Investigator initiated randomised controlled trials

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How to Design and Perform your Clinical Studies in Infectious Diseases and Clinical Microbiology
ESCMID Postgraduate Education Course
7 - 8 November 2014, Tübingen, Germany

Investigator-initiated vs. industry RCTs

Industry

- Testing new drugs
- Excellent basic science and preclinical data
- Excellent logistics, well structured organization
- Regulatory authorities experience
- Monitoring complete
- Use of CRO

Investigator-initiated

- Better understanding of disease mechanisms
- Clinical expertise and access to patients
- Better definitions of target population
- Endpoints not driven by marketing issues
- Agenda not tight

Investigator-initiated vs. industry RCTs

Industry

- Testing new drugs
- Excellent basic science and preclinical data
- Excellent logistics, well structured organization
- Regulatory authorities experience
- Monitoring complete
- Use of CRO

Investigator-initiated

- Limited resources
- Data collected often less complete
- Monitoring restricted
- Limited knowledge of regulatory issues
- Longer trials
- Slow recruitment
- Trials frequently stopped before attained a predefined sample size

SPIRIT 2013 Statement

- Aim: to improve the completeness of trial protocols by producing evidence-based recommendations for a minimum set of items to be
- Trial protocol definition: the protocol is defined as a document that provides sufficient detail to enable understanding of the
  - background, rationale, objectives, study population, interventions, methods, statistical analyses, ethical considerations, dissemination plans, and administration of the trial;
  - Replication of key aspects of trial methods and conduct
  - Appraisal of the trial's scientific and ethical rigor from ethics approval to dissemination of results.

http://www.spirit-statement.org/

Advantages of guideline adherence

- Better trial design
- Attention to methodological and ethical aspects
- Organized protocol that is universally recognizable
- No omissions
- Avoid content replication
- Saves time
- Data available later for reporting by standards

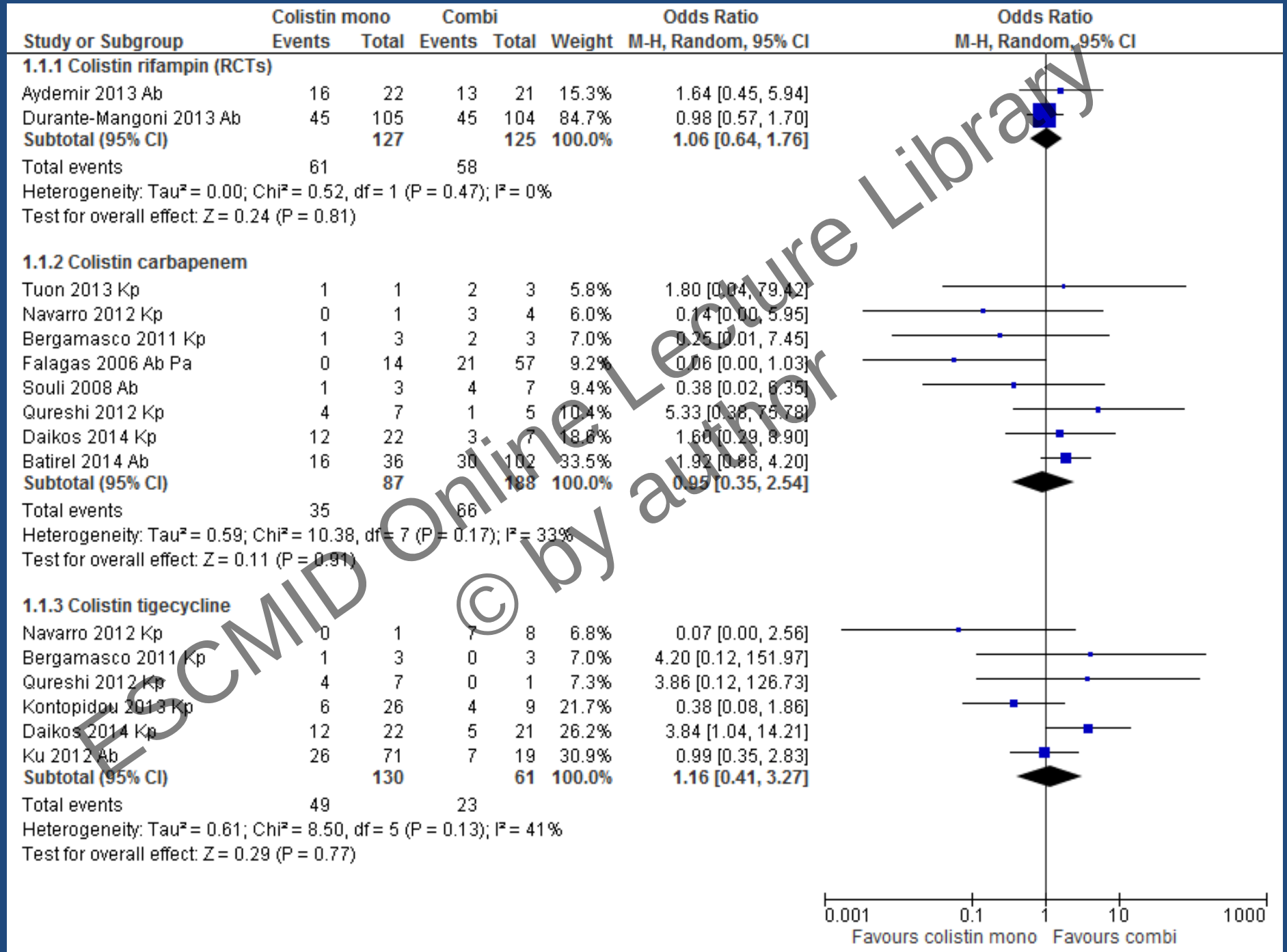
Administrative information

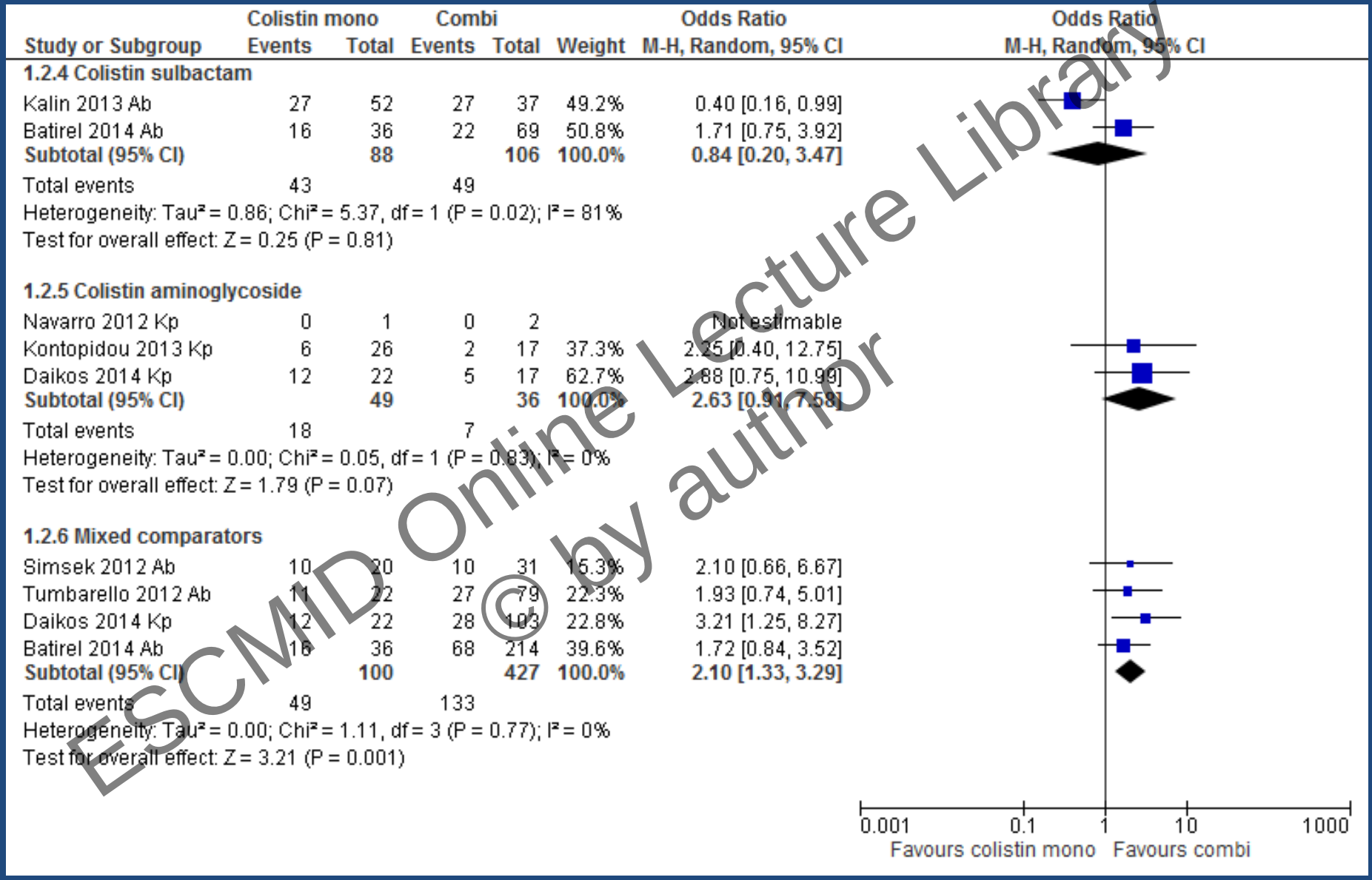
Item	Description
Title	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	Trial identifier and registry name
Protocol version	Date and version identifier
Funding	Sources and types of financial, material, and other support
Roles and responsibilities	• Responsibilities • Planned authorship

Introduction

Item	Description
Background and rationale	• Description of research question • Justification for undertaking the trial • Including summary of relevant studies • Explanation for choice of comparators
Objectives	Specific objectives or hypotheses
Trial design	• Type of trial • Allocation ratio • Framework (superiority, equivalence, non-inferiority, exploratory)

Bacteria	Carbapenem	% Synergy rate (95% CI)	% Antagonism rate (95% CI)	N Tests	N Bact	% Total synergy (I^2)
A. baumannii	Imipenem	56 (35-74)	8 (4-17)	11	82	77 (64-86), 48%
	Meropenem	86 (75-93)	7 (2-17)	9	71	
	Doripenem	88 (70-96)	9 (3-24)	6	33	
K. pneumoniae	Imipenem	41 (23-62)	24 (7-58)	5	58	44 (30-59), 51%
	Meropenem	34 (13-64)	9 (3-23)	6	39	
	Doripenem	63 (39-82)	10 (2-32)	6	19	
	Ertapenem	11 (3-29)	12 (3-42)	2	30	
P. aeruginosa	Imipenem	60 (18-91)	21 (11-38)	5	39	50 (30-69), 66%
	Meropenem	24 (15-38)	2 (0-16)	2	54	
	Doripenem	62 (38-81)	5 (1-20)	5	43	





Paul et al. J Antimicrob Chemother 2014

Methods

Item	Description
Study setting	Descriptive of study sites and locale
Eligibility criteria	Inclusion and exclusion criteria for participants
Interventions	• Interventions for each group with sufficient detail to allow replication • Criteria for discontinuing or modifying allocated interventions for a given trial participant • Strategies to improve adherence to interventions and procedures for monitoring adherence • Relevant concomitant care and interventions that are permitted or prohibited during the trial

Item	Description

Outcomes	• Primary - explain clinical relevance
	• Secondary
	  • Measurement variable
	  • Analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion)
	  • Time point for each outcome

Participant timeline	Intervention implementation, assessments, study visits Use figure
Sample size	Based on primary outcome and trial framework Clinical assumptions with references
Data monitoring	Description of any interim analyses and stopping guidelines • Who will have access to these interim results • Who will make the final decision to terminate the trial

Measures of outcome

- Primary outcomes in RCTs are frequently selected for sample size considerations
- RCTs should report also on the real outcome
- “Real” outcome
  - Individual patient
  - Beneficial and adverse outcomes
  - Decision making
  - Measurable objectively

Median duration, days (IQR)	Control group N = 377	Intervention group N = 376	p value
Total antibiotic course	7 (5–9)	6 (4–9)	<0.0001
Broad-spectrum antibiotic[a]	4 (0–7)	2 (0–5)	0.0003
Narrow to intermediate-spectrum antibiotic[a]	4 (0–8)	5 (0–7)	0.13
Intravenous administration	4 (0–8)	3 (0–6)	0.004
Oral therapy	4 (0–7)	4 (0–7)	0.84

aAntibiotic spectrum was classified as narrow to intermediate (amoxicillin/clavulanate or aminoglycosides or glycopeptides-linezolid) or broad spectrum (third-generation cephalosporins, piperacillin/tazobactam, imipenem or fluoroquinolones).

	Control group N = 377	Intervention group N = 376	p value
60 days in-hospital mortality, *n* (%)	38 (10.1)	37 (9.8)	0.91
ICU admission within 7 days of randomization, *n* (%)	6 (1.6)	7 (1.9)	0.78
New course of antibiotic therapy, *n* (%)	25 (6.6)	17 (4.5)	0.21
Antibiotic treatment for relapsing infection, *n* (%)	30 (7.9)	13 (3.4)	0.01
Length of stay, days (median, IQR)			
Overall population	15 (9–27)	15 (9–25)	0.95
Community-acquired infection	6 (3–14)[a]	5 (3–10)[b]	0.06

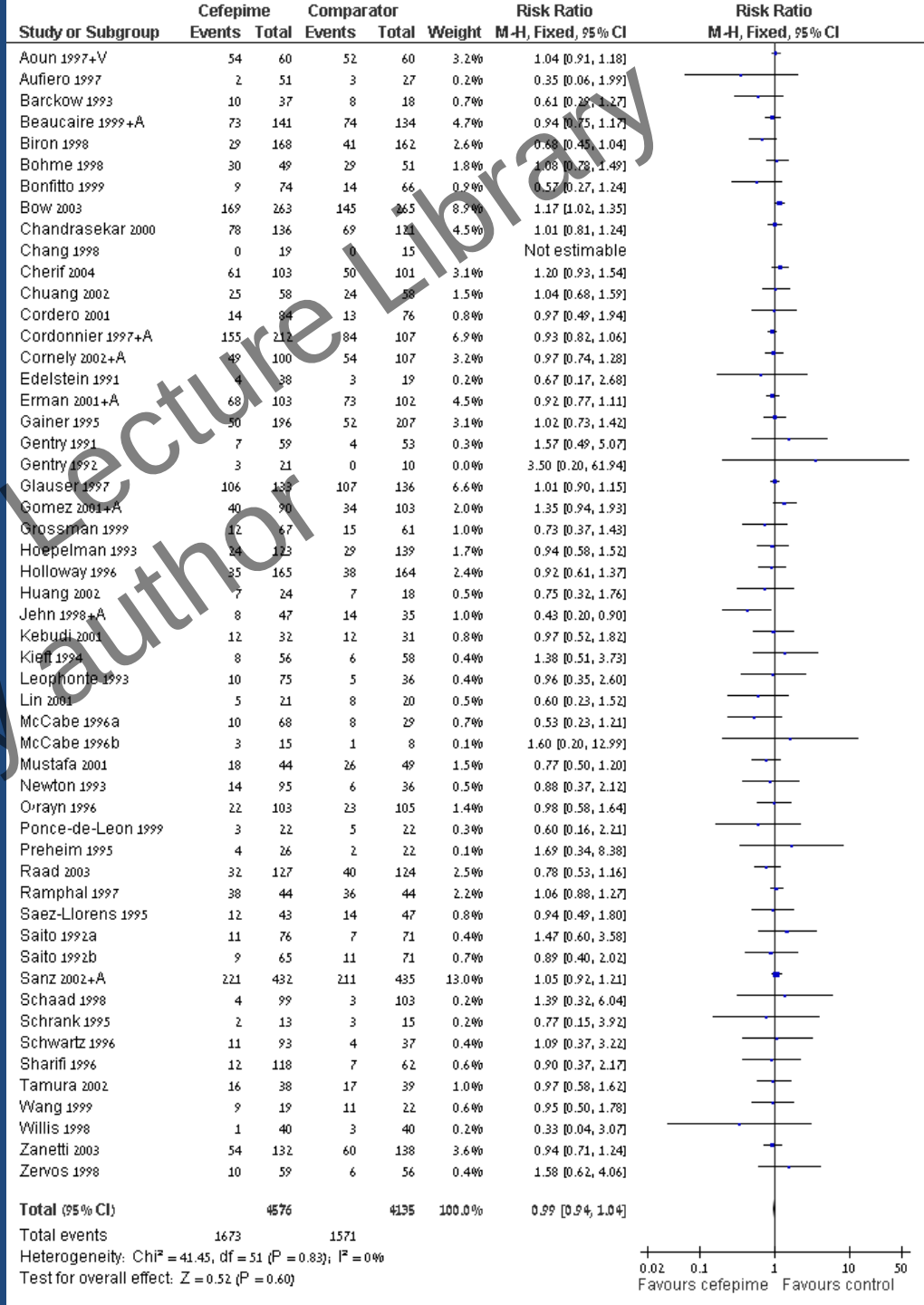
Lesprit et al. Clinical impact of unsolicited post-prescription antibiotic review in surgical and medical wards: a randomized controlled trial. Clin Microbiol Infect. 2013 Feb;19(2):E91-7.

Cefepime vs. other beta-lactam

Clinical failure

RR 0.99, 95% CI 0.94-1.04

Yahav et al. Lancet Infect Dis 2007:7 338-348

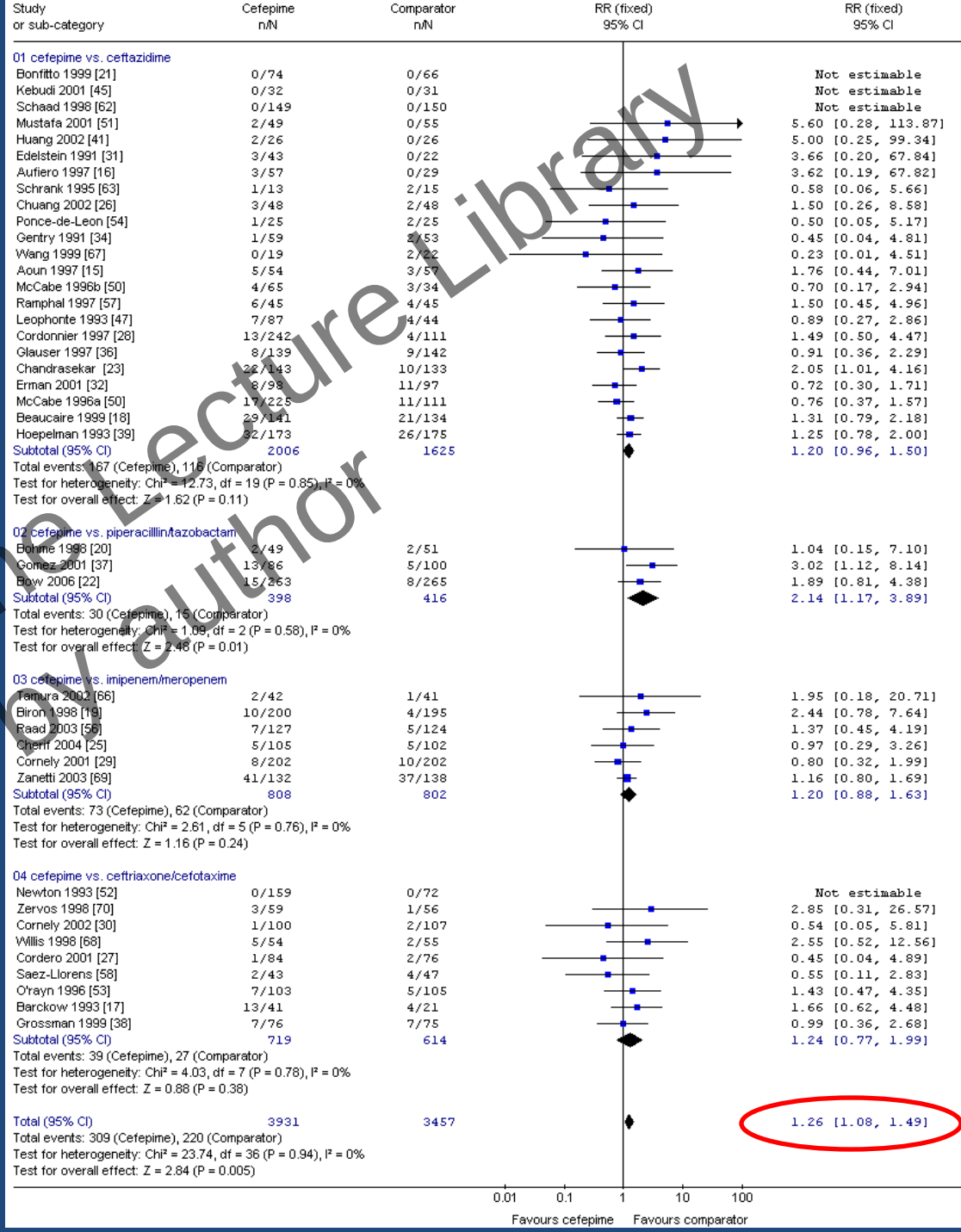


Cefepime vs. other beta-lactam

All-cause mortality

41/57 studies

RR 1.26, 95% CI 1.08-1.49



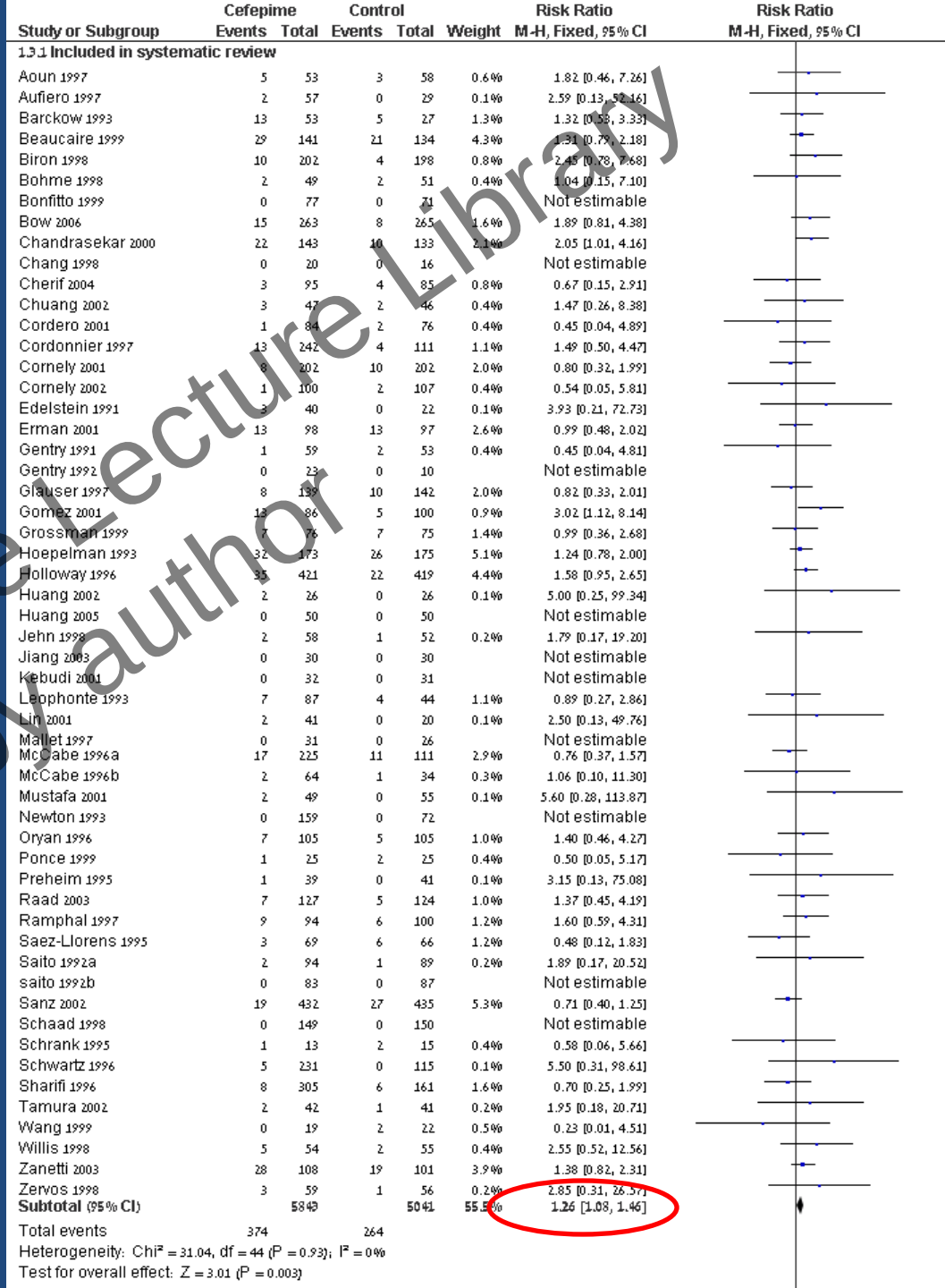
Cefepime vs. other beta-lactam

All-cause mortality

55/57 studies

RR 1.26, 95% CI 1.08-1.46

FDA review http://www.fda.gov/Drugs



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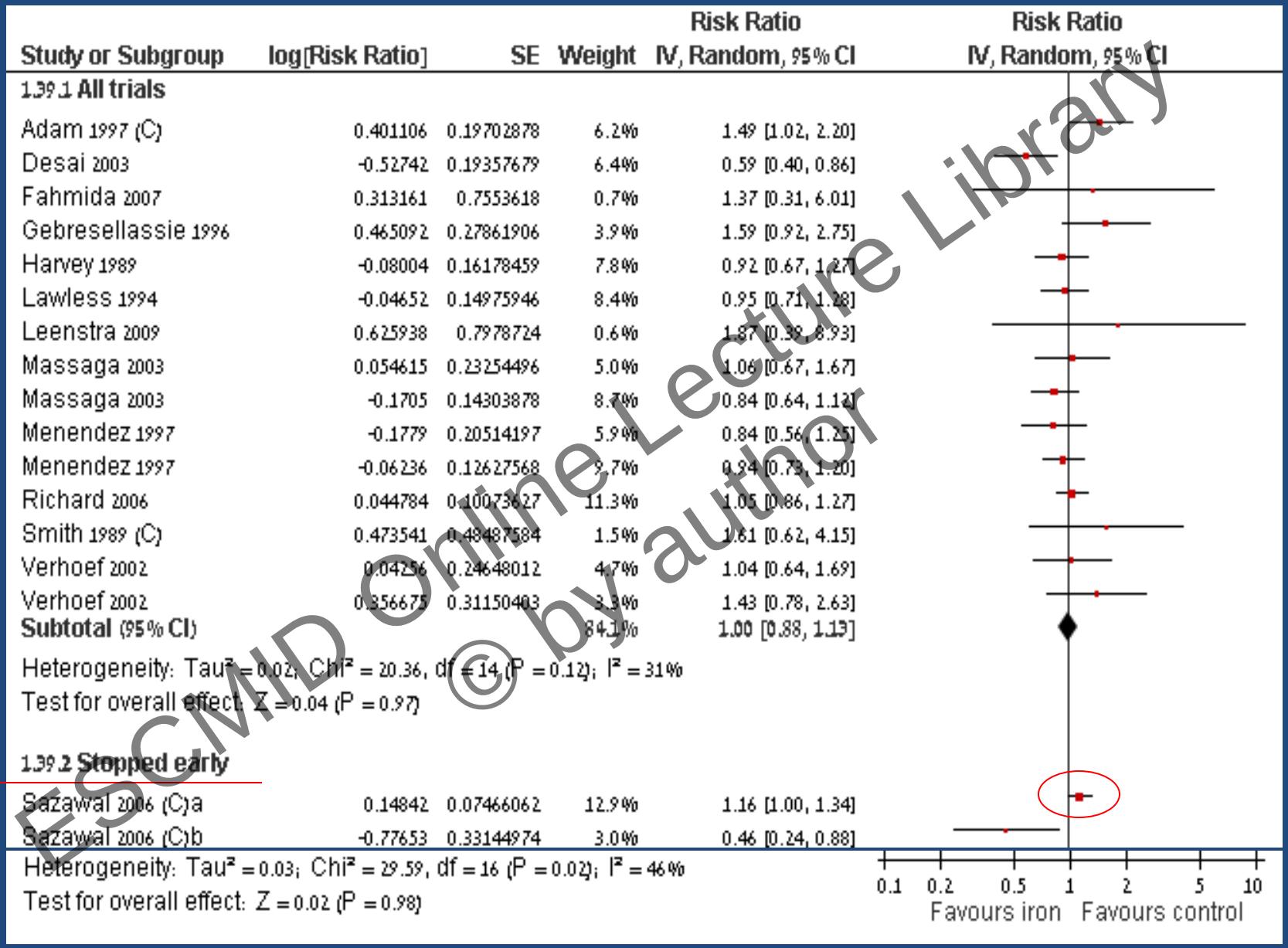
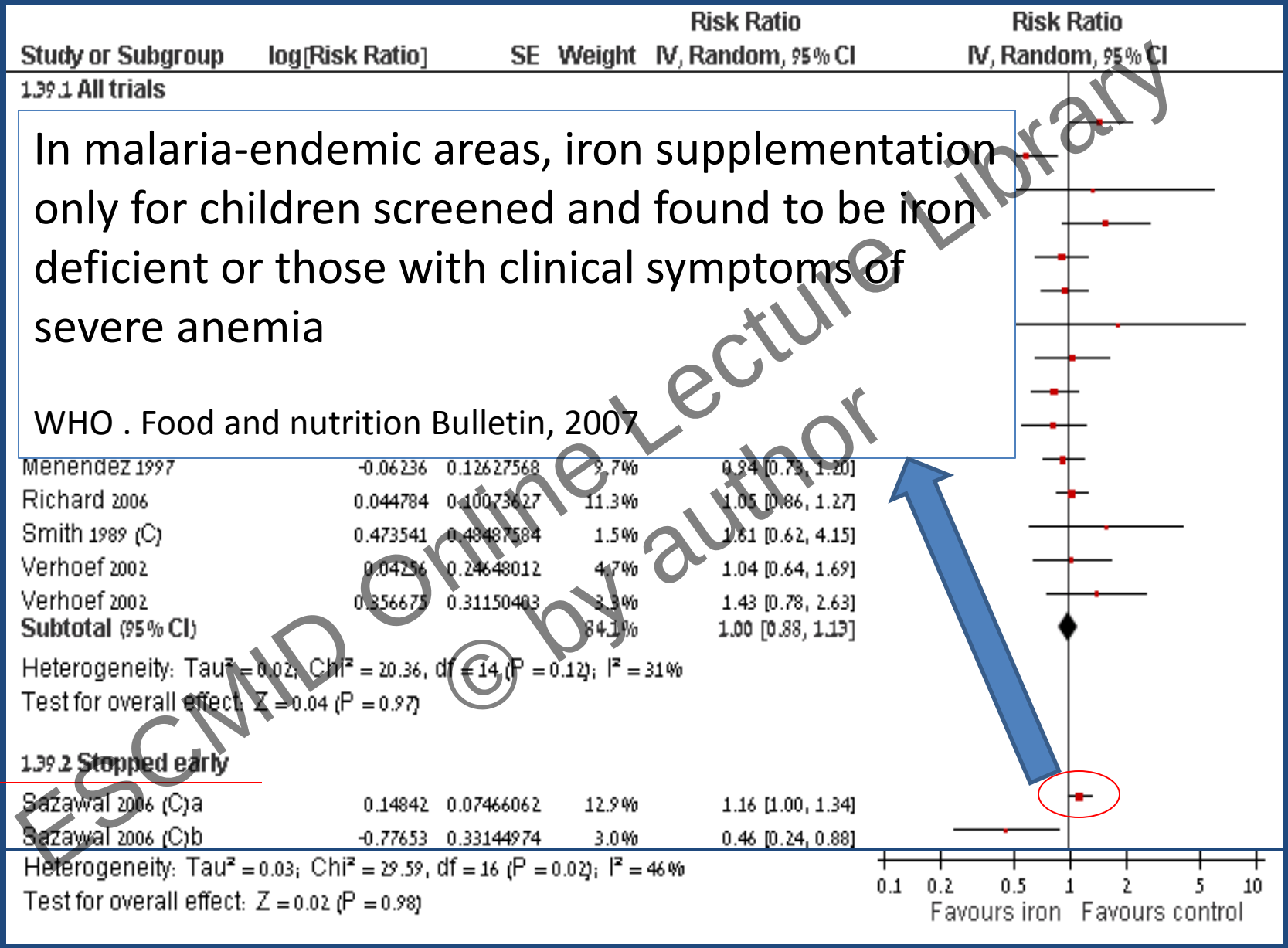


Oral iron supplementation for preventing or treating anaemia among children in malaria-endemic areas. Cochrane Database of Systematic Reviews 2009, Issue 3.



Oral iron supplementation for preventing or treating anaemia among children in malaria-endemic areas. Cochrane Database of Systematic Reviews 2009, Issue 3.

Explanation

- *"On the recommendation of the data and safety monitoring board, we stopped treatment in the iron, folic acid, and zinc group and in the iron and folic acid group on Aug 19, 2003… significantly (<0·05) higher rates of total adverse effects in the groups taking iron and folic acid than in the placebo group"*

Sazawal et al. Lancet 2006; 367: 133–43

What happens when no sample size is planned?

"All eligible patients were included in the study during a 2-year study period"

	Pip-Tazo (n = 30)	IMP (n = 32)	p value
Clinical response	14 (46.7)	9 (28.1)	0.130
Relapse	0/14	2/9 (2.2)	0.058
Microbiological response			
Complete response	23/24 (95.8[a])	24/25 (96[a])	1.000
Partial response	1/24 (4.2[a])	1/25 (4[a])	
Surgical intervention			
None	3 (10)	4 (12.5)	0.739
Debridement	5 (16.7)	4 (12.5)	
Ray resection	4 (13.3)	2 (6.3)	
Amputation	18 (60)	22 (68.8)	
Side effects			
Total	9 (30)[b]	3 (9.4)	0.055
Hepatotoxicity[c]	5 (16.7)	1 (3.1)	
Nephrotoxicity[d]	6 (20)	1 (3.1)	
Hematological side effects	2 (6.7)	–	
Other (nausea)	–	1 (3.1)	

Data are given as n (%).

Saltoglu et al. Piperacillin/tazobactam versus imipenem/cilastatin for severe diabetic foot infections. Clin Microbiol Infect 2010.

Do you think such a study should be have been done

A. No

B. Yes

Do you think such a study should published in a medical journal

A. No

B. Yes

Table 5. Outcomes

Characteristic	Deferasirox ($n=11$)	Placebo ($n=9$)	P value
ITT population			
Global success at EOT, *n* (%)	3 (27)	3 (33)	1
Global success at 30 days, *n* (%)	2 (18)	6 (67)	0.06
Global success at 90 days, *n* (%)	2 (18)	5 (56)	0.2
Clinical response, *n* (%)			
at EOT	7 (64)	9 (100)	0.08
at 30 days	4 (36)	8 (89)	0.03
at 90 days	2 (18)	7 (78)	0.01
Radiographic response, *n* (%)			
at EOT[a]	4 (36)	3 (33)	0.6
PP population			
Global success, *n* (%)			
at EOT	2/6 (33)	3/8 (38)	0.7
at 30 days	1/6 (17)	6/8 (75)	0.05
at 90 days	1/6 (17)	4/8 (50)	0.2
Survival, *n* (%)			
at EOT	6/6 (100)	8/8 (100)	1
at 30 days	4/6 (67)	8/8 (100)	0.2
at 90 days	1/6 (17)	7/8 (88)	0.02
Clinical response, *n* (%)			
at EOT	5/6 (83)	8/8 (100)	0.5
at 30 days	3/6 (50)	8/8 (100)	0.06
at 90 days	1/6 (17)	7/8 (88)	0.02

Spellberg et al. The Deferasirox-AmBisome Therapy for Mucormycosis (DEFEAT Mucor) study: a randomized, double-blinded, placebo-controlled trial. J Antimicrob Chemother. 2012 Mar;67(3):715-22

Do you think such a study should be have been done

A. No

B. Yes

Do you think such a study should published in a medical journal

A. No

B. Yes

Small trials

- “Negative and inconclusive as well as positive results should be published or otherwise made publicly available“
- Results will be used when compiling the evidence
- Mandatory registry of trial results might obviate the need to publish unpowered trials in medical journals

However

- Adequate sample size should be planned

WMA Declaration of Helsinki

Item	Description
Allocation Sequence generation	• Method of generating the allocation sequence • Stratification • Any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions
Allocation concealment mechanism	Mechanism of implementing the allocation, describing the steps to conceal the sequence until interventions are assigned
Blinding (masking)	Who will be blinded after assignment to interventions • Trial participants • Care providers • Outcome assessors • Data analysts How is blinding achieved Circumstances under which un-blinding is permissible

Adequate allocation generation/ concealment

"Determination of whether a patient would be treated by streptomycin and bed-rest (S case) or by bed-rest alone (C case) was made by reference to a statistical series based on random sampling numbers drawn up for each sex at each centre by Professor Bradford Hill; the details of the series were unknown to any of the investigators or to the coordinator and were contained in a set of sealed envelopes, each bearing on the outside only the name of the hospital and a number. After acceptance of a patient by the panel, and before admission to the streptomycin centre, the appropriate numbered envelope was opened at the central office; the card inside told if the patient was to be an S or a C case, and this information was then given to the medical officer of the centre"

Streptomycin treatment of pulmonary tuberculosis: a Medical Research Council investigation. BMJ 1948;2:769-82.

Which variable has been shown empirically to have the largest effect on study results, if at all?

A. Randomization sequence generation

B. Randomization allocation concealment

C. Double-blinding

D. None shown to significantly affect results

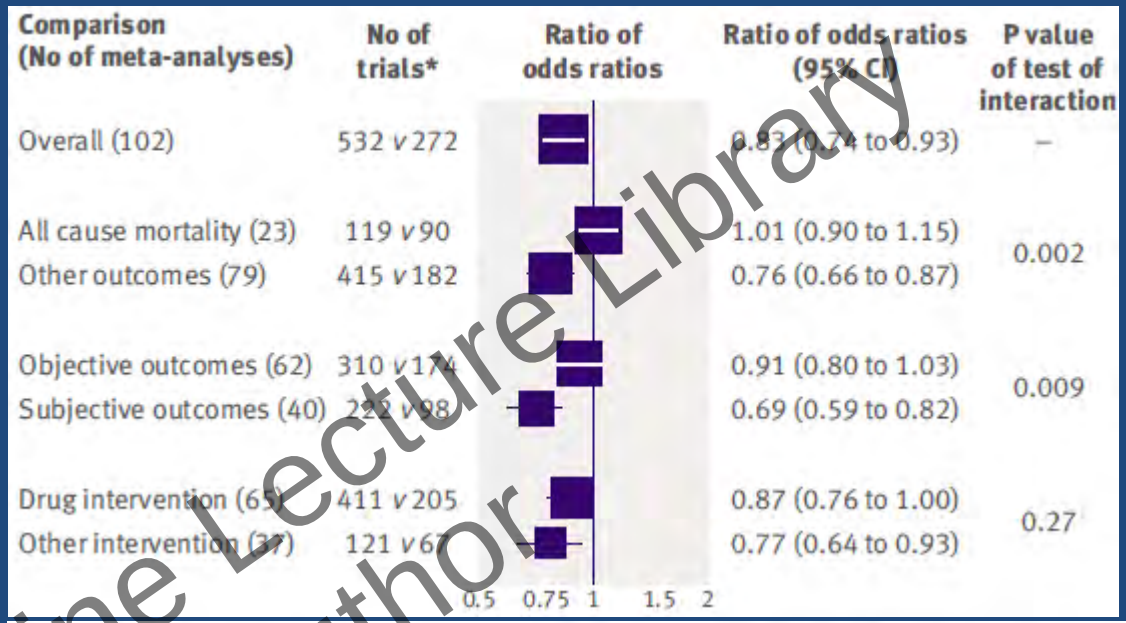
Empirical evidence

Variable	Ratio of odds ratio (95% confidence intervals); adequate = referent (1)	P-value
Allocation concealment		<0.001
Inadequate	0.59 (0.48-0.73)	
Unclear	0.67 (0.60-0.75)	
Allocation generation		
Unclear	0.95(0.81-1.12)	0.58
Blinding		
No double-blinding	0.83 (0.71-0.96)	0.01

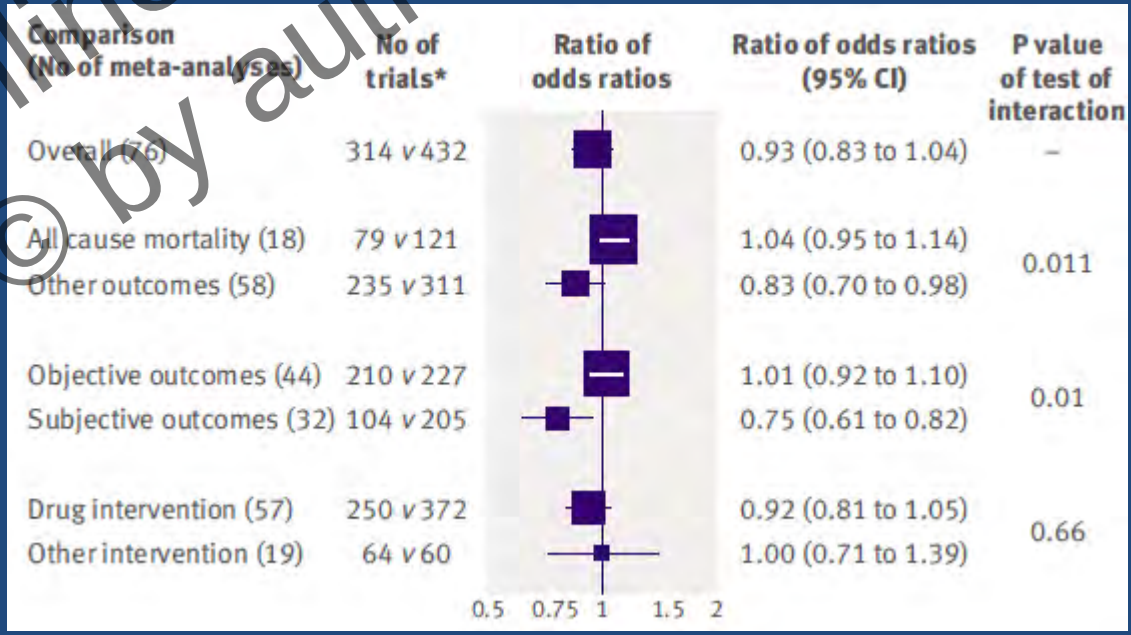
Adequate methods are the reference

Schulz KF, Chalmers I, Hayes RJ, Altman DG. JAMA 1995;273(5):408-12

Allocation concealment



Double-blinding



Wood L, Egger M, Gluud LL, Schulz KF, Jüni P, Altman DG, Gluud C, Martin RM, Wood AJ, Sterne JA. BMJ 2008; 336(7644):601-5

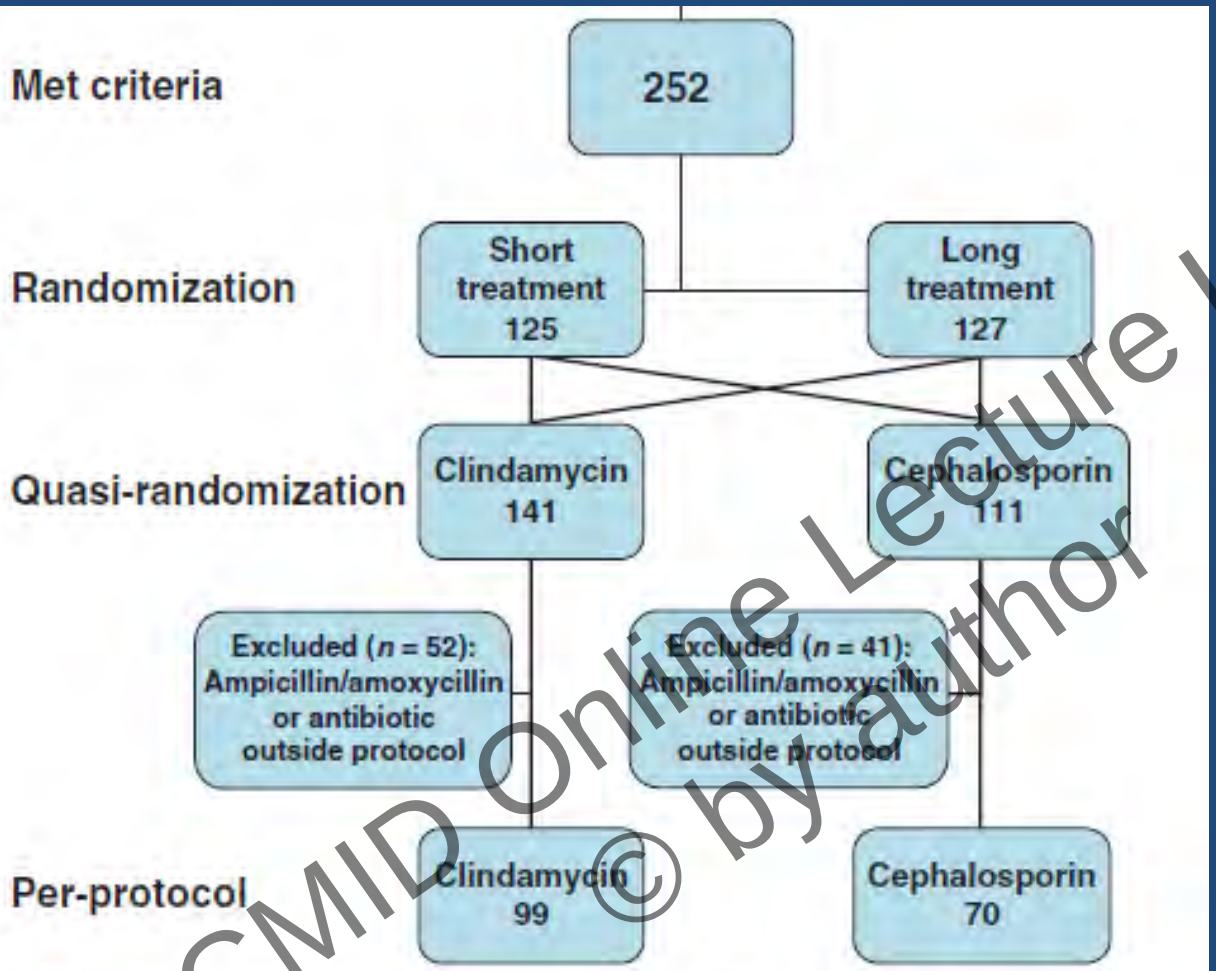


FIG. 1. Flow chart. Randomization was performed by contacting a special ward of the Children's Hospital (Helsinki, Finland). A computer-generated number was given by telephone.

Children born on an odd day were given clindamycin; children with an even birthday received first-generation cephalosporin.

Peltola et al. Clindamycin vs. first-generation cephalosporins for acute osteoarticular infections of childhood--a prospective quasi-randomized controlled trial. Clin Microbiol Infect. 2012 Jun;18(6):582-9

Data collection, management and monitoring

Item	Description
Data collection	Who, when , how Design case report form (CRF) – decide on platform
Data management	Data entry, coding, security, and storage processes to promote data quality
Data monitoring	• Composition of data monitoring committee (DMC) or an explanation of why a DMC is not needed • Plans for collecting, assessing, reporting, and managing adverse events
Auditing	Frequency and procedures for auditing trial conduct

Statistical analysis and ethics

Item	Description
Statistical methods	Statistical methods for analyzing primary and secondary outcomes. • Define analysis population • Define subgroups • Prepare you log file
Research ethics approval	Always obtain
Consent/ assent	• Discuss informed consent processes appropriate for the trial • Plan for patients who cannot provide informed consent • Informed consent form
Confidentiality	How personal information about potential and enrolled participants will be collected, shared, and maintained
Declaration of interests	

Methods of reporting

Number of patients	Voriconazole	Placebo	P-value
Randomized	10	15	
Pulmonary infiltrates	0	5	0.06
Any infection	3	6	0.25
Length of hospital stay (mean days)	31.9	37.3	0.09
Deaths	0	2	NS

Vehreschild et al. A double-blind trial on prophylactic voriconazole or placebo during induction chemotherapy for acute myelogenous leukaemia. J Infect 2007;5:445449

What would be the most true statement regarding this trial?

A. Advantage to voriconazole over placebo

B. No advantage to voriconazole over placebo (non-inferiority)

C. No significant differences between voriconazole and placebo

D. Equivalence

Preferred methods of reporting

Number of patients	Voriconazole	Placebo	P-value	Risk ratio (95% CI)
Randomized	10	15		
Pulmonary infiltrates	0	5	0.06	0.13 [0.01, 2.16]
Any infection	3	6	0.25	0.75 [0.24, 2.33]
Deaths	0	2	NS	0.29 [0.02, 5.49]

What would be the most true statement regarding this trial?

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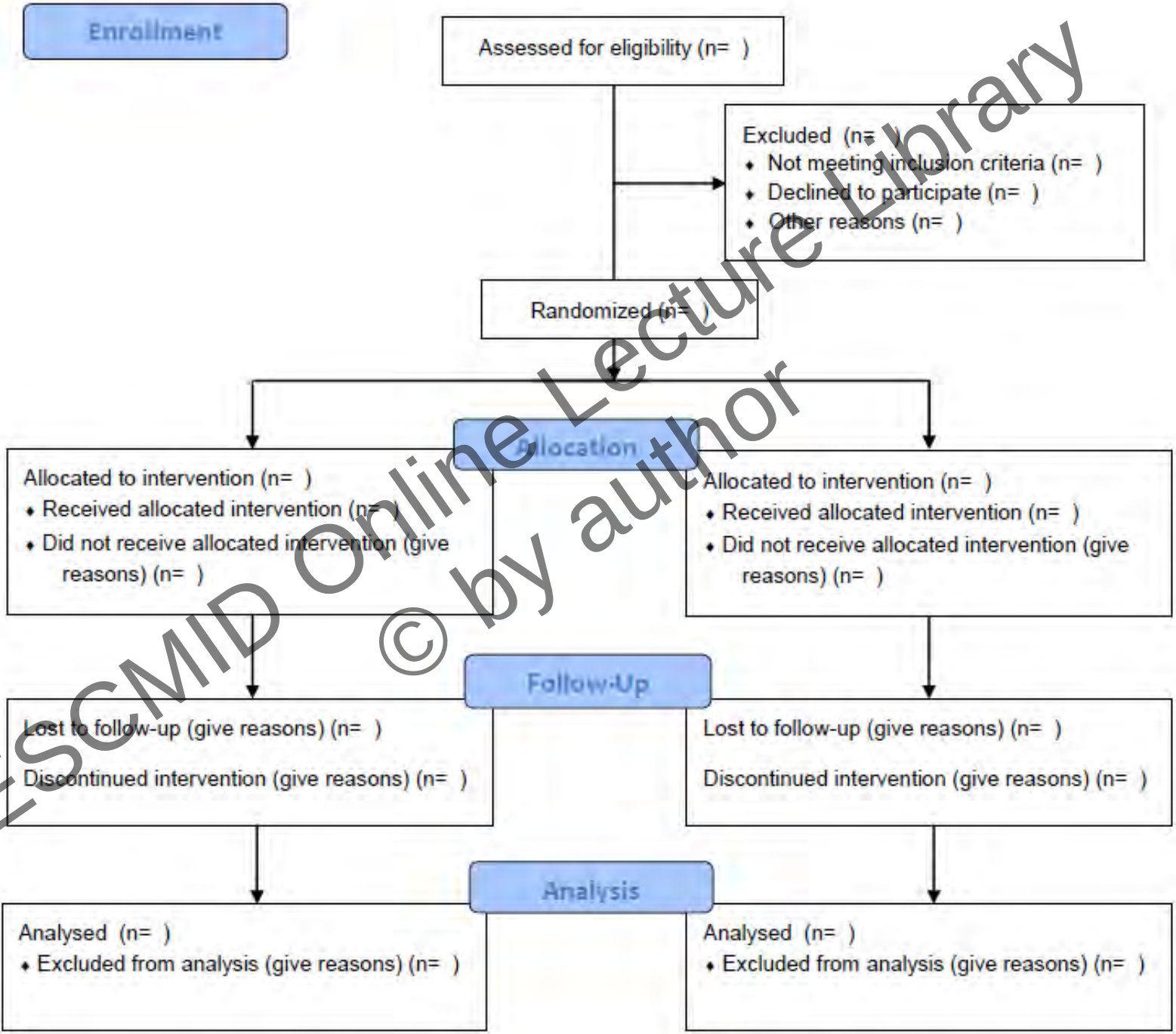
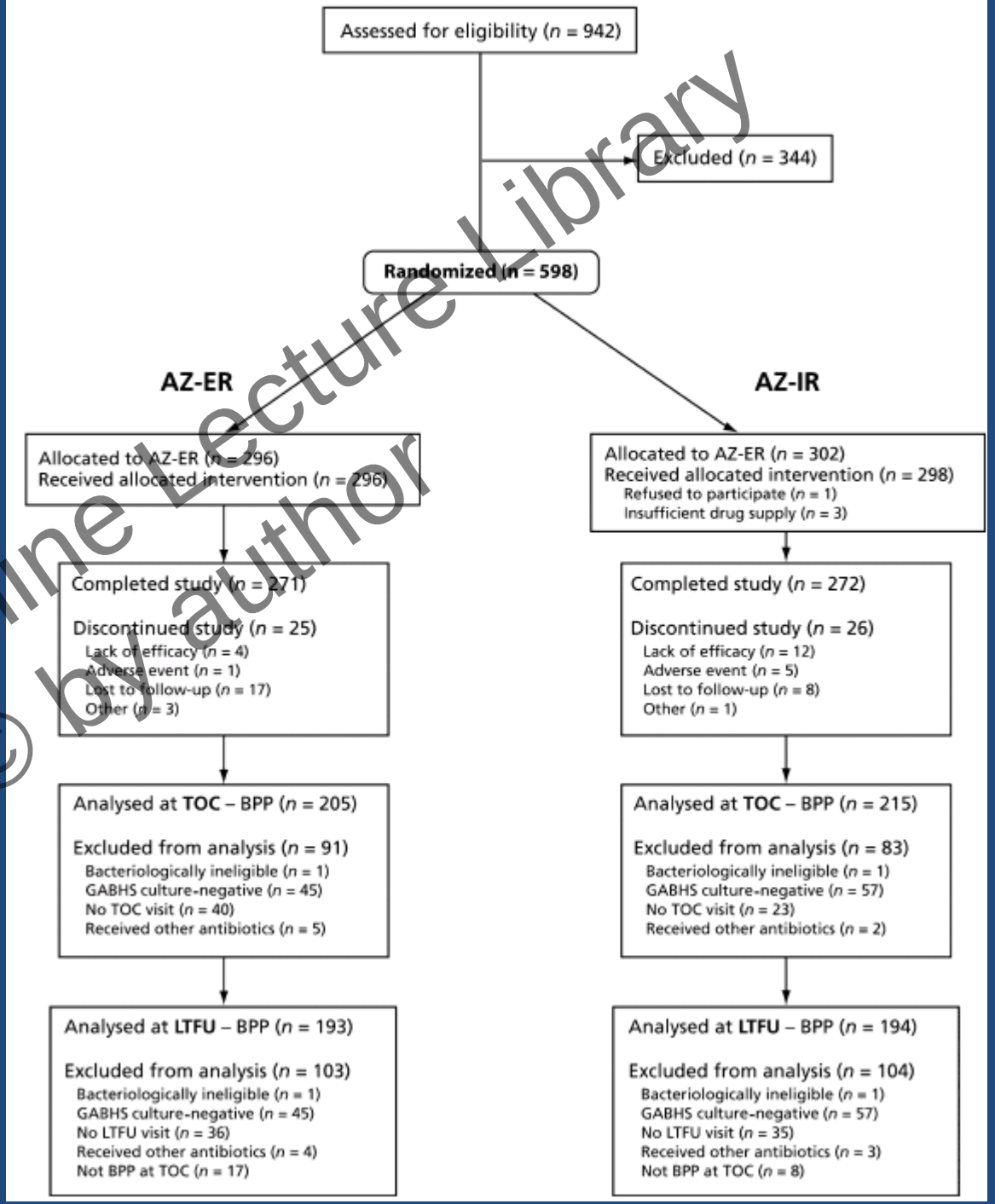


Single-dose extended-release oral azithromycin vs. 3-day azithromycin for the treatment of group A b-haemolytic streptococcal pharyngitis/ tonsillitis in adults and adolescents: a double-blind, double-dummy study

BPP - bacteriological per-protocol
TOC - test-of-cure
LTFU - long-term follow-up



Jorgensen DM. Clin Microbiol Infect 2009 15(12):1103-10

In this RCT where outpatients with clinical signs/ symptoms of streptococcal tonsillitis plus a positive rapid antigen detection test or culture for group A beta-haemolytic Streptococcus (GAS) were randomized to 2 different antibiotic regimens, which population would be of most interest to you?

A. All patients with culture-proven GAS tonsillitis (mITT)
B. All patients adhering to the full treatment regimen (per protocol)
C. Culture-proven and adhering patients (mITT per protocol)
D. All randomized patients

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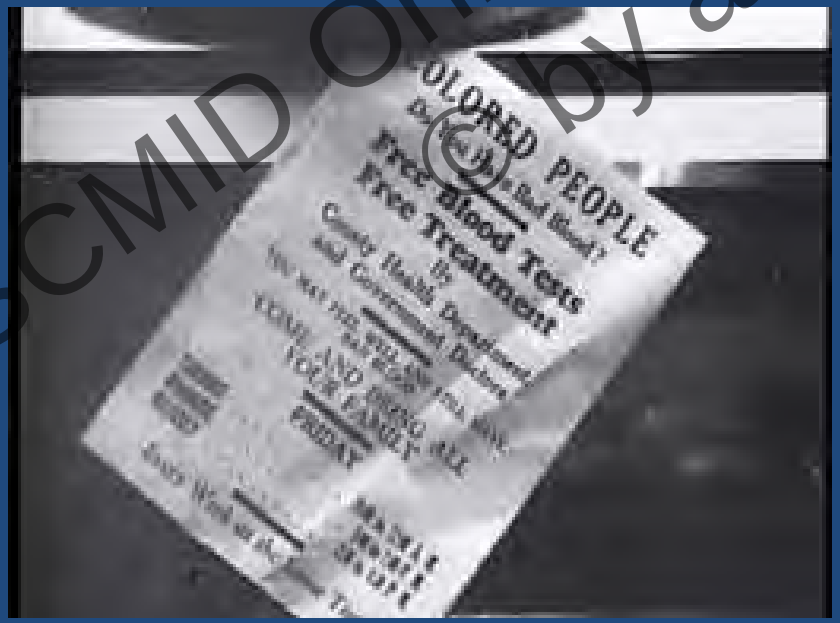
Research - 1932



The New York Times

Syphilis Victims in U.S. Study Went Untreated for 40 Years

By JEAN HELLER
The Associated Press

WASHINGTON, July 25—For 40 years the United States Public Health Service has conducted a study in which human beings with syphilis, who were induced to serve as guinea pigs, have gone without medical treatment for the disease and a few have died of its late effects, even though an effective therapy was eventually discovered.

The study was conducted to determine from autopsies what the disease does to the human body.

Officials of the health service who initiated the experiment have long since retired. Current officials, who say they have serious doubts about the morality of the study, also say that it is too late to treat the syphilis in any surviving participants.

Doctors in the service say they are now rendering whatever other medical services they can give to the survivors while the study of the disease's effects continues.

Dr. Merlin K. DuVal, Assistant Secretary of Health, Education and Welfare for Health and Scientific Affairs, expressed shock on learning of the study. He said that he was making an immediate investigation.

The experiment, called the Tuskegee Study, began in 1932 with about 600 black men.

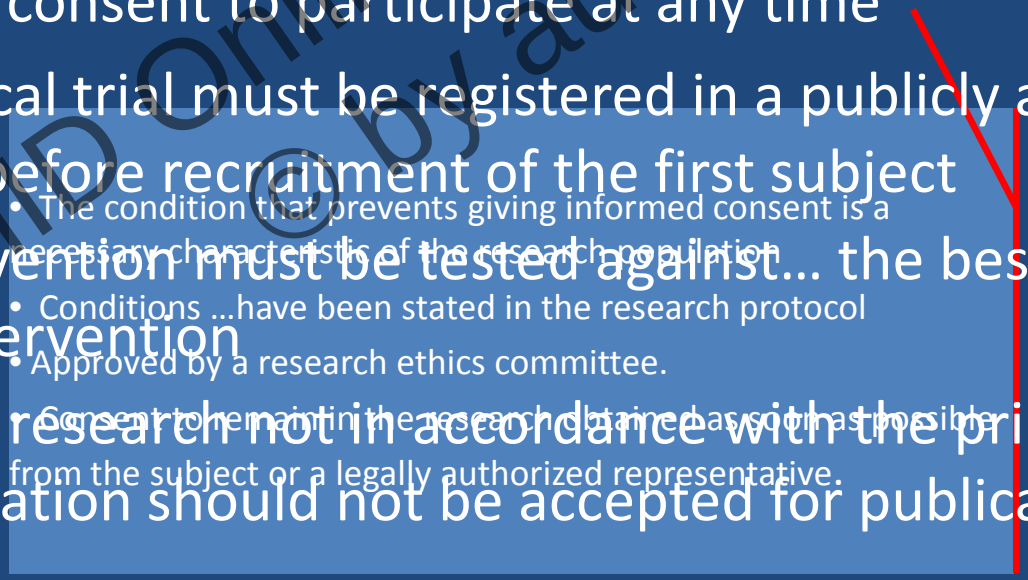
Example

- *"Patients were not told before admission that they were to get special treatment; C patients did not know throughout their stay in hospital that they were control patients in a special study; they were in fact treated as they would have been in the past, the sole difference being that they had been admitted to the centre more rapidly than was normal. Usually they were not in the same wards as S patients, but the same regimen was maintained."*

Streptomycin treatment of pulmonary tuberculosis: a Medical Research Council investigation. BMJ 1948;2:769-82.

Since then…

- The research protocol must be submitted for… approval to a research ethics committee before the study begins
- Each potential subject must be adequately informed… of the study and …the right to refuse to participate in the study or to withdraw consent to participate at any time
- Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject
- New intervention must be tested against… the best current proven intervention
- Reports of research not in accordance with the principles of this Declaration should not be accepted for publication



WMA Declaration of Helsinki

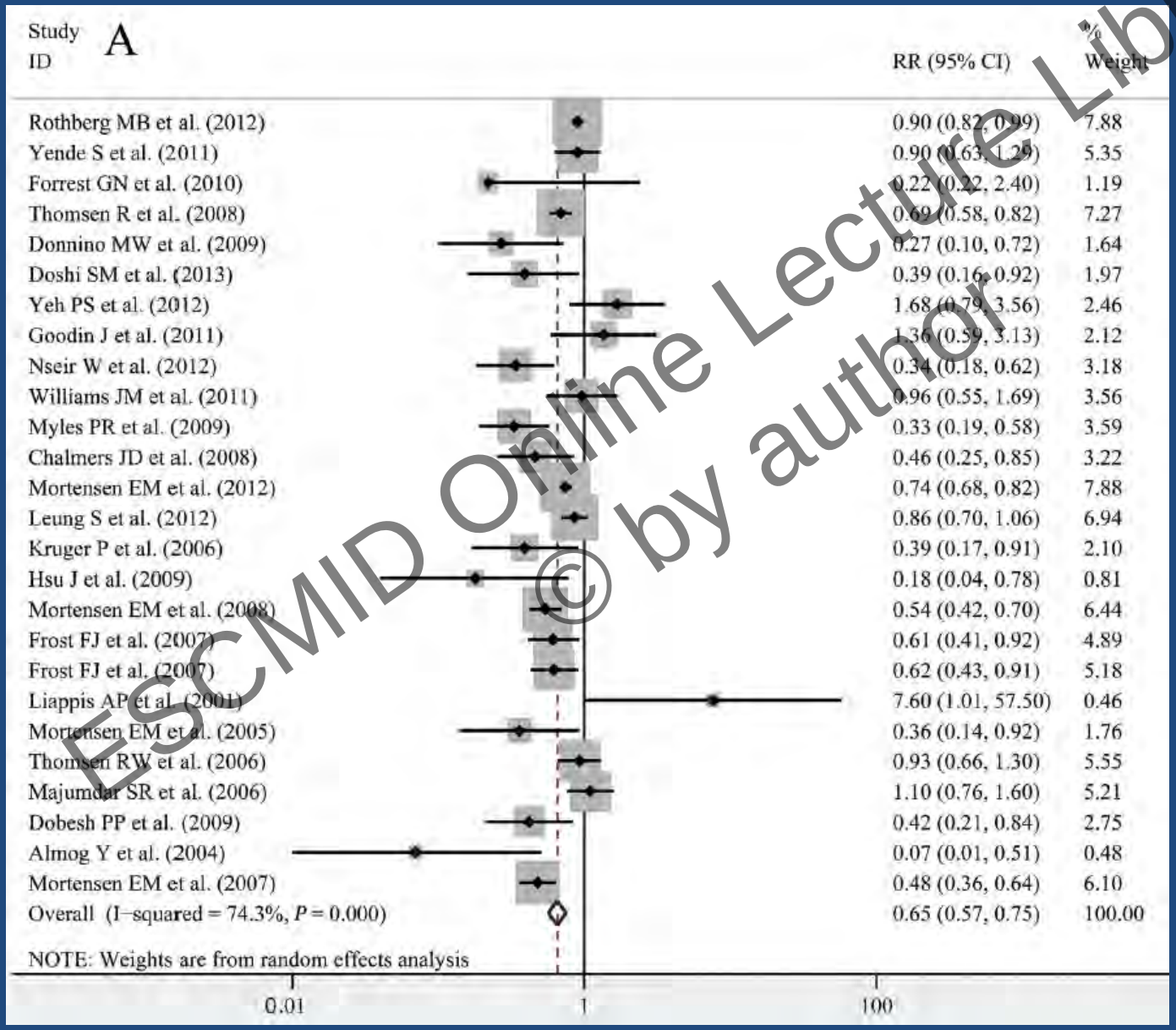
Grey zone

- Best current proven intervention
- Critically-ill patients
- Quality improvement interventions
  - Infection control
- Intervention not applied directly to the individual patient
  - Decision support systems
- Non-interventional studies

Advantages of guideline adherence

- Better trial design
- Attention to methodological and ethical aspects
- Organized protocol that is universally recognizable
- No omissions
- Avoid content replication
- Saves time
- Data available later for reporting by standards

Statins for sepsis – observational studies



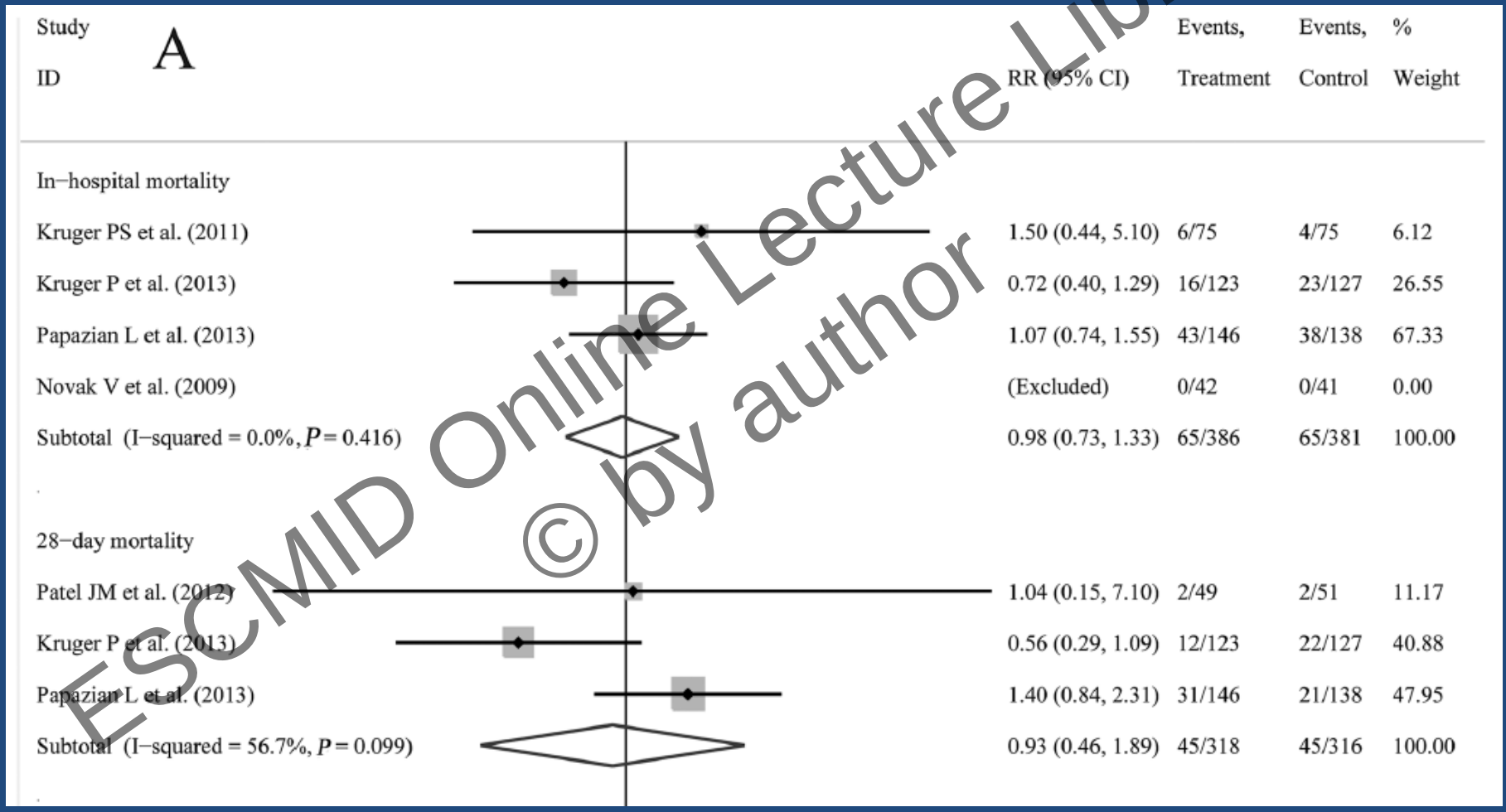
Adjusted effect estimates

Pooled RR 0.65 (0.57-0.75)

Statins for sepsis – RCTs

Wan et al. Crit Care. 2014

Statins for sepsis – RCTs



Pooled RRs 0.98 (0.73-1.33) and 0.92 (0.46-1.89)

Invest your time in RCTs

Thank you