meta-regression - death rate

Regression of Log risk ratio on Death rate in study



Meta-regression - age

Regression of Log risk ratio on Mean age



Conditions favoring SR/ MA

- ✓ There is no clear answer to my question
- ✓ My question is relevant elsewhere
- ✓ Randomized controlled trials were performed addressing my question



- ✗ Too many systematic reviews!

Available software

	RevMan	Comprehensive Meta-analysis
Costs	Free	License
Intervention reviews	+	+ More types of effect measures/ combination
Subgroup analyses	+ complicated	+ easy
Meta-regression	Not available	+ easy
Diagnostic reviews	Partial	Not available
Ease of use	Limited	Works as excel
Graphics	Friendly	Less friendly
Write-up	Full guidance	No support

Thank you

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