Introduction to Systematic Reviews

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Case Study 1: “Egg on their faces: the story of human albumin solution”*

- Human albumin solution, a blood product, has been used in the treatment of blood loss and burns since the attack on Pearl Harbour over half a century ago.
- In the UK alone, an estimated 100,000 patients are treated with human albumin solution each year, at a cost to the NHS of close to 12 million.
- In 1996, the global albumin market was worth £900,000.
- But is human albumin administration beneficial?

*1. Roberts I, et al. Egg on their faces. The story of human albumin solution. Eval Health Prof. 2002;25(1):130-8.
2. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. BMJ 1998;317:235-40.

“Egg on their faces: the story of human albumin solution”

- To answer this question a systematic review of controlled trials comparing albumin with crystalloid was conducted by the Cochrane Injuries Group.
- 30 RCTs including 1419 randomised patients identified.
- A meta-analysis showed that the risk of death among those treated with albumin was higher than in the comparison groups.
- The pooled risk ratio was 1.68 (95% CI 1.26, 2.23)
- The data suggested that for every seventeen critically ill patients treated with albumin there is one extra death.

Roberts I, et al. Egg on their faces. The story of human albumin solution. Eval Health Prof. 2002;25(1):130-8.

“Egg on their faces: the story of human albumin solution”

- “Despite vigorous attempts by the plasma products industry to limit the impact of the systematic review on albumin sales, the use of albumin declined steeply.
- Throughout the UK albumin sales fell by 40%.
- The decline in albumin use occurred despite vigorous criticism of the review in the letters pages of the BMJ.
- The decline in albumin sales is a clear indication that doctors took into account the evidence presented in the systematic review and that many doctors changed their practice in response.”

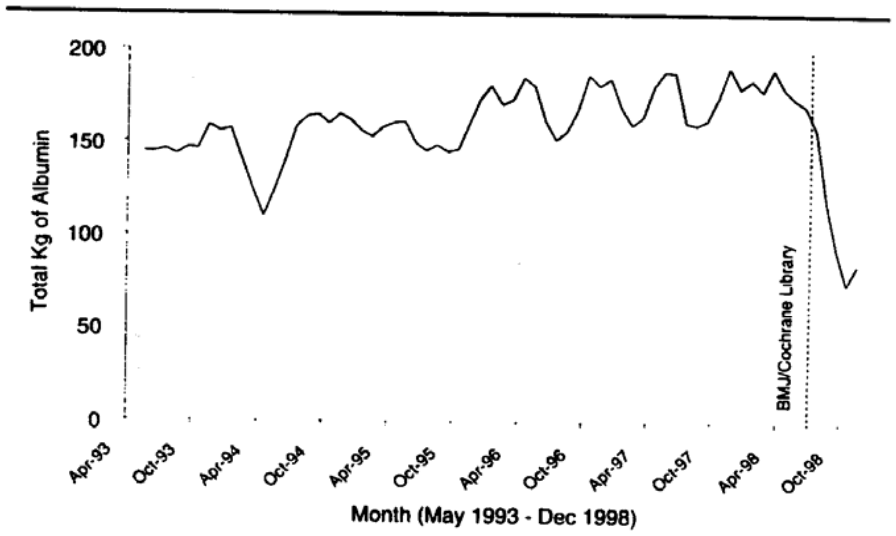


Figure 1: Albumin Sales in Scotland and Northern Ireland Before and After Publication of Systematic Review on Human Albumin Administration in Critically Ill Patients

Roberts I, et al. Egg on their faces. The story of human albumin solution. Eval Health Prof. 2002;25(1):130-8.

Annals of Internal Medicine | ARTICLE

Patient Survival after Human Albumin Administration

A Meta-Analysis of Randomized, Controlled Trials

Mahlon M. Wilkes, PhD, and Roberta J. Navickis, PhD

Purpose: To test the hypothesis that albumin administration is not associated with excess mortality.

Data Sources: Computer searches of the MEDLINE and EMBASE databases, the Cochrane Library, and Internet documents; hand searching of medical journals; inquiries to investigators and medical directors; and review of reference lists.

Study Selection: Randomized, controlled trials comparing albumin therapy with crystalloid therapy, no albumin, or lower doses of albumin.

Data Extraction: Two investigators independently extracted data. The primary end point was relative risk for death. Criteria used to assess methodologic quality were blinding, method of allocation concealment, presence of mortality as a study end point, and crossover. Small-trial bias was also investigated.

Data Synthesis: Fifty-five trials involving surgery or trauma, burns, hypoalbuminemia, high-risk neonates, ascites, and other indications were included. Albumin administration did not significantly affect mortality in any category of indications. For all trials, the relative risk for death was 1.11 (95% CI, 0.95 to 1.28). Relative risk was lower among trials with blinding (0.73 [CI, 0.48 to 1.12]; $n = 7$), mortality as an end point (1.00 [CI, 0.84 to 1.18]; $n = 17$), no crossover (1.04 [CI, 0.89 to 1.22]; $n = 35$), and 100 or more patients (0.94 [CI, 0.77 to 1.14]; $n = 10$). In trials with two or more such attributes, relative risk was further reduced.

Conclusions: Overall, no effect of albumin on mortality was detected; any such effect may therefore be small. This finding supports the safety of albumin. The influence of methodologic quality on relative risk for death suggests the need for further well-designed clinical trials.

Ann Intern Med. 2001;135:149-164. www.annals.org

For author affiliations, current addresses, and contributions, see end of text.

See editorial comment on pp 205-208.

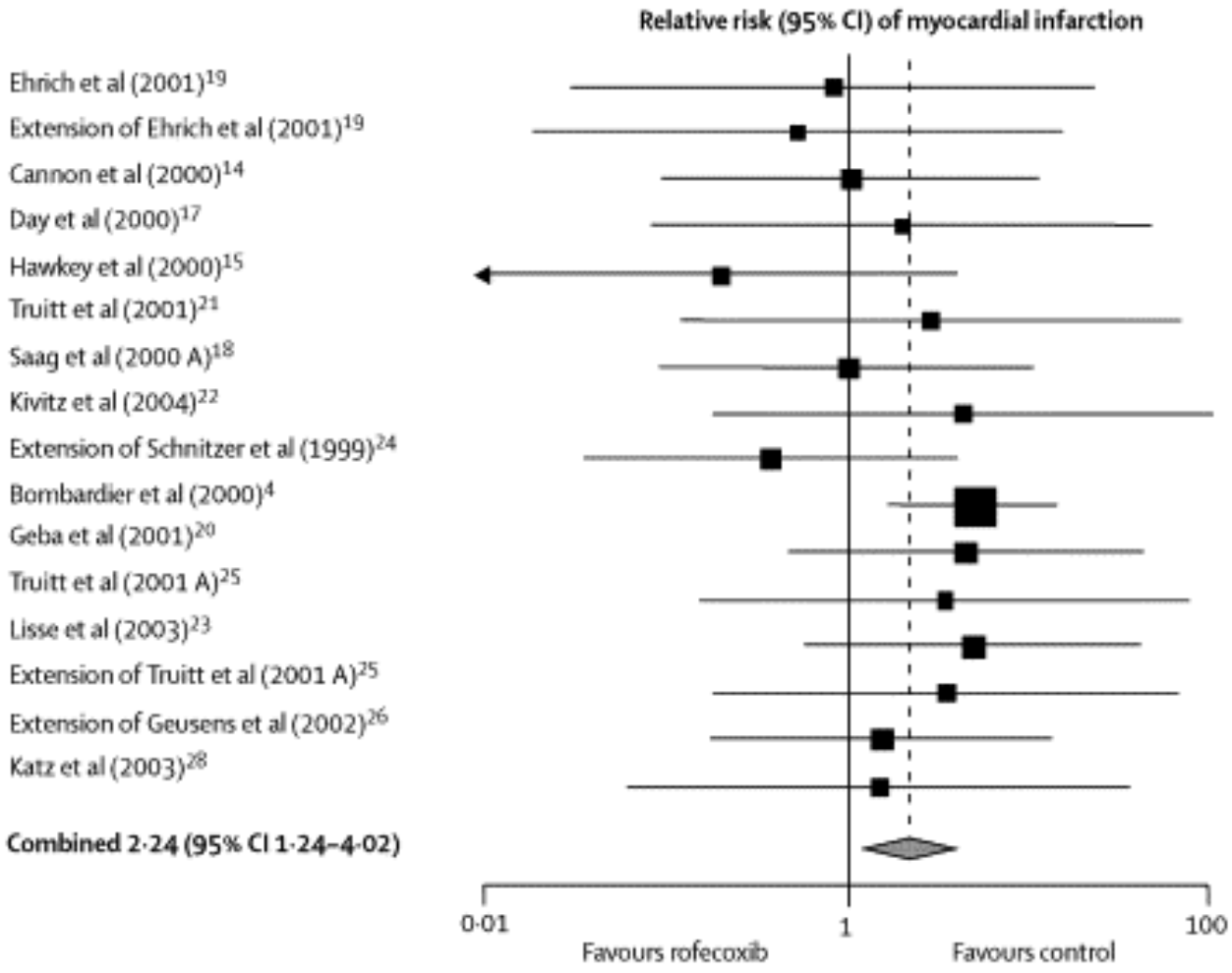
Funded by: Plasma Protein Therapeutics Association (PPTA), the primary advocate for the world's leading producers of plasma-based and recombinant biological therapeutics

Case study 2: The Vioxx story

- On Sept 30, 2004, Merck announced the withdrawal of rofecoxib (Vioxx) because of an increased cardiovascular risk in patients taking the drug for >18 months
- Decision was based on the 3-year results of the unpublished APPROVe study, a RTC of rofecoxib for the prevention of colorectal polyps in patients with a history of colorectal adenomas
- By 2004, rofecoxib had been taken by ~ 80 million people (sales US$2·5 billion)
- Juni et al. did a meta-analysis of 18 RCTs and 11 observational studies
- By the end of 2000 (52 events, 20742 patients) the relative risk from RTCs was 2·30 (95% CI 1·22–4·33, p=0·010), and 1 year later (64 events, 21432 patients) it was 2·24 (1·24–4·02, p=0·007).
- Juni et al. concluded that “rofecoxib should have been withdrawn several years earlier; the reasons why manufacturer and drug licensing authorities did not continuously monitor and summarise the accumulating evidence need to be clarified”

Juni et al. Lancet 2004 Dec 4-10;364(9450):2021-9

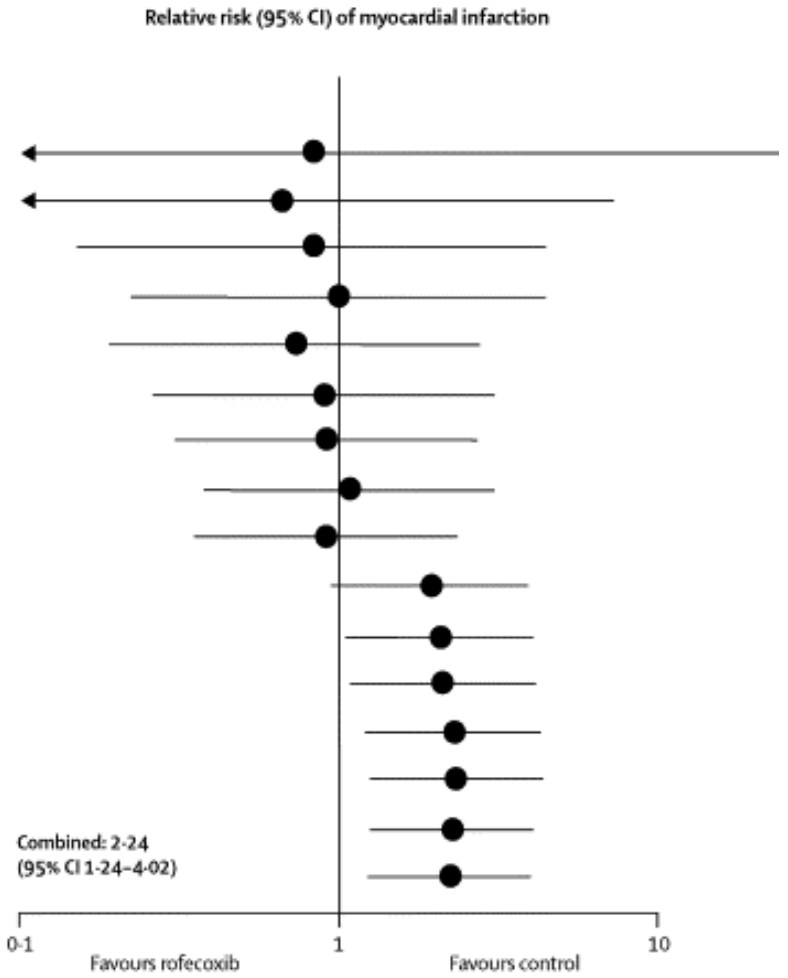
Case study 2: The Vioxx story



Juni et al. Lancet 2004 Dec 4-10;364(9450):2021-9

Case study 2: The Vioxx story

Year	Patients	Events	p
1997	523	1	0·916
1998	615	2	0·736
	1399	5	0·828
	2208	6	0·996
	2983	8	0·649
	3324	9	0·866
1999	4017	12	0·879
	5059	13	0·881
2000	5193	16	0·855
	13 269	40	0·070
	14 247	44	0·034
	15 156	46	0·025
	20 742	52	0·010
2001	20 742	58	0·007
	20 742	63	0·007
	21 432	64	0·007



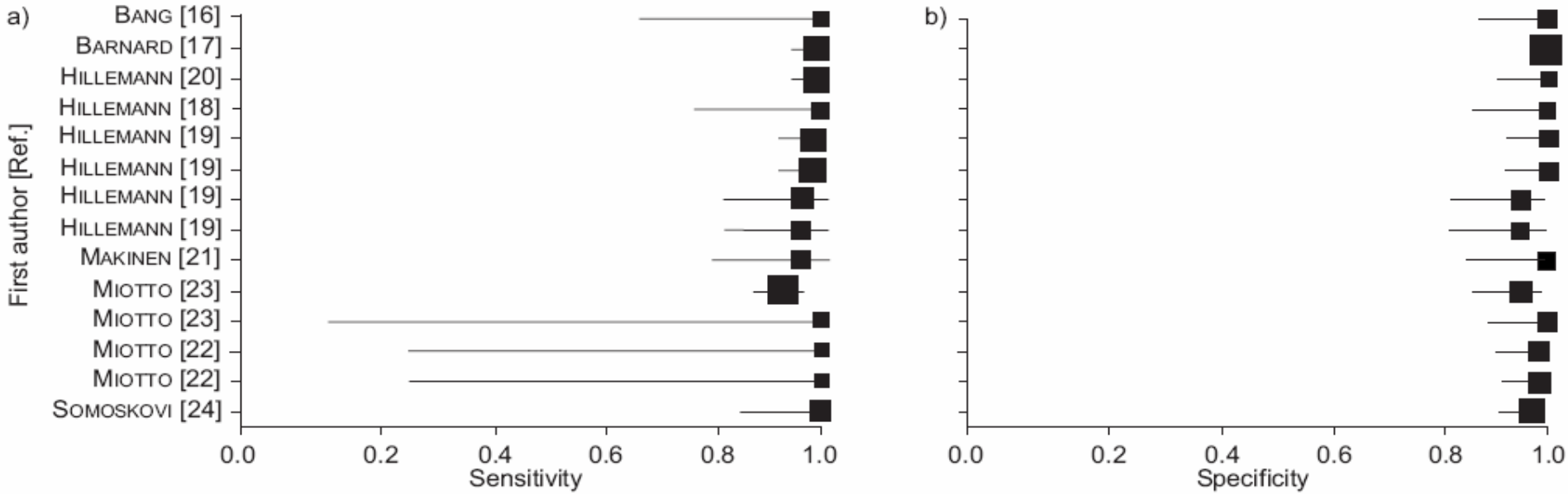
Juni et al. Lancet 2004 Dec 4-10;364(9450):2021-9

Case study 3: line probe assays for rapid diagnosis of MDR-TB

Eur Respir J 2008; 32: 1–10
DOI: 10.1183/09031936.00061808

GenoType MTBDR assays for the diagnosis of multidrug-resistant tuberculosis: a meta-analysis

D.I. Ling*, A.A. Zwerling* and M. Pai*,#



Ling, Zwerling & Pai. ERJ 2008

New WHO policy on line probe assays (2008)

World Health Organization

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Tuberculosis (TB)

WHO > Programmes and projects > Tuberculosis (TB) > TB news - past home page features

printable version

Rapid tests for drug-resistant TB to be available in developing countries

WHO/G. Thomas

30 JUNE 2008 | GENEVA -- People in low-resource countries who are ill with multidrug-resistant TB (MDR-TB) will get a faster diagnosis -- in two days, not the standard two to three months -- and appropriate treatment thanks to two new initiatives unveiled today by WHO, the Stop TB Partnership, UNITAID and the Foundation for Innovative New Diagnostics (FIND).

MDR-TB is a form of TB that responds poorly to standard treatment because of resistance to the first-line drugs isoniazid and rifampicin. At present it is estimated that only 2% of MDR-TB cases worldwide are being diagnosed and treated appropriately, mainly because of inadequate laboratory services. The initiatives announced today should increase that proportion at least seven-fold over the next four years, to 15% or more.

"I am delighted that this initiative will improve both the technology needed to diagnose TB quickly, and increase the availability of drugs to treat highly resistant TB," said British Prime Minister Gordon Brown, who helped launch the Stop TB Partnership's Global Plan to Stop TB in 2006 and whose government is a founding member of UNITAID. "The UK is committed to stopping TB around the world, from our funding of TB prevention programmes in poor countries, to our support of cutting edge research to develop new drugs."

In developing countries most TB patients are tested for MDR-TB only after they fail to respond to standard treatments. Even then, it takes two months or more to confirm the diagnosis. Patients have to wait for the test results before they can receive life-saving second-line drugs. During this period, they can spread the multidrug-resistant disease to others. Often the patients die before results are known, especially if they are HIV-infected in addition to having MDR-TB.

RELATED DOCUMENTS

WHO policy statement [pdf 78kb]

Expert group report - *Molecular line probe assays for rapid screening of patients at risk of MDR-TB* [pdf 892kb]

Further information on the UNITAID MDR-TB diagnostic initiative [pdf 652kb]

Feasibility study - Am J Respir Crit Care Med, Vol 177, pp 787-792, 2008 (American Thoracic Society - official journal). *Rapid molecular screening for multidrug-resistant tuberculosis in a high-volume public health laboratory in South Africa* [pdf 402kb]

Turning evidence into policy and policy into practice - the steps to building Lesotho's modern TB central laboratory [pdf 2.71Mb]

GenoType MTBDR assays for the diagnosis of multidrug-resistant tuberculosis: a meta-analysis. *Eur Resp J* 2008

A commercial line probe assay for the rapid detection of rifampicin resistance in Mycobacterium tuberculosis: a

http://www.who.int/tb/features_archive/mdrtb_rapid_tests/en/index.html

EXPERT REVIEWS

Rapid diagnosis of drug-resistant TB using line probe assays: from evidence to policy

Expert Rev. Resp. Med. 2(5), 583–588 (2008)

Daphne I Ling,
Alice A Zwerling and
Madhukar Pai†

Growing concerns about the spread of multidrug-resistant tuberculosis (MDR-TB) and the emergence of extensively drug-resistant TB have triggered substantial interest in the development and application of rapid tests for the detection of drug-resistant TB. Molecular assays to detect

New initiatives by WHO, Stop TB Partnership, UNITAID and FIND

Rapid tests for drug-resistant TB to be made available in developing countries

The availability of rapid tests to detect MDR-TB in several developing countries was announced on 30 June 2008 during a press conference held at Palais des Nations. *From left to right:* Dr. Robert Matiru, General Manager, Global Drug Facility; Dr. Giorgio Roscigno, FIND CEO; Dr. Mario Raviglione, Director, WHO Stop TB Department; and Dr. Jorge Bermudez, Executive Secretary of UNITAID

Geneva -- People in low-resource countries who are ill with multidrug-resistant (MDR) TB will get a faster diagnosis -- in two days, not the standard two to three months -- and appropriate treatment thanks to two new initiatives unveiled today by the World Health Organization (WHO), the Stop TB Partnership, UNITAID and the Foundation for Innovative New Diagnostics (FIND).

MDR-TB is a form of TB that responds poorly to standard treatment because of resistance to the first-line drugs isoniazid and rifampicin. At present it is estimated that only 2% of MDR-TB cases worldwide are being diagnosed and treated appropriately, mainly because of inadequate laboratory services. The initiatives announced today should increase that proportion at least seven-fold over the next four years, to 15% or more.

Countries that will receive MDR-TB diagnostics through this initiative:

Azerbaijan, Bangladesh, Côte d'Ivoire, the Democratic Republic of Congo, Ethiopia, Georgia, Indonesia, Kazakhstan, Kyrgyzstan, Lesotho, Republic of Moldova, Myanmar, Tajikistan, Ukraine, Uzbekistan, Viet Nam

http://www.finddiagnostics.org/

How evidence informs practice and policy: examples from TB

OPEN ACCESS Freely available online

PLoS MEDICINE

Research in Translation

Evidence-Based Tuberculosis Diagnosis

Madhukar Pai*, Andrew Ramsay, Richard O'Brien

There is great excitement in the tuberculosis (TB) scientific community over the introduction of new tools into TB control activities. The development of new tools is an important component of the Global Plan to Stop TB and the World Health Organization's new global Stop TB Strategy [1,2]. Anticipating the introduction of new tools, the Stop TB Partnership has established a Retooling Task Force to develop a framework for engaging policy makers to foster accelerated adoption and implementation of new tools into TB control programs [3].

While new tools offer great promise in clinical medicine and in public health, limited resources and the movement toward evidence-based guidelines and policies require careful validation of new tools prior to their introduction for routine use. The world spends an estimated US$1 billion per year on diagnostics for TB [4]. It is important to ensure that

steps involved in the policy process include a comprehensive review of the evidence, as well as expert opinion and judgment (Box 1).

High-quality evidence on TB diagnostics is critical for the development of evidence-based policies on TB diagnosis, and, ultimately, for effective control of the global TB epidemic. While primary diagnostic trials are needed to generate data on test accuracy and operational performance, systematic reviews provide the best synthesis of current evidence on any given diagnostic test [8]. Although a large number of trials on TB diagnostics have been published, surprisingly, no systematic reviews were published until recently. In the past few years, at least 30 systematic reviews and meta-analyses have been published on various TB tests [9–38]. These reviews have synthesized the results of more than 1,000 primary studies, providing valuable insights into the diagnostic accuracy of various tests (Table 1, Box 2).

in the latter setting. However, meta-analyses on IGRAs have highlighted the lack of evidence on the predictive ability of these assays in identifying those individuals with TB infection who are at highest risk for progressing to active disease. Several cohort studies are ongoing (reviewed elsewhere [39]), and these should provide useful evidence on this unresolved issue.

For active TB, serological tests have been attempted for decades. Two meta-analyses have convincingly shown that existing commercial antibody-based tests have poor accuracy and limited clinical utility [29,30]. Despite this evidence, dozens of commercial serological tests continue to be marketed, mostly in private sectors of countries that lack diagnostic regulatory bodies [4].

Nucleic acid amplification tests (NAATs) were considered to be a major breakthrough in TB diagnosis when they were first introduced. A series of meta-analyses have shown

Pai M, Ramsay A, O'Brien R (2008) Evidence-based tuberculosis diagnosis. PLoS Med 5(7): e156.

What is evidence-based medicine?

The practice of EBM is the integration of

- individual clinical expertise

  with the

- best available external clinical evidence from systematic research and
- patient's values and expectations

http://www.cebm.net/index.asp

The importance of research synthesis

- We need evidence for both clinical practice and for public health decision making
- Where does evidence come from?
  - An good review is a state-of-the-art synthesis of current evidence on a given research question
  - Given the explosion of medical literature, and the fact that time is always scarce, review articles play a big role in decision-making
  - According to one estimate, to keep up to date in Internal Medicine, need to read 17 articles a day, 365 days a year!

The importance of research synthesis

- Given that most clinicians and public health professionals do not have the time to track down all the original articles, critically read them, and obtain the evidence they need for their questions,
  - Systematic reviews and clinical practice guidelines may be their best source of evidence
    - Several “pre-digested” sources of evidence are currently available
    - The EBM movement is heavily dependent on these pre-appraised evidence sources

Hierarchy of evidence

Grade of Recommendation	Level of Evidence	Therapy/Prevention, Aetiology/Harm	Prognosis	Diagnosis	Economic analysis
A	1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; or a CPG† validated on a test set.	SR (with homogeneity*) of Level 1 diagnostic studies; or a CPG validated on a test set.	SR (with homogeneity*) of Level 1 economic studies
	1b	Individual RCT (with narrow Confidence Interval‡)	Individual inception cohort study with ≥ 80% follow-up	Independent blind comparison of an appropriate spectrum of consecutive patients, all of whom have undergone both the diagnostic test and the reference standard.	Analysis comparing all (critically-validated) alternative outcomes against appropriate cost measurement, and including a sensitivity analysis incorporating clinically sensible variations in important variables.
	1c	All or none§	All or none case-series¶	Absolute SpPins and SnNouts††	Clearly as good or better‡‡, but cheaper. Clearly as bad or worse but more expensive. Clearly better or worse at the same cost.
B	2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs.	SR (with homogeneity*) of Level ≥2 diagnostic studies	SR (with homogeneity*) of Level ≥2 economic studies
	2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; or CPG not validated in a test set.	Independent blind comparison but either in non-consecutive patients, or confined to a narrow spectrum of study individuals (or both), all of whom have undergone both the diagnostic test and the reference standard; or a diagnostic CPG not validated in a test set.	Analysis comparing a limited number of alternative outcomes against appropriate cost measurement, and including a sensitivity analysis incorporating clinically sensible variations in important variables.
	2c	"Outcomes" Research	"Outcomes" Research		
	3a	SR (with homogeneity*) of case-control studies			
	3b	Individual Case-Control Study		Independent blind comparison of an appropriate spectrum, but the reference standard was not applied to all study patients	Analysis without accurate cost measurement, but including a sensitivity analysis incorporating clinically sensible variations in important variables.
C	4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies¶¶)	Reference standard was not applied independently or not applied blindly	Analysis with no sensitivity analysis
D	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory

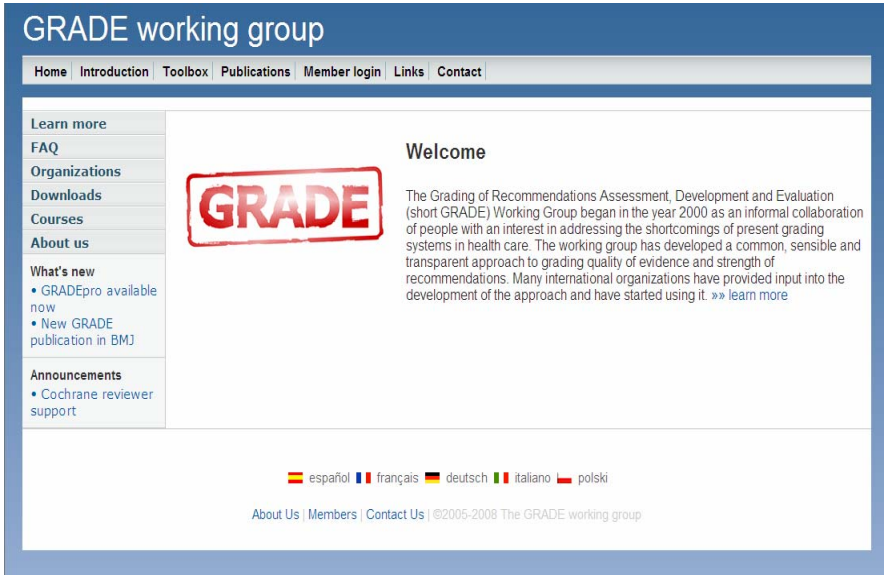
Guidelines and recommendations: GRADE

ANALYSIS

RATING QUALITY OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

GRADE: an emerging consensus on rating quality of evidence and strength of recommendations

Guidelines are inconsistent in how they rate the quality of evidence and the strength of recommendations. This article explores the advantages of the GRADE system, which is increasingly being adopted by organisations worldwide



http://www.gradeworkinggroup.org/

Guidelines and recommendations: GRADE

Box 2 | Quality of evidence and definitions

High quality— Further research is very unlikely to change our confidence in the estimate of effect

Moderate quality— Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality— Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality— Any estimate of effect is very uncertain

Factors in deciding on quality of evidence

Factors that might decrease quality of evidence

- Study limitations
- Inconsistency of results
- Indirectness of evidence
- Imprecision
- Publication bias
- Factors that might increase quality of evidence
- Large magnitude of effect
- Plausible confounding, which would reduce a demonstrated effect
- Dose-response gradient

http://www.gradeworkinggroup.org/

Guidelines and recommendations: GRADE

What do we mean by the strength of a recommendation?

The strength of a recommendation reflects the extent to which we can be confident that the desirable effects of an intervention outweigh the undesirable effects. Desirable effects of an intervention include reduction in morbidity and mortality, improvement in quality of life, reduction in the burden of treatment (such as having to take drugs or the inconvenience of blood tests), and reduced resource expenditures. Undesirable consequences include adverse effects that have a deleterious impact on morbidity, mortality, or quality of life or increase use of resources.

Quality of evidence

High quality	⊕⊕⊕⊕	or A
Moderate quality	⊕⊕⊕◯	or B
Low quality	⊕⊕◯◯	or C
Very low quality	⊕◯◯◯	or D

Strength of recommendation

Strong recommendation for using an intervention	↑ ↑	or 1
Weak recommendation for using an intervention	↑ ?	or 2
Weak recommendation against using an intervention	↓ ?	or 2
Strong recommendation against using an intervention	↓ ↓	or 1

Fig 2 Representations of quality of evidence and strength of recommendations

Determinants of strength of recommendation

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Costs (resource allocation)	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted

http://www.gradeworkinggroup.org/

Essay

Doing New Research? Don't Forget the Old

Nobody should do a trial without reviewing what is known

Mike Clarke

On May 2, 1898, George Gould used his address to the founding meeting of the Association of Medical Librarians in Philadelphia to present a vision of the future of health information. 'I look forward,' he said, 'to such an organisation of the literary records of medicine that a puzzled worker in any part of the civilised world shall in an hour be able to gain a knowledge pertaining to a subject of the experience of every other man in the world' [1]. Has his vision been realised? good quality, but some of it is not. Thus, anyone wishing to use the health literature to make well-informed decisions must both identify the relevant research from amidst this vast amount of information and then appraise it. This is an impossible task for many. Even though making access to the literature easier and cheaper will increase the ability of people to find research, it will also reveal just how much information there is out there and how daunting is the task of making sense of it.

with one or more search engines? Almost certainly, as the speed of the search increased through these four

Citation: Clarke M (2004) Doing new research? Don't forget the old. PLoS Med 1(2): e35.

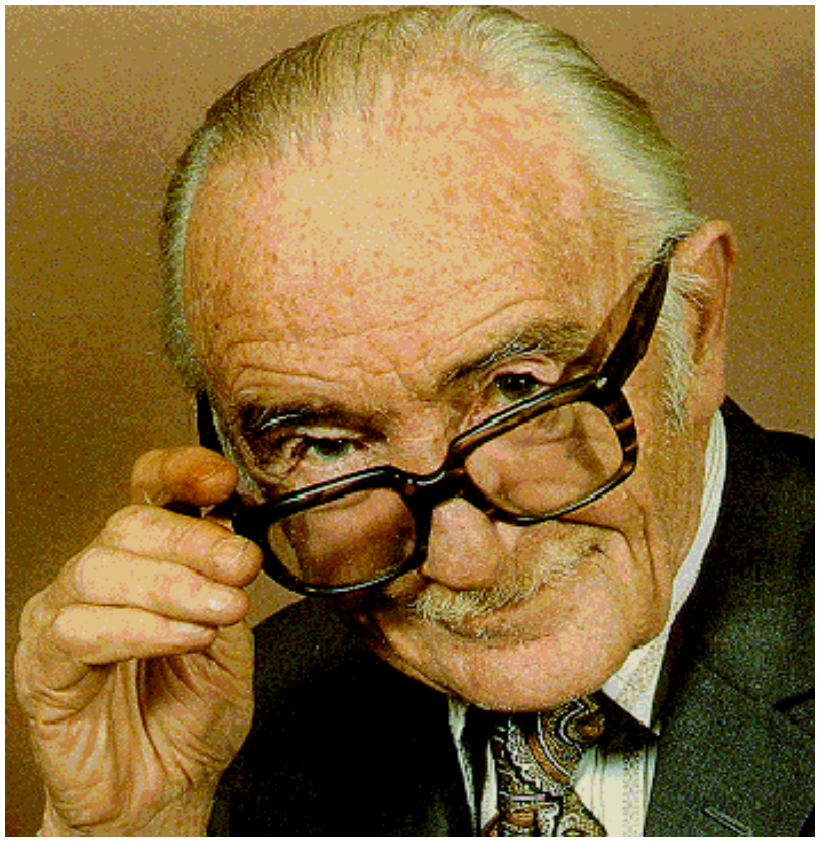
Mike Clarke is dir Cochrane Centre, mclarke@cochra

Box 1. Practical Suggestions for Researchers

- Conduct a systematic review of your research question before embarking on a new study, or identify a relevant review done by someone else.
- Design your study to take account of the relevant successes and failures of the prior studies, and of the evidence within them.
- Discuss the findings of your study in the context of an updated systematic review of relevant research.
- Publish the systematic review within, alongside, or shortly after the report of your study.
- Provide information from your study to others doing systematic reviews of similar topics.

Prof Archibald Cochrane, CBE (1909 - 1988)

- The Cochrane Collaboration is named in honour of Archie Cochrane, a British researcher.
- In 1979 he wrote, *"It is surely a great criticism of our profession that we have not organised a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomized controlled trials"*



Source: http://www.cochrane.org/cochrane/archieco.htm

The Cochrane Collaboration

- Archie Cochrane's challenge led to the establishment during the 1980s of an international collaboration to develop the *Oxford Database of Perinatal Trials*.
- His encouragement, and the endorsement of his views by others, led to the opening of the first Cochrane centre (in Oxford, UK) in 1992 and the founding of The **Cochrane Collaboration** in 1993.

Source: http://www.cochrane.org/cochrane/archieco.htm

The Cochrane Library

Evidence for healthcare decision-making

Welcome to The Cochrane Library

The Cochrane Library contains high-quality, independent evidence to inform healthcare decision-making. It includes reliable evidence from Cochrane and other systematic reviews, clinical trials, and more. Cochrane reviews bring you the combined results of the world's best medical research studies, and are recognised as the gold standard in evidence-based health care.

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Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases

Anti-histamines for prolonged non-specific cough in children

Exercise for the management of cancer-related fatigue in adults

Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes

Dopamine agonist therapy in early Parkinson's disease

House dust mite control measures for asthma

Interventions for enhancing medication adherence

Cognitive-behavioural interventions for preventing youth gang involvement for children and young people (7-16)

Interventions for treating wrist fractures in children

Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment

Short-course versus long-course antibiotic therapy for non-severe community-acquired pneumonia in children aged 2 months to 59 months

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As a new user we recommend you use the following resources to help you navigate through the evidence and get the most out of The Cochrane Library. More

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As a clinician you are under constant pressure to have high-quality, up-to-date evidence at your fingertips. More

For Researchers

The internet has given us instant access to a huge amount of research, but the large volume of available information is a problem in itself. More

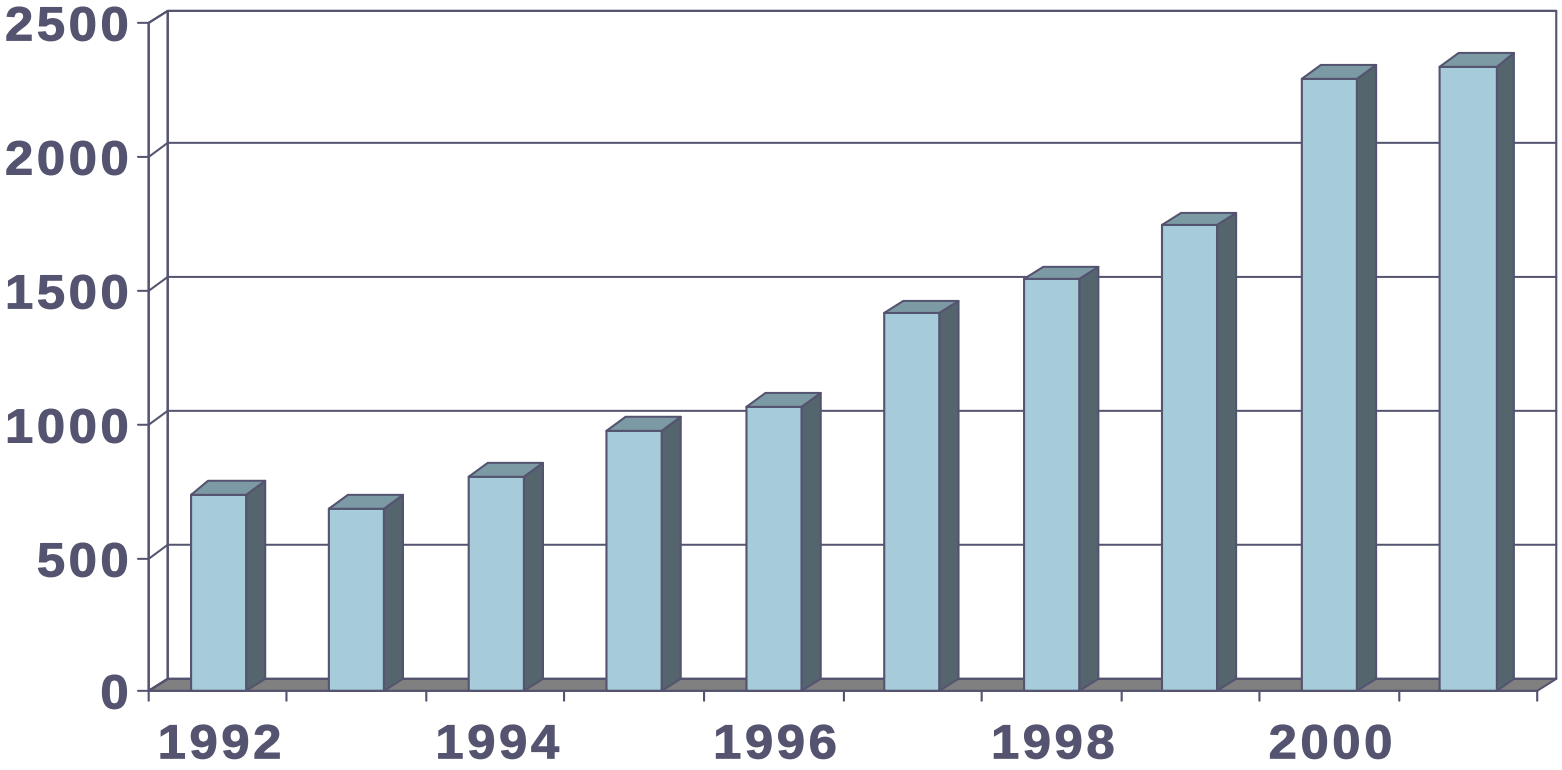
For Patients

Healthcare consumers and patients need high-quality evidence about the effectiveness of treatments. More

For Policy Makers

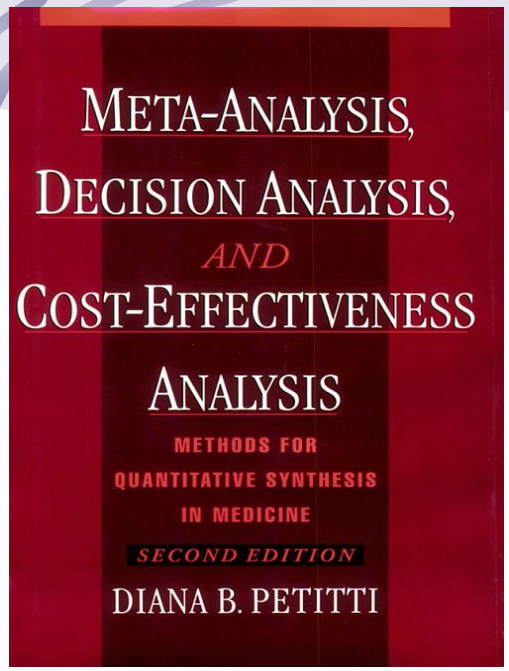
As a policy maker or healthcare manager you are a generalist in search of high-quality information across a broad range of issues. More

Systematic reviews/meta-analyses indexed in PubMed – 10 years



Search: meta-analysis(MeSH) OR meta-analysis(tw) OR systematic review(tw)

2500 SRs per year, of which about 20% are Cochrane reviews (estimate by Moher et al. PLoS Med 2007)


META-ANALYSIS,
DECISION ANALYSIS,
AND
COST-EFFECTIVENESS
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METHODS FOR
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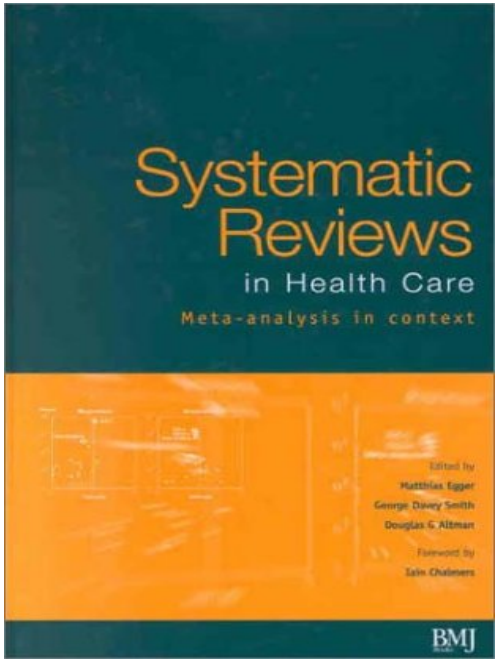
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Meta-analysis in context
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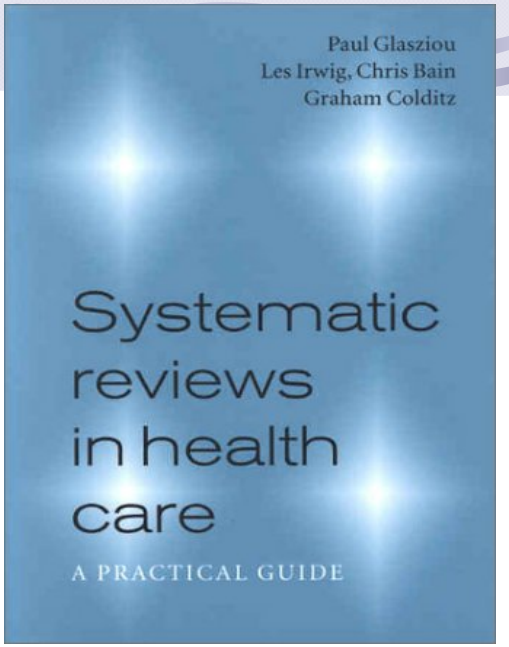
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Les Irwig, Chris Bain
Graham Colditz
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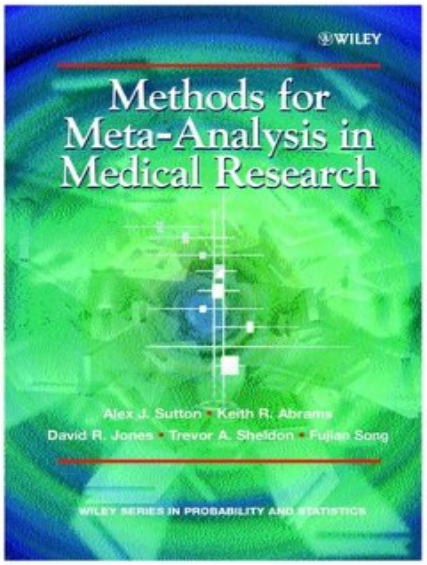
care
A PRACTICAL GUIDE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Methods for
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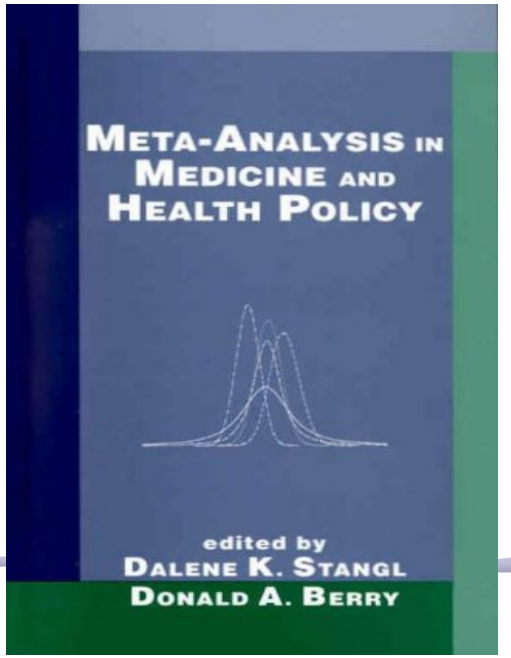
Medical Research
Alex J. Sutton • Keith R. Abrams
David R. Jones • Trevor A. Sheldon • Fujian Song
WILEY SERIES IN PROBABILITY AND STATISTICS


META-ANALYSIS IN
MEDICINE AND
HEALTH POLICY
edited by
DALENE K. STANGL
DONALD A. BERRY

March/April 1997
Volume 126 • Number 2

ACP Journal Club

Linking Research to Practice in Internal Medicine

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Vol. 2 No. 5 pp. 129-160 SEPTEMBER/OCTOBER 1997

Evidence-Based Medicine

American College of Physicians

BMJ Publishing Group

Centre for Reviews and Dissemination

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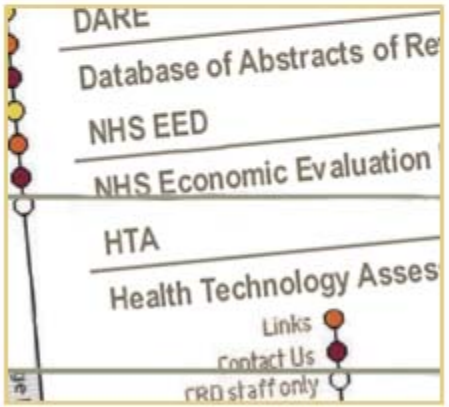


Centre for Reviews and Dissemination databases

CRD was established in January 1994, and produces and promotes the use of research based knowledge in health and social care.

DARE – (Database of Abstracts of Reviews of Effects) contains over 4000 abstracts of quality assessed and critically appraised systematic reviews. The database focuses on the effects of interventions used in health and social care.

NHS Economic Evaluation Database (NHS EED) contains over 6000 abstracts of quality assessed economic evaluations. The database aims to assist decision-makers by systematically identifying and describing economic evaluations, appraising their quality and highlighting their relative strengths and weaknesses.

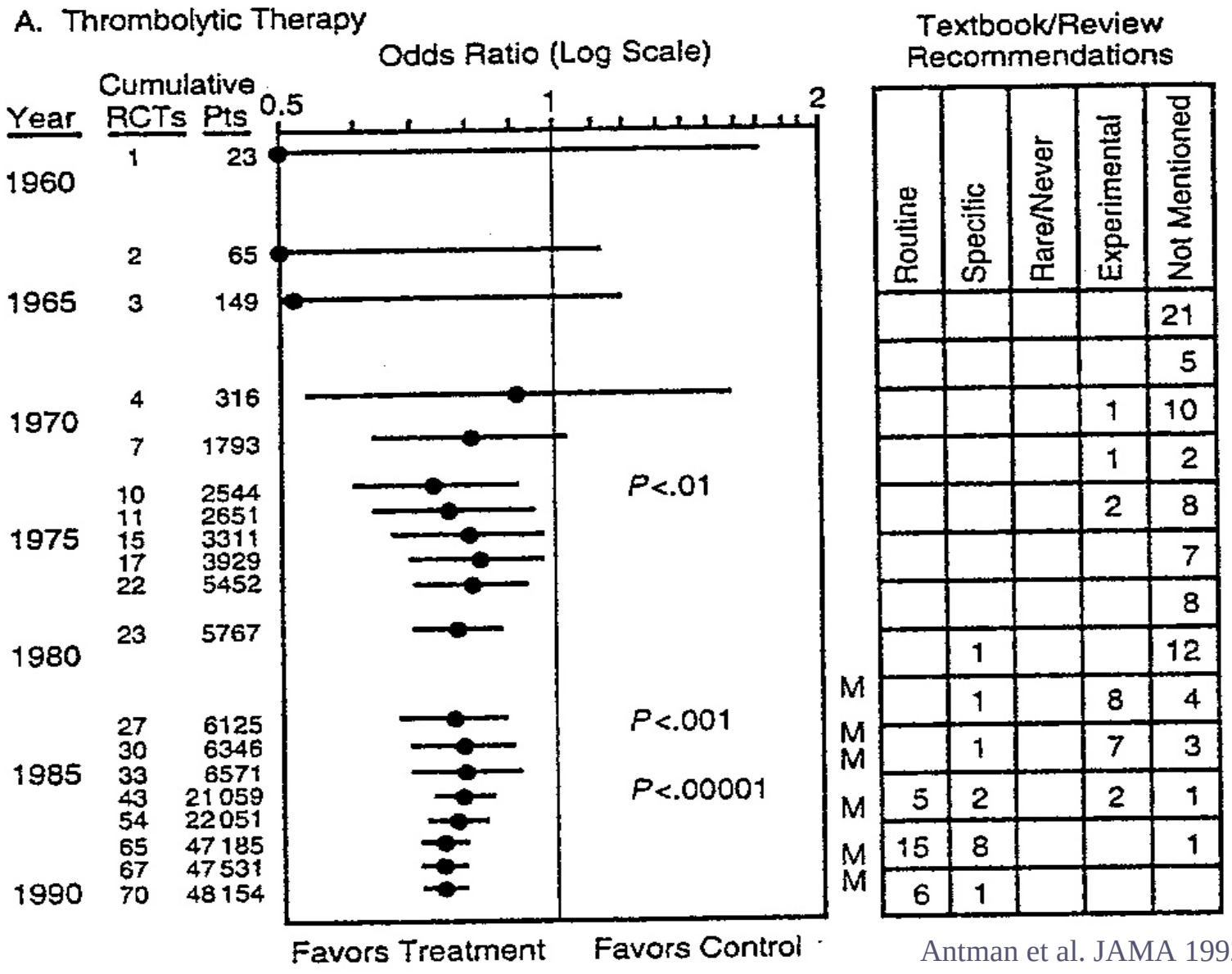
Both *DARE* and *NHS EED* include details of abstracts in the process of being written and these can be 'fast-tracked' on request.

The *HTA* database brings together details of completed and ongoing health technology assessments from around the world. The abstracts in the database are descriptive rather than analytical and do not form critical appraisals of the reports. The database is produced in collaboration with the INAHTA Secretariat, based at SBU, Sweden.

Are textbooks good sources of current evidence?

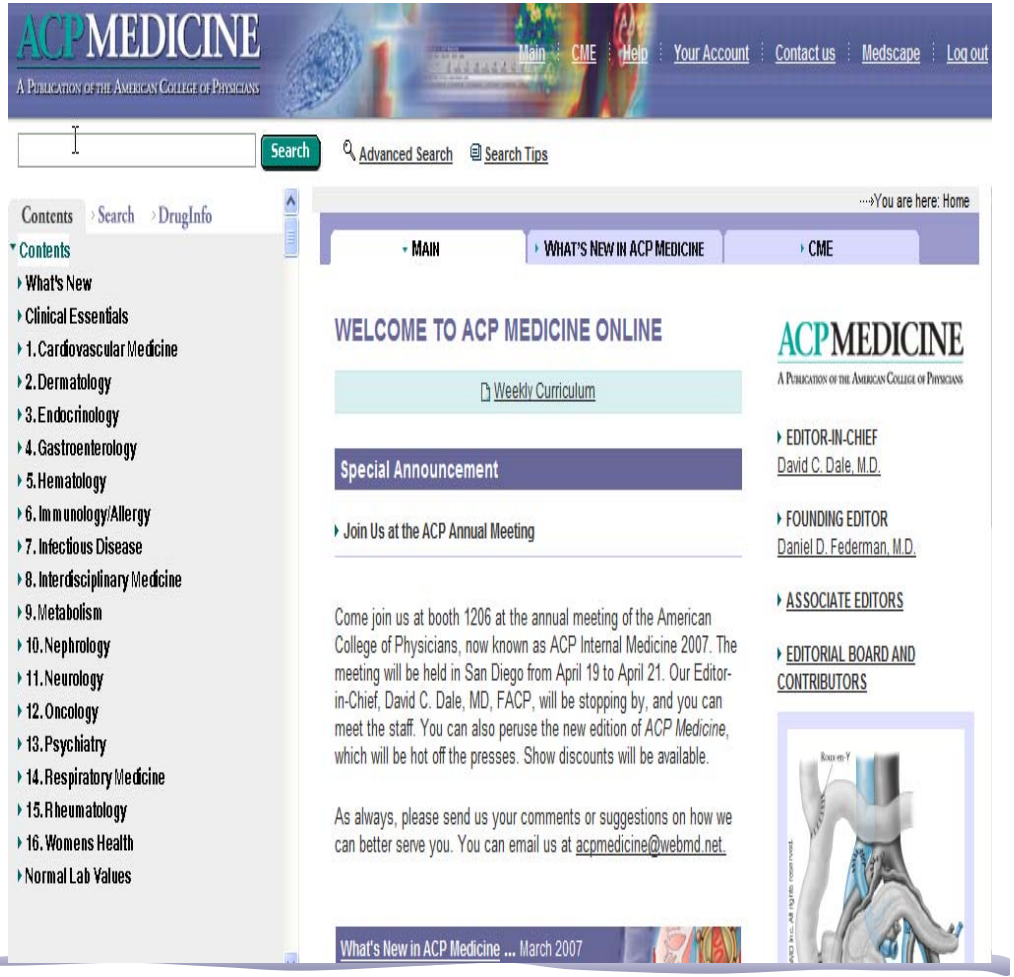
- Not always!
  - They are better for background questions than foreground questions
  - They are not updated frequently and often lag behind current evidence by many years
- Exceptions:
  - ACP Medicine [Scientific American Medicine]
  - UpToDate
  - Clinical Evidence
  - Harrison's Online
  - Emedicine (totally online text)

Evidence vs. textbook recommendations



Antman et al. JAMA 1992

Are textbooks good sources of current evidence?



Systematic reviews are done in different domains

OPEN ACCESS Freely available online

PLoS MEDICINE

Tuberculosis among Health-Care Workers in Low- and Middle-Income Countries: A Systematic Review

Rajnish Joshi[1,2], Arthur L. Reingold[1], Dick Menzies[3], Madhukar Pai[3*]

1 Division of Epidemiology, School of Public Health, University of California Berkeley, Berkeley, California, United States of America, 2 Department of Medicine, Mahatma Gandhi Institute of Medical Sciences, Sevagram, Maharashtra, India, 3 Montreal Chest Institute, McGill University, Montreal, Canada

Meta-analysis of “rates”

Systematic reviews are done in different domains

Annals of Internal Medicine | ARTICLE

Meta-analysis: New Tests for the Diagnosis of Latent Tuberculosis Infection: Areas of Uncertainty and Recommendations for Research

Dick Menzies, MD, MSc; Madhukar Pai, MD, PhD; and George Comstock, MD, DrPH

OPEN ACCESS Freely available online PLOS MEDICINE

Commercial Serological Antibody Detection Tests for the Diagnosis of Pulmonary Tuberculosis: A Systematic Review

Karen R. Steingart[1,2], Megan Henry[3], Suman Laal[4,5,6], Philip C. Hopewell[1,2], Andrew Ramsay[7], Dick Menzies[8,9], Jane Cunningham[7], Karin Weldingh[10], Madhukar Pai[8,9*]

Meta-analysis of “diagnostic accuracy [diagnosis]”

Systematic reviews are done in different domains

Tropical Medicine and International Health doi:10.1111/j.1365-3156.2006.01571.x

VOLUME 11 NO 6 PP 789–799 JUNE 2006

Chloroquine or amodiaquine combined with sulfadoxine–pyrimethamine for uncomplicated malaria: a systematic review

Jimee Hwang[1], Edward Bitarakwate[2], Madhukar Pai[3], Arthur Reingold[3], Philip J. Rosenthal[4] and Grant Dorsey[4]

1 *Department of Internal Medicine, University of California San Francisco, San Francisco, CA, USA*
2 *Elizabeth Glaser Pediatric AIDS Foundation, Kampala, Uganda*
3 *Division of Epidemiology, School of Public Health, University of California Berkeley, Berkeley, CA, USA*
4 *Department of Infectious Diseases, University of California San Francisco, San Francisco, CA, USA*

Meta-analysis of “RCTs [therapy]”

Systematic reviews are done in different domains

REVIEW ARTICLE

Risk of Tuberculosis From Exposure to Tobacco Smoke

A Systematic Review and Meta-analysis

Michael N. Bates, PhD; Asheena Khalakdina, PhD; Madhukar Pai, MD, PhD; Lisa Chang, MPH; Fernanda Lessa, MD, MPH; Kirk R. Smith, PhD

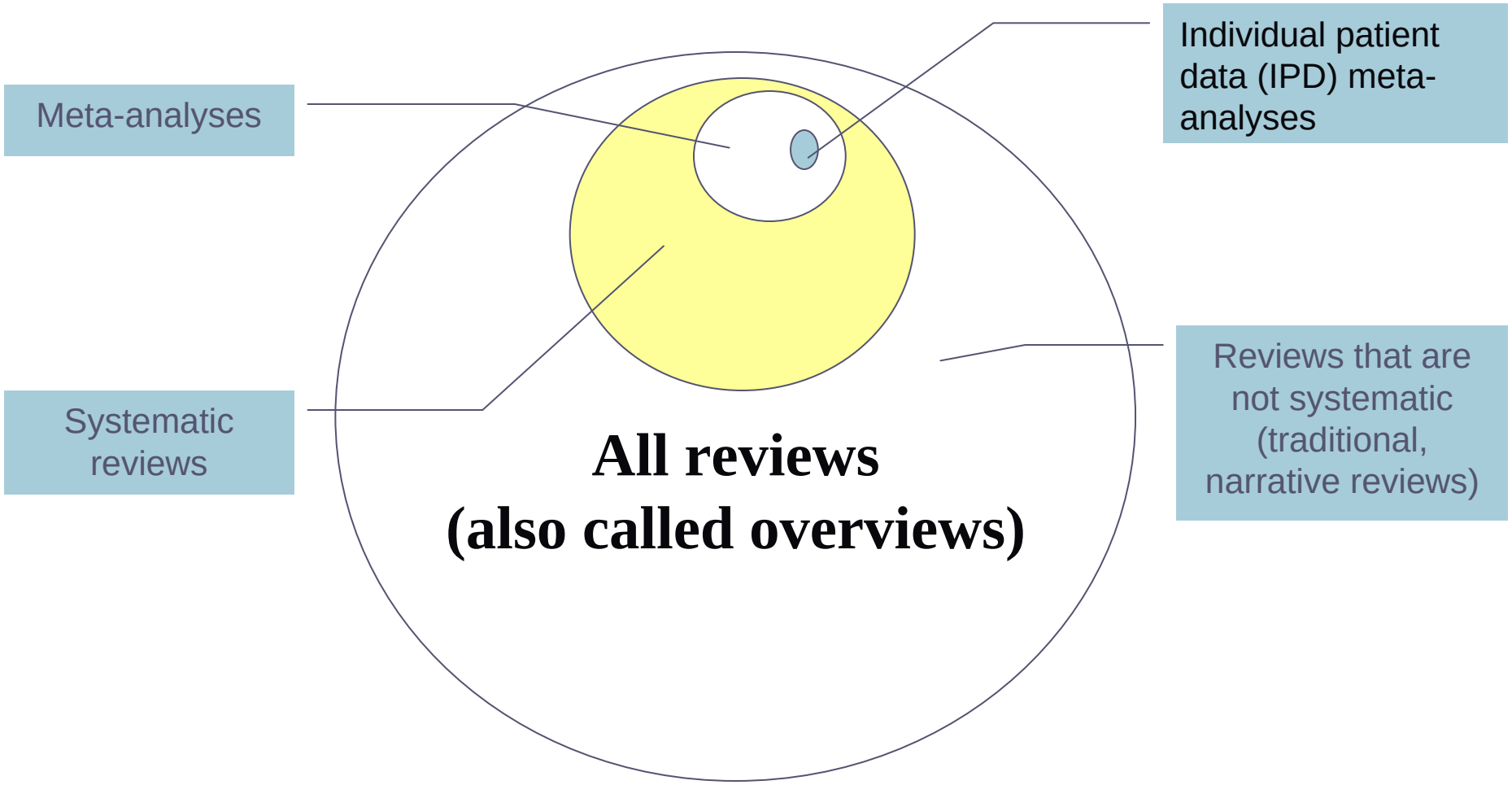
Arch Intern Med. 2007;167:335-342

Meta-analysis of “observational studies [etiology]”

Are these the same or different?

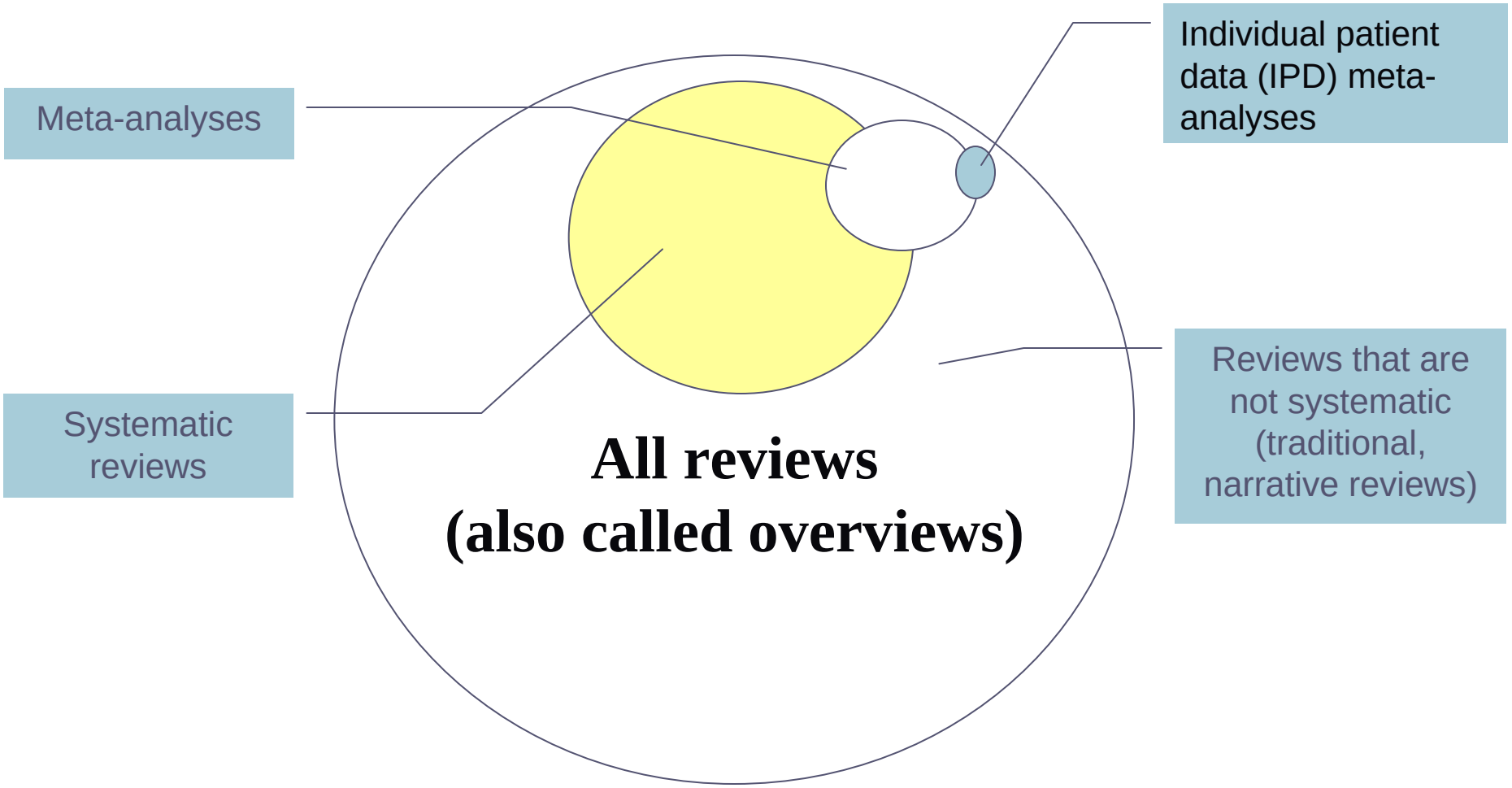
- Traditional, narrative review
- Systematic review
- Overview
- Meta-analysis
- Pooled analysis

Types of review articles



Pai M, et al. Systematic reviews and meta-analyses: An illustrated, step-by-step guide. *Natl Med J India* 2004;17(2):86-95.

In practice, not all meta-analyses are conducted as part of systematic reviews



Some definitions

- Traditional, narrative reviews, usually written by experts in the field, are qualitative, narrative summaries of evidence on a given topic. Typically, they involve informal and subjective methods to collect and interpret information.
- "A systematic review is a review in which there is a comprehensive search for relevant studies on a specific topic, and those identified are then appraised and synthesized according to a predetermined and explicit method."*

*Klassen et al. Guides for reading and interpreting systematic reviews. Arch Pediatr Adolesc Med 1998;152:700-704.

Some definitions

- "A meta-analysis is the statistical combination of at least 2 studies to produce a single estimate of the effect of the healthcare intervention under consideration."*
- Individual patient data meta-analyses (pooled analyses) involves obtaining raw data on all patients from each of the trials directly and then re-analyzing them.

*Klassen et al. Guides for reading and interpreting systematic reviews. Arch Pediatr Adolesc Med 1998;152:700-704.

Narrative vs. Systematic Reviews

TABLE I. Comparison of traditional and systematic reviews

Components of a review	Traditional, narrative reviews	Systematic reviews
Formulation of the question	Usually address broad questions	Usually address focused questions
Methods section	Usually not present, or not well-described	Clearly described with pre-stated criteria about participants, interventions and outcomes
Search strategy to identify studies	Usually not described; mostly limited by reviewers' abilities to retrieve relevant studies; usually not reproducible and prone to selective citation	Clearly described and usually exhaustive; transparent, reproducible and less prone to selective citation
Quality assessment of identified studies	Usually all identified studies are included without explicit quality assessment	Only high-quality studies are included using pre-stated criteria; if lower-quality studies included, the effects of this are tested in subgroup analyses
Data extraction	Methods usually not described	Usually undertaken by more than one reviewer onto pre-tested data forms; attempts often made to obtain missing data from authors of primary studies
Data synthesis	Qualitative description employing the 'vote counting' approach, where each included study is given equal weight, irrespective of study size and quality	Meta-analysis assigns higher weights to effect measures from more precise studies; pooled, weighted effect measures with confidence limits provide power and precision to results
Heterogeneity	Usually dealt with in a narrative fashion	Heterogeneity dealt with by graphical and statistical methods; attempts are often made to identify sources of heterogeneity
Interpreting results	Prone to cumulative systematic biases and personal opinion	Less prone to systematic biases and personal opinion

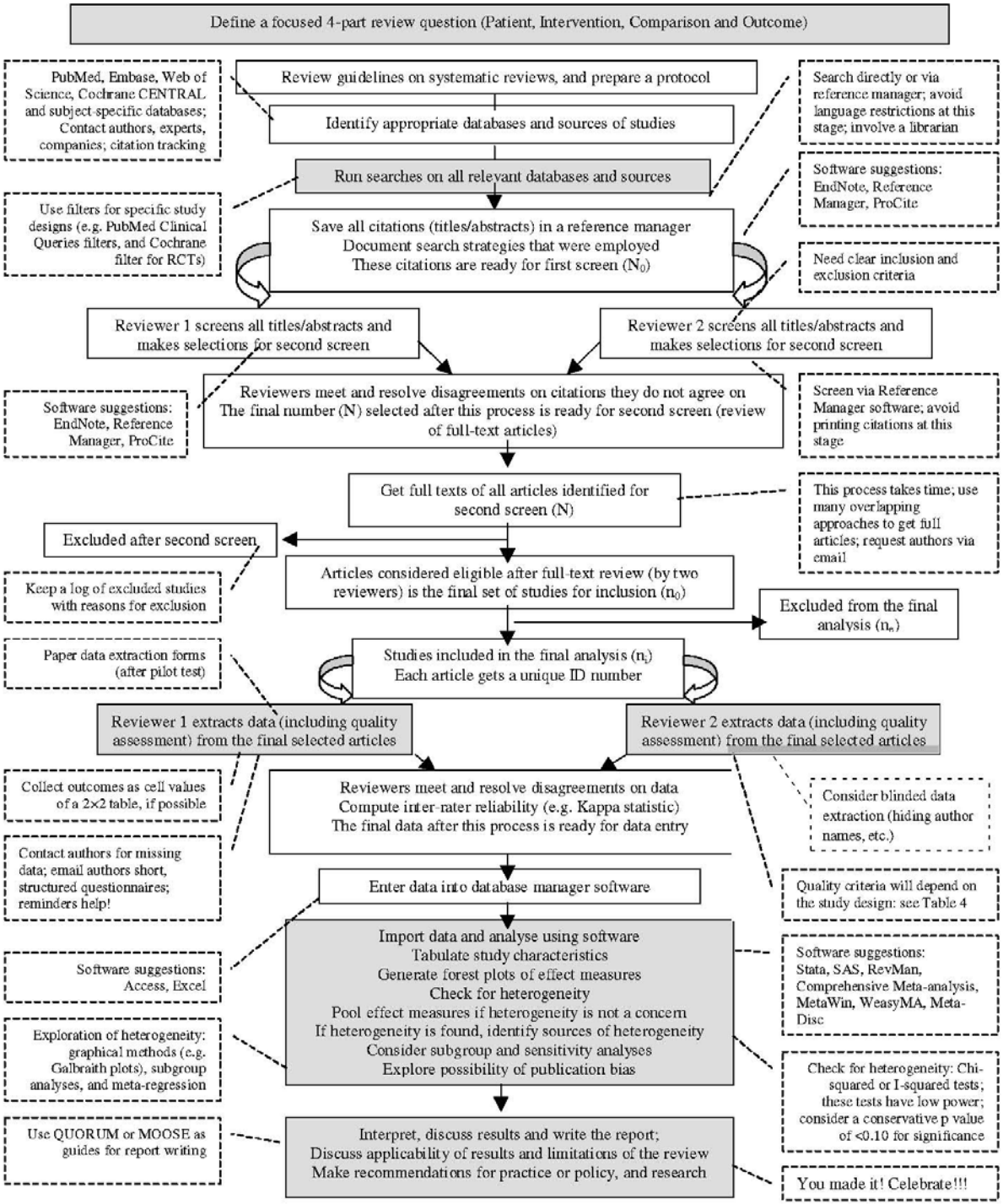
Pai M, et al. Systematic reviews and meta-analyses: An illustrated, step-by-step guide. *Natl Med J India* 2004;17(2):86-95.

Elements of a Systematic Review

- Formulate the review question & write a protocol
- Search for and include primary studies
- Assess study quality
- Extract data
- Analyze data
- Interpret results & write a report

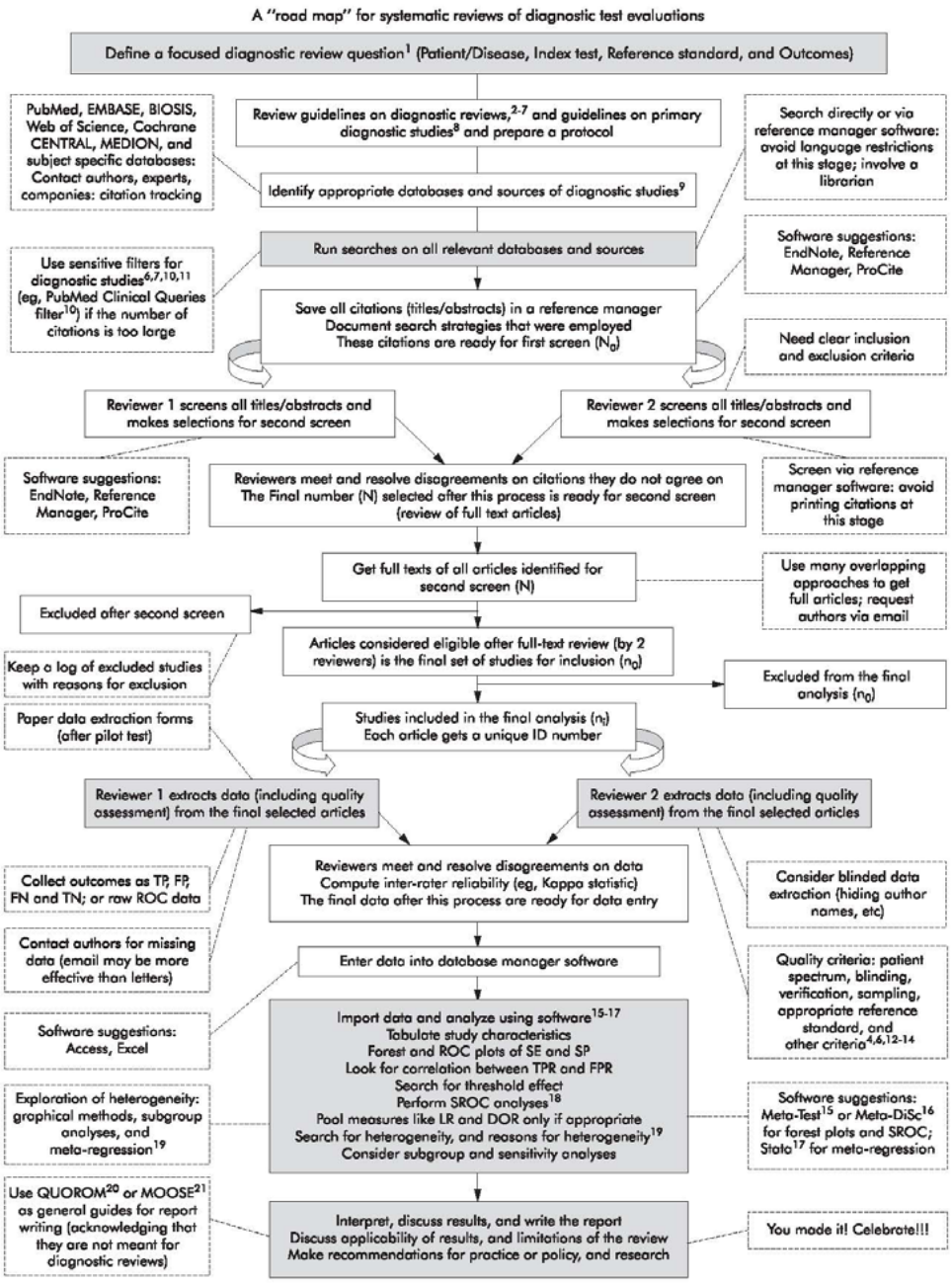
Pai M, et al. Systematic reviews and meta-analyses: An illustrated, step-by-step guide. *Natl Med J India* 2004;17(2):86-95.

Road map for systematic reviews



Pai M, et al. *Natl Med J India* 2004;17(2):86-95.

Road map for diagnostic reviews



Se = sensitivity; Sp = specificity; LR = likelihood ratios; DOR = diagnostic odds ratios; ROC = receiver operating characteristic; SROC = summary receiver operating characteristic; TP = true positives; FP = false positives; TN = true negatives; FN = false negatives; TPR = true positive rate; FPR = false positive rate. Superscripts indicate reference numbers.

Pai M, et al. *EBM 2004*.

All systematic reviews are not meta-analyses!

- “...it is always appropriate and desirable to systematically review a body of data, but it may sometimes be inappropriate, or even misleading, to statistically pool results from separate studies. Indeed, it is our impression that reviewers often find it hard to resist the temptation of combining studies even when such meta-analysis is questionable or clearly inappropriate.”
  - Egger et al. Systematic reviews in health care. London: BMJ books, 2001:5.

All reviews are not systematic!

- In 1987, Cynthia Mulrow published an interesting article entitled “The Medical Review Article: State of the Science.”
- She examined 50 review articles published in 4 major general medical journals [Annals of Internal Med; Archives of Internal Med; JAMA; New Engl J Med]
- Findings:
  - 80% addressed a focused review question
  - 2% described the method of locating evidence
  - 2% used explicit criteria for selecting studies for inclusion
  - 2% assessed the quality of the primary studies
  - 6% performed a quantitative analysis

Mulrow C. The medical review article: state of the science. Annals Int Med 1987;106:485-88.

All reviews are not systematic!

- In 1999, Cynthia Mulrow's survey was repeated.
- This time 158 reviews published in 6 major general medical journals [Annals of Internal Med; JAMA; New Engl J Med; BMJ; Am J Med; J of Int Med]
- Findings:
  - 34% addressed a focused review question
  - 28% described the method of locating evidence
  - 14% used explicit criteria for selecting studies for inclusion
  - 9% assessed the quality of the primary studies
  - 21% performed a quantitative analysis

McAlister et al. The medical review article revisited: has the science improved? Annals Int Med 1999;131:947-51

All systematic reviews are not systematic!

OPEN ACCESS Freely available online

PLoS MEDICINE

Editorial

Many Reviews Are Systematic but Some Are More Transparent and Completely Reported than Others

The *PLoS Medicine* Editors

OPEN ACCESS Freely available online

PLoS MEDICINE

Epidemiology and Reporting Characteristics of Systematic Reviews

David Moher[1,2,3*], Jennifer Tetzlaff[1], Andrea C. Tricco[1,4], Margaret Sampson[1], Douglas G. Altman[5]

1 Chalmers Research Group, Children's Hospital of Eastern Ontario Research Institute, Ottawa, Canada, 2 Department of Paediatrics, Faculty of Medicine, University of Ottawa, Ottawa, Canada, 3 Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Canada, 4 Institute of Population Health, University of Ottawa, Ottawa, Canada, 5 Centre for Statistics in Medicine, Oxford, United Kingdom

Moher et al. PLoS Med 2007

All systematic reviews are not systematic!

- 300 SRs were identified (one month)
- Majority (272 [90.7%]) reported in specialty journals
- Most reviews (213 [71.0%]) were categorized as therapeutic, and included a median of 16 studies
- Reviews typically searched a median of three electronic databases and two other sources
- Most (197/295 [66.8%]) reviews reported information about quality assessment, while few (68/294 [23.1%]) reported assessing for publication bias.
- A little over half (161/300 [53.7%]) reported combining their results statistically, of which most (147/161 [91.3%]) assessed for consistency across studies.
- There were large differences between Cochrane reviews and non-Cochrane reviews in the quality of reporting

Moher et al. PLoS Med 2007

When can meta-analyses mislead?

- When a meta-analysis is done outside of a systematic review
- When poor quality studies are included or when quality issues are ignored
- When small and inconclusive studies are included
- When inadequate attention is given to heterogeneity
  - Indiscriminate data aggregation can lead to inaccurate conclusions
- When reporting biases are a problem
  - Publication bias
  - Time lag bias
  - Duplicate publication bias
  - Language bias
  - Outcome reporting bias

Egger M et al. Uses and abuses of meta-analysis. Clinical Medicine 2001;1:478-84.

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy

Erick H. Turner, M.D., Annette M. Matthews, M.D., Eftihia Linardatos, B.S., Robert A. Tell, L.C.S.W., and Robert Rosenthal, Ph.D.

ABSTRACT

BACKGROUND

Evidence-based medicine is valuable to the extent that the evidence base is complete and unbiased. Selective publication of clinical trials — and the outcomes within those trials — can lead to unrealistic estimates of drug effectiveness and alter the apparent risk–benefit ratio.

METHODS

We obtained reviews from the Food and Drug Administration (FDA) for studies of 12 antidepressant agents involving 12,564 patients. We conducted a systematic literature search to identify matching publications. For trials that were reported in the literature, we compared the published outcomes with the FDA outcomes. We also compared the effect size derived from the published reports with the effect size derived from the entire FDA data set.

RESULTS

Among 74 FDA-registered studies, 31%, accounting for 3449 study participants, were not published. Whether and how the studies were published were associated with the study outcome. A total of 37 studies viewed by the FDA as having positive results were published; 1 study viewed as positive was not published. Studies viewed by the FDA as having negative or questionable results were, with 3 exceptions, either not published (22 studies) or published in a way that, in our opinion, conveyed a positive outcome (11 studies). According to the published literature, it appeared that 94% of the trials conducted were positive. By contrast, the FDA analysis showed that 51% were positive. Separate meta-analyses of the FDA and journal data sets showed that the increase in effect size ranged from 11 to 69% for individual drugs and was 32% overall.

- False positive results that are not replicated
- Publication bias
- Initially strong effects are often contradicted later
  - There are lessons to be learnt from the genetic epi and genome-wide association studies!

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

Human Heredity

Hum Hered 2007;64:203–213
DOI: 10.1159/000103512

Received
Accepted
Published

Non-Replication and Inconsistency in the Genome-Wide Association Setting

John P.A. Ioannidis

Clinical and Molecular Epidemiology Unit and Evidence-Based Medicine and Clinical Trials Unit, Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Biomedical Research Institute-Foundation for Research and Technology-Hellas, Ioannina, Greece; Department of Medicine, Tufts University School of Medicine, Boston, Mass., USA

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available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

EJC

Almost all articles on cancer prognostic markers report statistically significant results

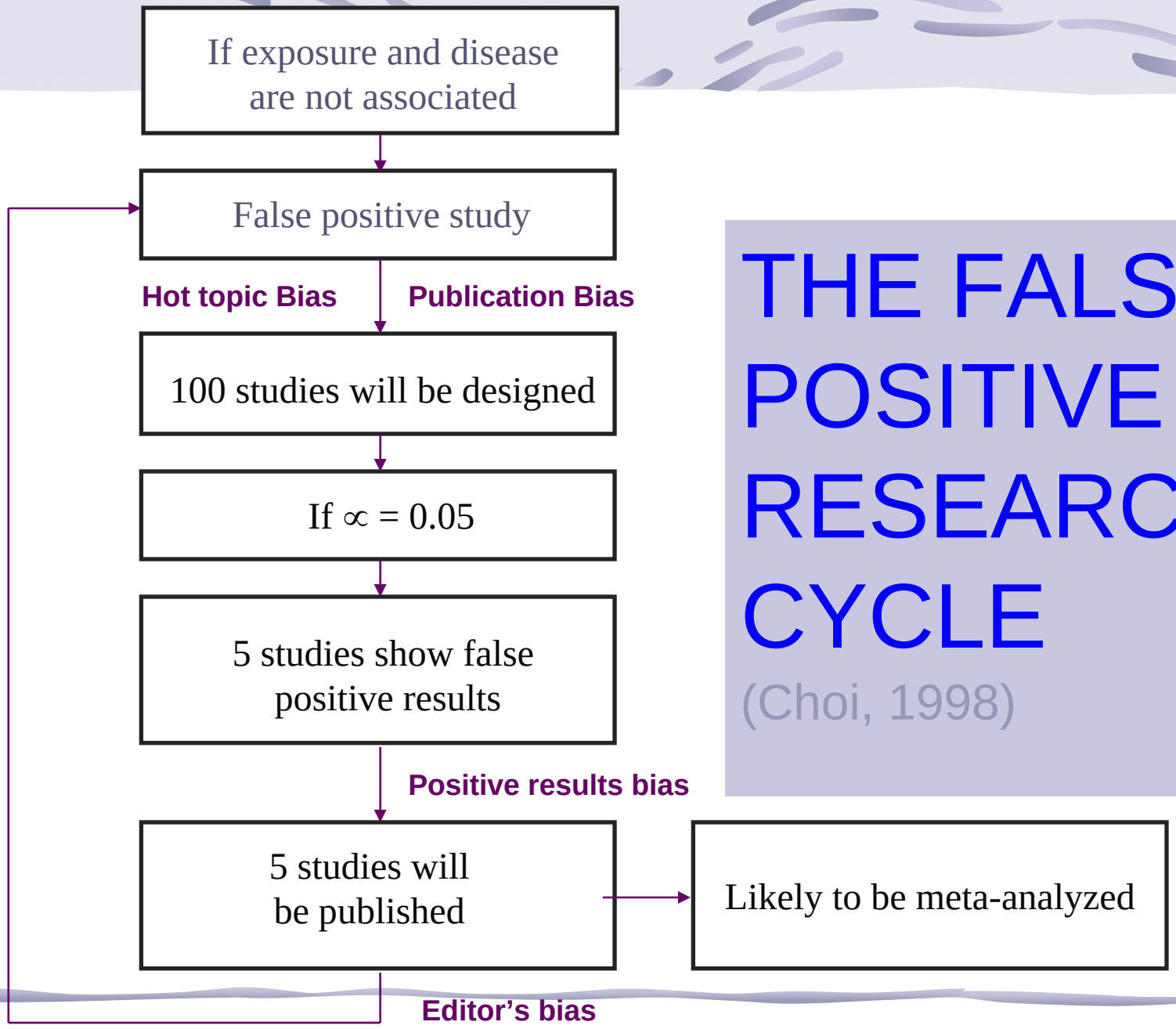
Panayiotis A. Kyzas[a], Despina Denaxa-Kyza[a], John P.A. Ioannidis[a,b,c,]*

Why Most Discovered True Associations Are Inflated

John P. A. Ioannidis

THE FALSE POSITIVE RESEARCH CYCLE

(Choi, 1998)



Courtesy: Bernard Choi, PHAC

Empirical Evidence for Selective Reporting of Outcomes in Randomized Trials

Comparison of Protocols to Published Articles

An-Wen Chan, MD, DPhil
Asbjørn Hróbjartsson, MD, PhD
Mette T. Haahr, BSc
Peter C. Gøtzsche, MD, DrMedSci
Douglas G. Altman, DSc

Context Selective reporting of outcomes within published studies based on the nature or direction of their results has been widely suspected, but direct evidence of such bias is currently limited to case reports.

Objective To study empirically the extent and nature of outcome reporting bias in a cohort of randomized trials.

Design Cohort study using protocols and published reports of randomized trials approved by the Scientific-Ethical Committees for Copenhagen and Frederiksberg, Denmark, in 1994-1995. The number and characteristics of reported and unreported trial outcomes were recorded from protocols, journal articles, and a survey of trialists. An outcome was considered incompletely reported if insufficient data were presented in the published articles for meta-analysis. Odds ratios relating the completeness of outcome reporting to statistical significance were calculated for each trial and then pooled to provide an overall estimate of bias. Protocols and published articles were also compared to identify discrepancies in primary outcomes.

Main Outcome Measures Completeness of reporting of efficacy and harm outcomes and of statistically significant vs nonsignificant outcomes; consistency between primary outcomes defined in the most recent protocols and those defined in published articles.

Results One hundred two trials with 122 published journal articles and 3736 outcomes were identified. Overall, 50% of efficacy and 65% of harm outcomes per trial were incompletely reported. Statistically significant outcomes had a higher odds of being fully reported compared with nonsignificant outcomes for both efficacy (pooled odds ratio, 2.4; 95% confidence interval [CI], 1.4-4.0) and harm (pooled odds ratio, 4.7; 95% CI, 1.8-12.0) data. In comparing published articles with protocols, 62% of trials had at least 1 primary outcome that was changed, introduced, or omitted. Eighty-six percent of survey responders (42/49) denied the existence of unreported outcomes despite clear evidence to the contrary.

Conclusions The reporting of trial outcomes is not only frequently incomplete but also biased and inconsistent with protocols. Published articles, as well as reviews that incorporate them, may therefore be unreliable and overestimate the benefits of an intervention. To ensure transparency, planned trials should be registered and protocols should be made publicly available prior to trial completion.

SELECTIVE PUBLICATION OF STUDIES with statistically significant results has received widespread recognition.[1] In contrast, selective reporting of favorable outcomes within published studies has not undergone comparable empirical investigation. The existence of outcome reporting bias has been widely suspected for years,[2-12] but direct evidence is limited to case reports that have low generalizability[13-15] and may themselves be subject to publication bias.

Our study had 3 goals: (1) to determine the prevalence of incomplete outcome reporting in published reports of randomized trials; (2) to assess the association between outcome reporting and statistical significance; and (3) to evaluate the consistency between primary outcomes specified in trial protocols and those defined in the published articles.

METHODS

JAMA 2004

Selection in Reported Epidemiological Risks: An Empirical Assessment

Fotini K. Kavvoura[1], George Liberopoulos[1], John P. A. Ioannidis[1,2*]

1 Clinical and Molecular Epidemiology Unit, Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece, 2 Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts, United States of America

Funding: The authors received no specific funding for this study. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

Academic Editor: Eduardo L. Franco, McGill University, Canada

Citation: Kavvoura FK, Liberopoulos G, Ioannidis JPA (2007) Selection in reported epidemiological risks: An empirical assessment. PLoS Med 4(3): e79. doi:10.1371/journal.pmed.0040079

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Accepted: January 8, 2007
Published: March 6, 2007

Abbreviations: ANOVA, analysis of variance; CI, confidence interval; IQR, interquartile range

* To whom correspondence should be addressed. E-mail: jioannid@cc.uoi.gr

ABSTRACT

Background

Epidemiological studies may be subject to selective reporting, but empirical evidence thereof is limited. We empirically evaluated the extent of selection of significant results and large effect sizes in a large sample of recent articles.

Methods and Findings

We evaluated 389 articles of epidemiological studies that reported, in their respective abstracts, at least one relative risk for a continuous risk factor in contrasts based on median, tertile, quartile, or quintile categorizations. We examined the proportion and correlates of reporting statistically significant and nonsignificant results in the abstract and whether the magnitude of the relative risks presented (coined to be consistently $\geq$1.00) differs depending on the type of contrast used for the risk factor. In 342 articles (87.9%), $\geq$1 statistically significant relative risk was reported in the abstract, while only 169 articles (43.4%) reported $\geq$1 statistically nonsignificant relative risk in the abstract. Reporting of statistically significant results was more common with structured abstracts, and was less common in US-based studies and in cancer outcomes. Among 50 randomly selected articles in which the full text was examined, a median of nine (interquartile range 5–16) statistically significant and six (interquartile range 3–16) statistically nonsignificant relative risks were presented ($p = 0.25$). Paradoxically, the smallest presented relative risks were based on the contrasts of extreme quintiles; on average, the relative risk magnitude was 1.41-, 1.42-, and 1.36-fold larger in contrasts of extreme quartiles, extreme tertiles, and above-versus-below median values, respectively ($p < 0.001$).

Conclusions

Published epidemiological investigations almost universally highlight significant associations between risk factors and outcomes. For continuous risk factors, investigators selectively present contrasts between more extreme groups, when relative risks are inherently lower.

PLoS Med 2007

Contradicted and Initially Stronger Effects in Highly Cited Clinical Research

John P. A. Ioannidis, MD

Context Controversy and uncertainty ensue when the results of clinical research on the effectiveness of interventions are subsequently contradicted. Controversies are most prominent when high-impact research is involved.

Objectives To understand how frequently highly cited studies are contradicted or find effects that are stronger than in other similar studies and to discern whether specific characteristics are associated with such refutation over time.

Design All original clinical research studies published in 3 major general clinical journals or high-impact-factor specialty journals in 1990-2003 and cited more than 1000 times in the literature were examined.

Main Outcome Measure The results of highly cited articles were compared against subsequent studies of comparable or larger sample size and similar or better controlled designs. The same analysis was also performed comparatively for matched studies that were not so highly cited.

Results Of 49 highly cited original clinical research studies, 45 claimed that the intervention was effective. Of these, 7 (16%) were contradicted by subsequent studies, 7 others (16%) had found effects that were stronger than those of subsequent studies, 20 (44%) were replicated, and 11 (24%) remained largely unchallenged. Five of 6 highly-cited nonrandomized studies had been contradicted or had found stronger effects vs 9 of 39 randomized controlled trials ($P=.008$). Among randomized trials, studies with contradicted or stronger effects were smaller ($P=.009$) than replicated or unchallenged studies although there was no statistically significant difference in their early or overall citation impact. Matched control studies did not have a significantly different share of refuted results than highly cited studies, but they included more studies with "negative" results.

Conclusions Contradiction and initially stronger effects are not unusual in highly cited research of clinical interventions and their outcomes. The extent to which high citations may provoke contradictions and vice versa needs more study. Controversies are most common with highly cited nonrandomized studies, but even the most highly cited randomized trials may be challenged and refuted over time, especially small ones.

JAMA. 2005;294:218-228 www.jama.com

CLINICAL RESEARCH ON IMPORTANT questions about the efficacy of medical interventions is sometimes followed by subsequent studies that either reach opposite conclusions or suggest that the original claims were too strong. Such disagreements may upset clinical practice and acquire publicity in both scientific circles and in the lay press. Several empirical investigations have tried to address whether specific types of studies are more likely to be contradicted and to explain observed controversies. For example, evidence exists that small studies may sometimes be refuted by larger ones.[1,2]

Similarly, there is some evidence on disagreements between epidemiological studies and randomized trials.[3-5] Prior investigations have focused on a variety of studies without any particular attention to their relative importance and scientific impact. Yet, most research publications have little impact while a small minority receives

Discrepancies between meta-analyses

A guide to interpreting discordant systematic reviews

Alejandro R. Jadad, MD, DPhil; Deborah J. Cook, MD, MSc; George P. Browman, MD, MSc

Abstract

SYSTEMATIC REVIEWS ARE BECOMING prominent tools to guide health care decisions. As the number of published systematic reviews increases, it is common to find more than 1 systematic review addressing the same or a very similar therapeutic question. Despite the promise for systematic reviews to resolve conflicting results of primary studies, conflicts among reviews are now emerging. Such conflicts produce difficulties for decision-makers (including clinicians, policy-makers, researchers and patients) who rely on these reviews to help them make choices among alternative interventions when experts and the results of trials disagree. The authors provide an adjunct decision tool — a decision algorithm — to help decision-makers select from among discordant reviews.

Résumé

LES EXAMENS CRITIQUES SYSTÉMATIQUES DEVIENNENT des outils importants pour guider les

Education

Éducation

Dr. Jadad is with the Health Information Research Unit, Department of Clinical Epidemiology and Biostatistics, and Drs. Cook and Browman are with the Departments of Clinical Epidemiology and Biostatistics and of Medicine, McMaster University, Hamilton, Ont.

This article has been peer reviewed.

Can Med Assoc J 1997;156:1411-6

Discrepancies between meta-analyses and mega-trials

The New England Journal of Medicine

Special Article

DISCREPANCIES BETWEEN META-ANALYSES AND SUBSEQUENT LARGE RANDOMIZED, CONTROLLED TRIALS

JACQUES LELORIER, M.D., PH.D., GENEVIÈVE GRÉGOIRE, M.D., ABDELTIF BENHADDAD, M.D., JULIE LAPIERRE, M.D., AND FRANÇOIS DERDERIAN, M.SC.

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Contemporary Clinical Trials 28 (2007) 324–328

Contemporary Clinical Trials

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Discussion

Mega-trials vs. meta-analysis: Precision vs. heterogeneity?

Ian Shrier [a,*], Robert W. Platt [b], Russell J. Steele [c]

Yes, there are problems, but

- meta-analysis has made and continues to make major contributions to medical research, clinical decision making, and standards of research reportage. However, it is no panacea. Readers need to examine any meta-analyses critically to see whether researchers have overlooked important sources of clinical heterogeneity among the included trials. They should demand evidence that the authors undertook a comprehensive search, avoiding covert duplicate data and unearthing unpublished trials and data. Lastly, readers and researchers alike need to appreciate that not every systematic review should lead to an actual meta-analysis...

David Naylor. BMJ 1997;315:617-619


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