KERALA UNIVERSITY OF HEALTH SCIENCES
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School of Public Health

NATIONAL CLINICAL EPIDEMIOLOGIST'S MEET (September 23 2022)

Session 2: Knowledge synthesis and interpretation

The Craft of Evidence Synthesis: An Overview

Prathap Tharyan

Adjunct Professor, Clinical Epidemiology Unit;

[Retired Professor of Psychiatry

& Former Director-Cochrane South Asia]

CHRISTIAN MEDICAL COLLEGE
VELLORE
INDIA

THE NATURE OF EVIDENCE

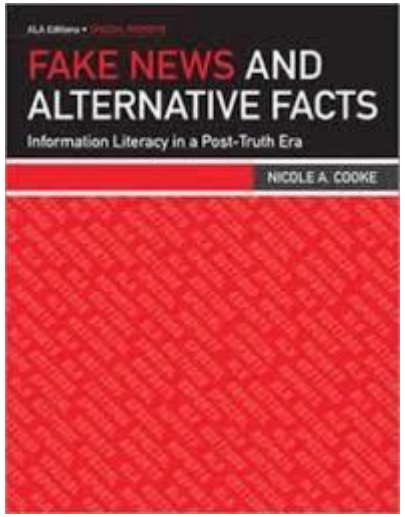
- Evidence refers to **verifiable facts and data** that support a practice or belief.
- However, people differ in what they consider as verifiable facts (or reliable evidence)
- Wide range of sources are used by people find reliable evidence - from personal beliefs and experiences to evidence from research studies

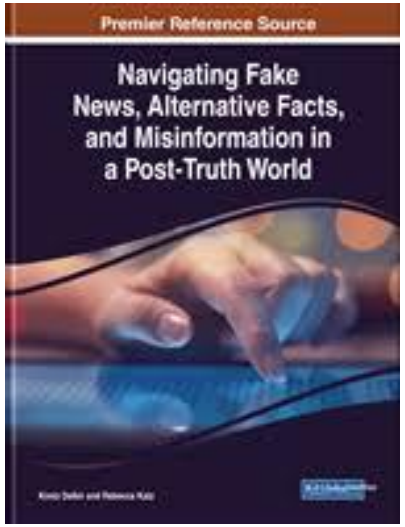
THE NATURE OF EVIDENCE











Open access, freely available online

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

PLoS Med 2005; 2(8): e124.

It can be proven that most claimed research findings are false.

CAN THE EVIDENCE BE TRUSTED?

Evidence-based medicine: can the evidence be trusted?

Indian Journal of Medical Ethics Vol VIII No 4 October - December 2011

PRATHAP THARYAN

Professor of Psychiatry, Prof BV Moses & ICMR Centre for Advanced Research in Evidence-Informed Healthcare, Christian Medical College, Vellore 632002, Tamil Nadu INDIA e-mail: prathap@cmcvellore.ac.in

- **Vested interests** within industry and academia determine what research is funded, how it is done and how it is reported.
- **Unnecessary, inappropriate or poorly designed, and poorly reported research** results in publications with **unreliable results** that lead to **sub-optimal health outcomes.**
- Many randomized controlled trials are **designed to deceive** by their **choice of comparators and outcomes,** and **manipulation of statistics** to produce desired outcomes that are **selectively reported**
- **Undisclosed conflict of interest**, **ghostwriting**, the **manufacturing of disease**, and the **marketing of research disguised as education** are common.

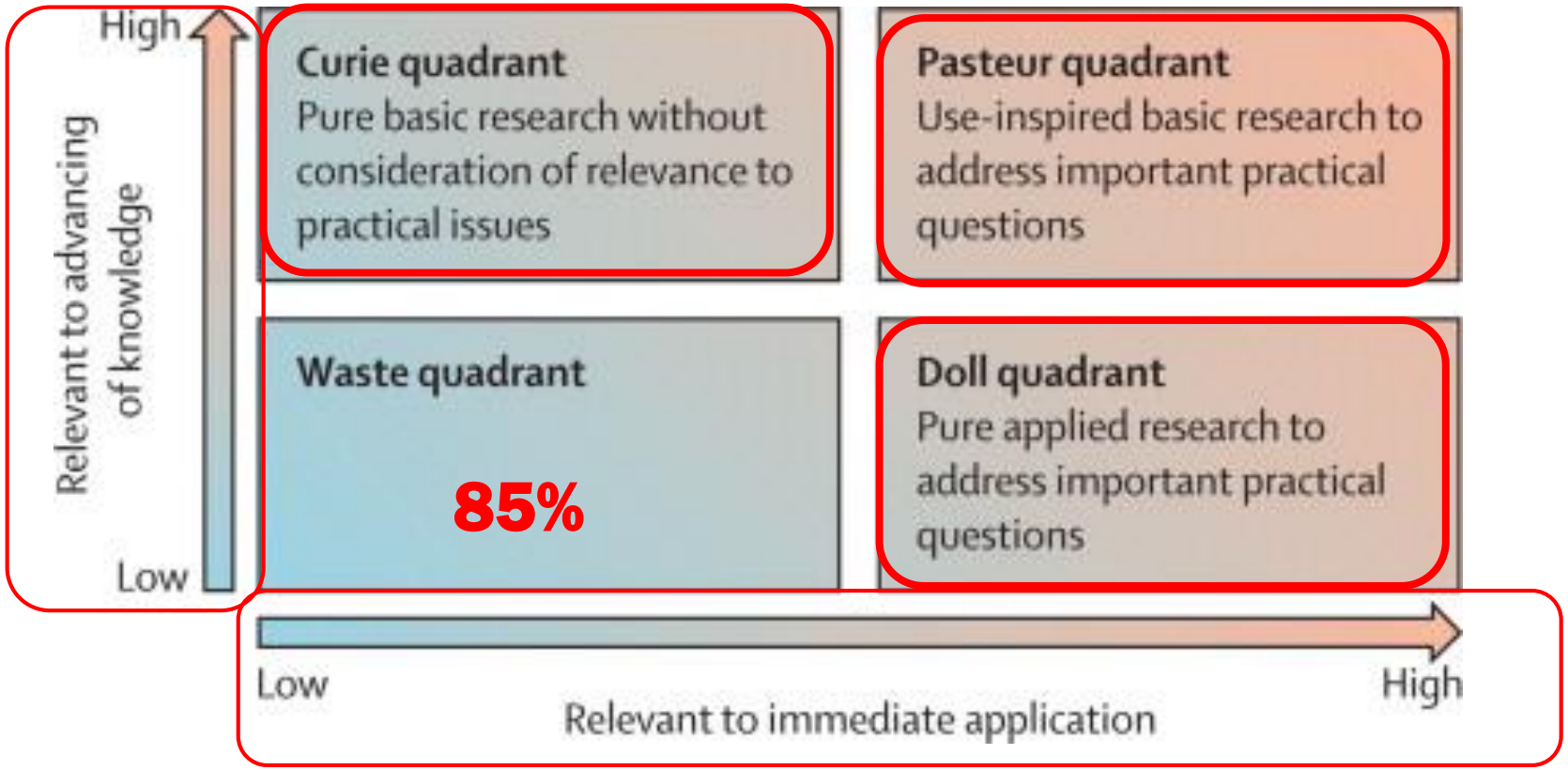


Figure . Classification of different categories of research

Research Waste: Studies that neither advance scientific knowledge nor have practical applications

Iain Chalmers, Michael B Bracken, Ben Djulbegovic, Silvio Garattini, Jonathan Grant, A Metin Gülmezoglu, David W Howells, John P A Ioannidis, Sandy Oliver. How to increase value and reduce waste when research priorities are set. **Lancet 2014**; 383 (9912): 156–65.

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More instances of plagiarism come to light



R. Prasad

CHENNAI:, MARCH 09, 2012 03:29 IST
UPDATED: AUGUST 02, 2016 09:07 IST

SHARE ARTICLE PRINT A | A | A

Three more instances of plagiarism committed by C.N.R. Rao, eminent scientist and Scientific Adviser to the Prime Minister, and S.B. Krupanidhi, senior professor at the Indian Institute of Science (IISc) in Bangalore, have come to light. Professor Krupanidhi's student Basant Chitara at the IISc is the first

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E

IR-Indian Institute of Chemical logy scientist has 28 papers with nipulated, duplicated images

R. Prasad

CHENNAI:, JUNE 08, 2019 17:25 IST
UPDATED: JUNE 08, 2019 17:25 IST

RTICLE PRINT A | A | A

"Research misconduct can harm patients, distort the evidence base, misdirect research effort, waste funds, and damage public trust in science".

- *Editorial, BMJ, 2012*

RELIABLE EVIDENCE IS IMPORTANT, ESPECIALLY IN PANDEMICS

Annals of Internal Medicine

IDEAS AND OPINIONS

A Rush to Judgment? Rapid Reporting and Dissemination of Results and Its Consequences Regarding the Use of Hydroxychloroquine for COVID-19

Alfred H.J. Kim, MD, PhD*; Jeffrey A. Sparks, MD, MMSc*; Jean W. Liew, MD; Michael S. Putman, MD; Francis Berenbaum, MD, PhD; Alí Duarte-García, MD, MS; Elizabeth R. Graef, DO; Peter Korsten, MD; Sebastian E. Sattui, MD; Emily Sirotich, BSc; Manuel F. Ugarte-Gil, MD, MSc; Kate Webb, MBBCh, PhD; and Rebecca Grainger, MBChB, PhD; for the COVID-19 Global Rheumatology Alliance†

The coronavirus disease 2019 (COVID-19) pandemic has placed the scientific and research communities under extraordinary pressure, to which they have responded with exceptional vigor and speed. This desire to quickly find safe and effective treatments may also lead to relaxed standards of data generation and interpretation, which may have undesirable downstream effects. The recent publication of a study evaluating hydroxychloroquine (HCQ) in COVID-19 is a useful test case, highlighting the challenges of conducting research during a pandemic.

action (PCR). Of the 5 patients receiving HCQ who had a baseline Ct of 22 or less on PCR (that is, higher viral burden), 4 still had detectable virus at day 6. Of the 9 patients with a baseline Ct greater than 22 on PCR, only 2 had detectable virus at day 6. Thus, another explanation is that the baseline viral load, not therapy with HCQ + AZM, affects viral load at day 6.

This problem may have been further exacerbated by issues with data measurement and imputation. Sites other than Marseille did not perform daily PCR testing, creating gaps in PCR data for control group patients

WHAT WE NEED

- For better health outcomes: Reliable evidence to inform decisions

Evidence that is relevant

Focused clinical questions

Studies addressing the question

Study designs and reports that provide reliable answers

Evidence that is evaluated

For completeness: All relevant studies

For risk of bias: Effects on the results

For clinical importance: Not just statistical significance

Evidence that is synthesized

Overall effects

Consistent effects

Contextualized effects

Evidence-informed healthcare is a two-stage process

Addressing the gaps between evidence and practice

Research Synthesis

Guideline development

Research



Evidence



Practice

Getting the evidence straight

Getting the evidence used

Glasziou P, Haynes B. *ACP J Club. 2005*

RESEARCH SYNTHESIS

Research (Evidence) synthesis is the process of finding and combining the results of multiple primary studies addressing the same research question(s)

Research synthesis aims to generate new knowledge:

By comparing and combining the results of multiple primary studies to confirm or refute existing (but sometimes uncertain) knowledge and to see how generalizable the results are

Systematic reviews and meta-analyses are the tools used in research synthesis

Research synthesis can be quantitative or qualitative (or both).

- “A systematic review involves **the application of scientific strategies, in ways that limit bias,** to the systematic assembly**,** critical appraisal, **and synthesis** of all relevant studies that address a specific clinical question.”
- A systematic review **may use quantitative methods (meta-analysis)** to synthesize the results from two or more studies for particular outcomes (if data are available and are similar).

- Cook et al, Ann Intern Med. 1997;126:376-380

WHAT ARE THE KEY CHARACTERISTICS OF A SYSTEMATIC REVIEW?

- The key characteristics of a systematic review are:
  a. a clearly stated set of objectives with an explicit, reproducible methodology;
  b. a systematic search that attempts to identify all studies that would meet the eligibility criteria;
  c. an assessment of the validity of the findings of the included studies (e.g., assessment of risk of bias and confidence in cumulative estimates); and
  d. systematic presentation, and synthesis, of the characteristics and findings of the included studies

- Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1

META-ANALYSIS

- The statistical method that combines the results of several independent studies

Not all systematic reviews contain meta-analyses

Attempts to provide an average result

Results from some studies contribute more weight to the pooled average.

Preferable to “vote counting”

The main advantage is increased power

This provides greater precision in the effect estimates compared to the individual studies

Can mislead if done outside a systematic review

Publication bias

Bias in the methods of studies

Inconsistency (heterogeneity) in the results of the studies

Contextual issues

STEPS IN DOING A SYSTEMATIC REVIEW

What authors DO

Protocol

STEP 1: Formulate the question (PICOTS)

STEP 2: Put together a team and register the title

STEP 3: Write a protocol (publish / PROSPERO)

Review

STEP 4: Locate and select studies

STEP 5: Assess studies for risk of bias

STEP 6: Retrieve data

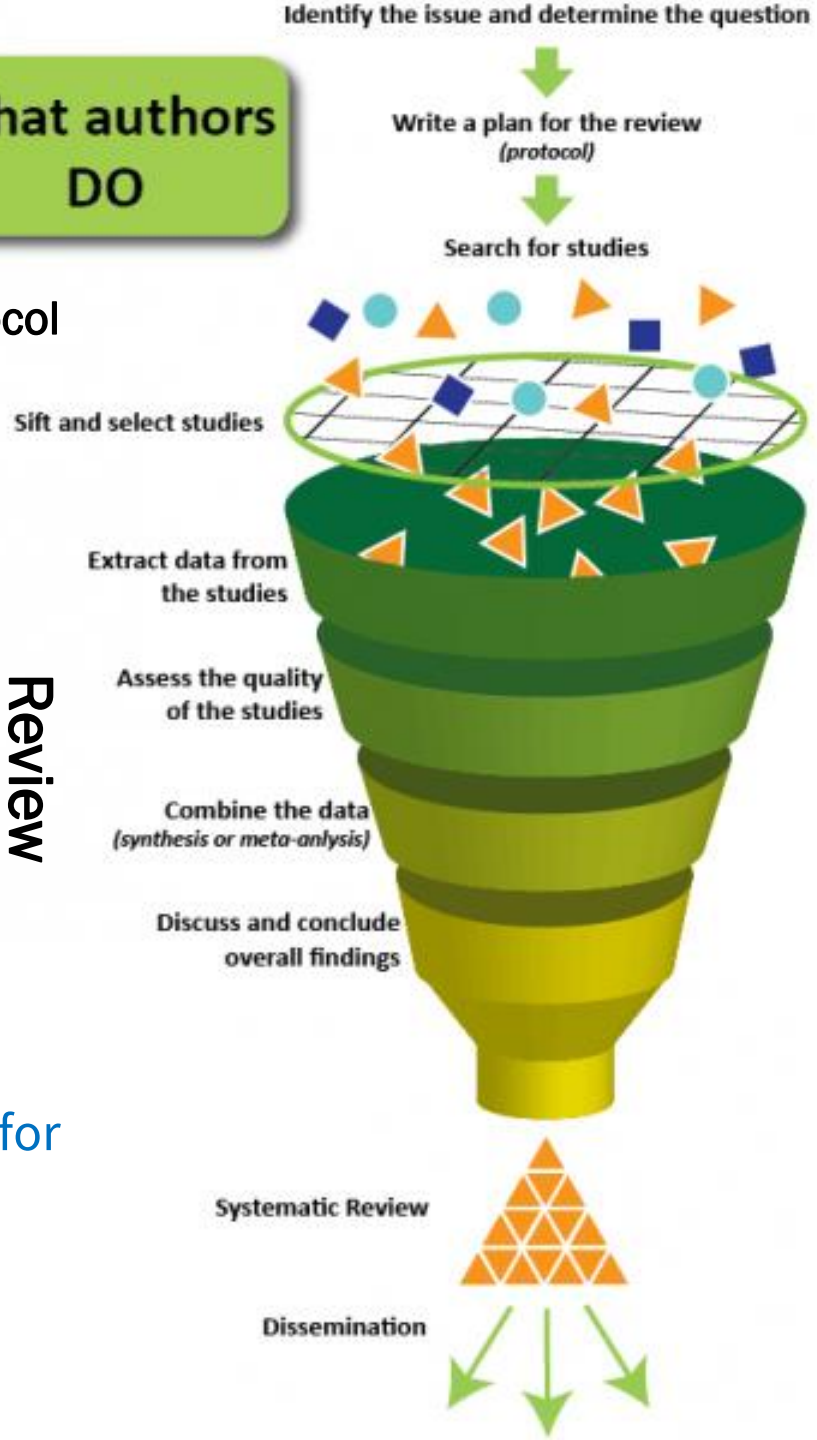
STEP 7:Enter data

STEP 8:Analyze and present results

STEP 9: Summarize results and GRADE levels of certainty

STEP 10: Interpret results and write review with implications for practice and research

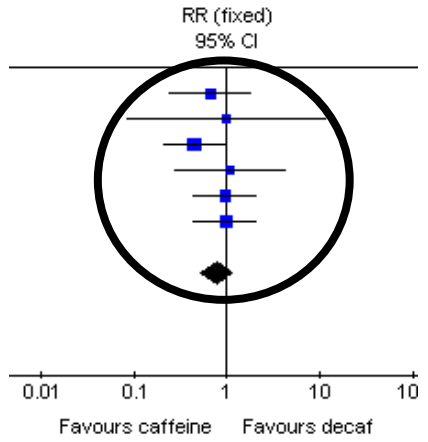
STEP 11: Publish and disseminate



Designed by Jessica Kaufman, Cochrane Consumers & Communication Review Group, Centre for Health Communication & Participation, La Trobe University, 2011

STEPS IN DOING A META-ANALYSIS

1. **Define comparisons for your review**
    1. Drug A versus B
    2. Drug C versus B
2. **Decide on the outcomes for each comparison**
    1. Death
    2. Relapse
3. **Enter data for outcome for each study reporting that outcome**
4. **Decide on summary estimate**
5. **Meta-analyze and interpret summary estimate with 95% CI**
6. **Assess heterogeneity**
    1. Explore causes of heterogeneity
    2. Incorporate heterogeneity
7. **Consider sensitivity analysis**
8. **Interpret results (GRADE SoF)**



EVIDENCE SYNTHESIS CAN IMPROVE HEALTH OUTCOMES

BY PROVIDING EVIDENCE ABOUT INTERVENTIONS THAT WORK OR DO NOT WORK OR CAUSE MORE HARM THAN GOOD

- Forest plot
- OR & 95% CI
- 33 trials
- 36,974 pts
- 1959-1988
- IV Streptokinase vs no Streptokinase to prevent death after Acute MI

6 trials showed clear benefit
Others too small
Pooled estimate:
Streptokinase saves lives

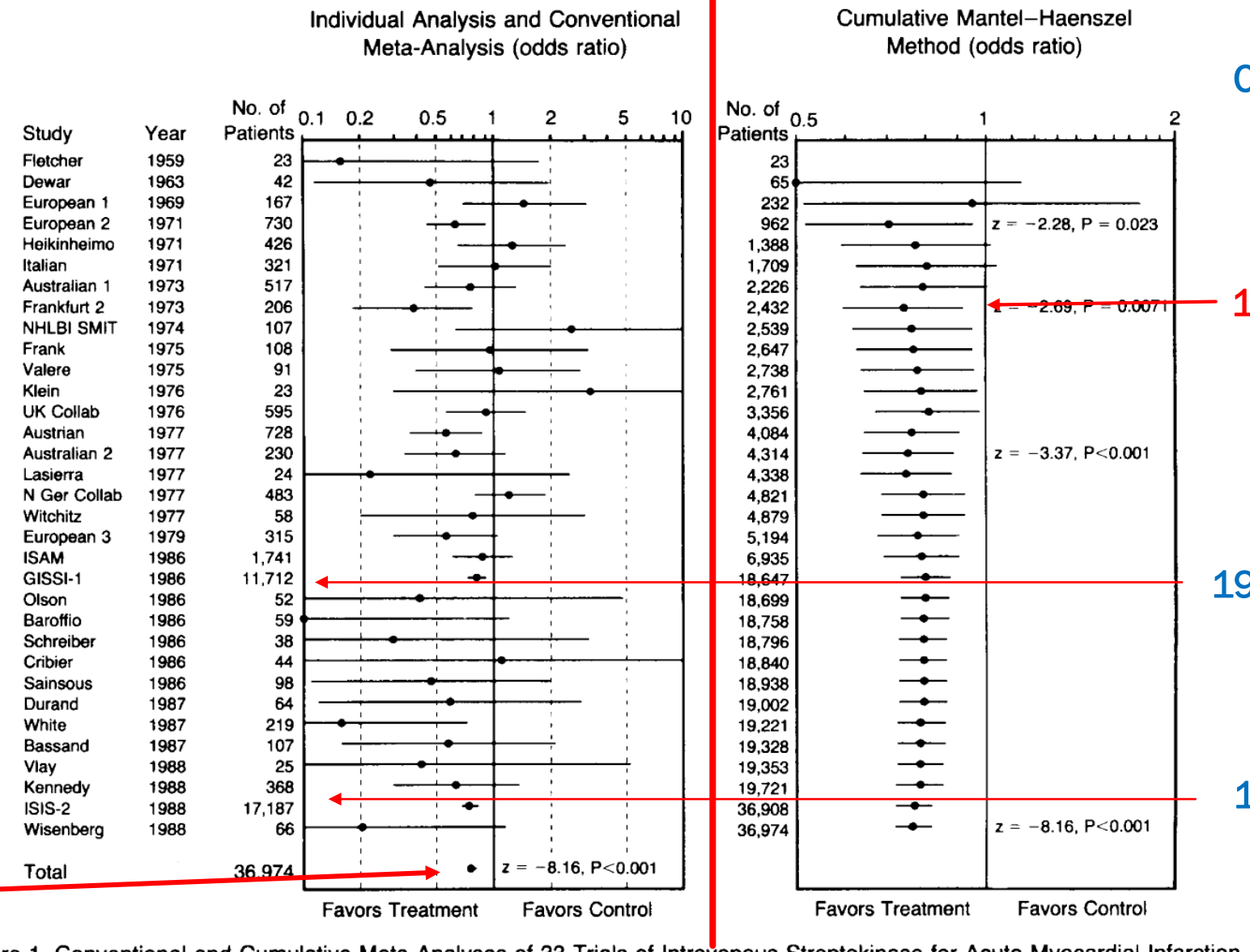


Figure 1. Conventional and Cumulative Meta-Analyses of 33 Trials of Intravenous Streptokinase for Acute Myocardial Infarction.

Cumulative meta-analysis

1973: 2432 pts

1986: GISSI-1: 11,712 pts

1988: ISIS-2: 17,187pts

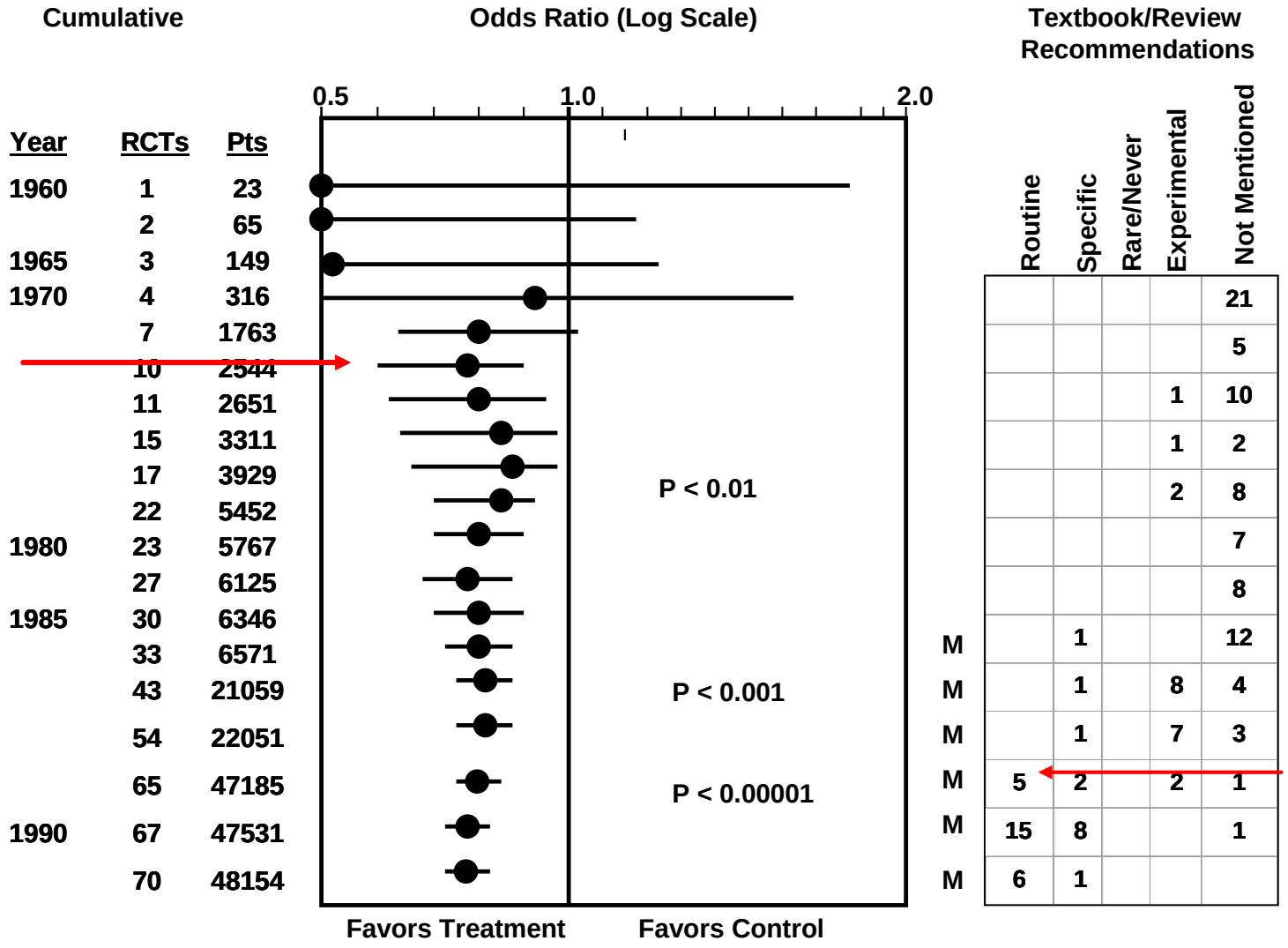
Clinical Trial > JAMA. 1992 Jul 8;268(2):240-8.

A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts. Treatments for myocardial infarction

E M Antman [1], J Lau, B Kupelnick, F Mosteller, T C Chalmers

Thrombolysis for acute MI

Evidence for benefit available from1973



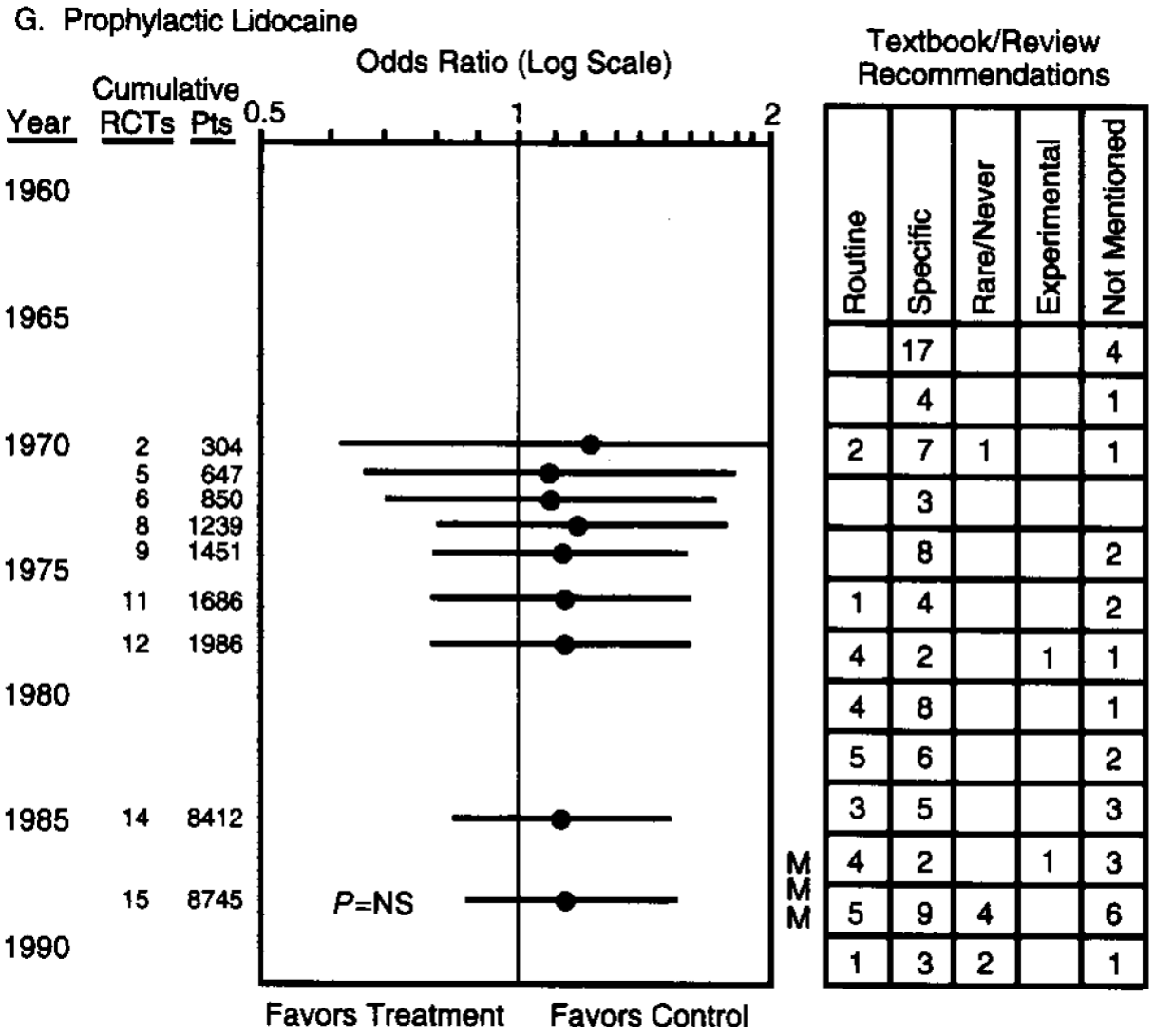
Recommendations only in mid-to-late 1980s

Clinical Trial > JAMA. 1992 Jul 8;268(2):240-8.

A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts. Treatments for myocardial infarction

E M Antman [1], J Lau, B Kupelnick, F Mosteller, T C Chalmers

Cumulative evidence of no benefit



Recommended into 1990s

Clinical Trial > JAMA. 1992 Jul 8;268(2):240-8.

A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts. Treatments for myocardial infarction

E M Antman [1], J Lau, B Kupelnick, F Mosteller, T C Chalmers

- *"advice on some life-saving therapies has been delayed for more than a decade, while other treatments have been recommended long after controlled research has shown them to be harmful."*

WHAT ARE THE VARIOUS HIERARCHIES OF EVIDENCE?

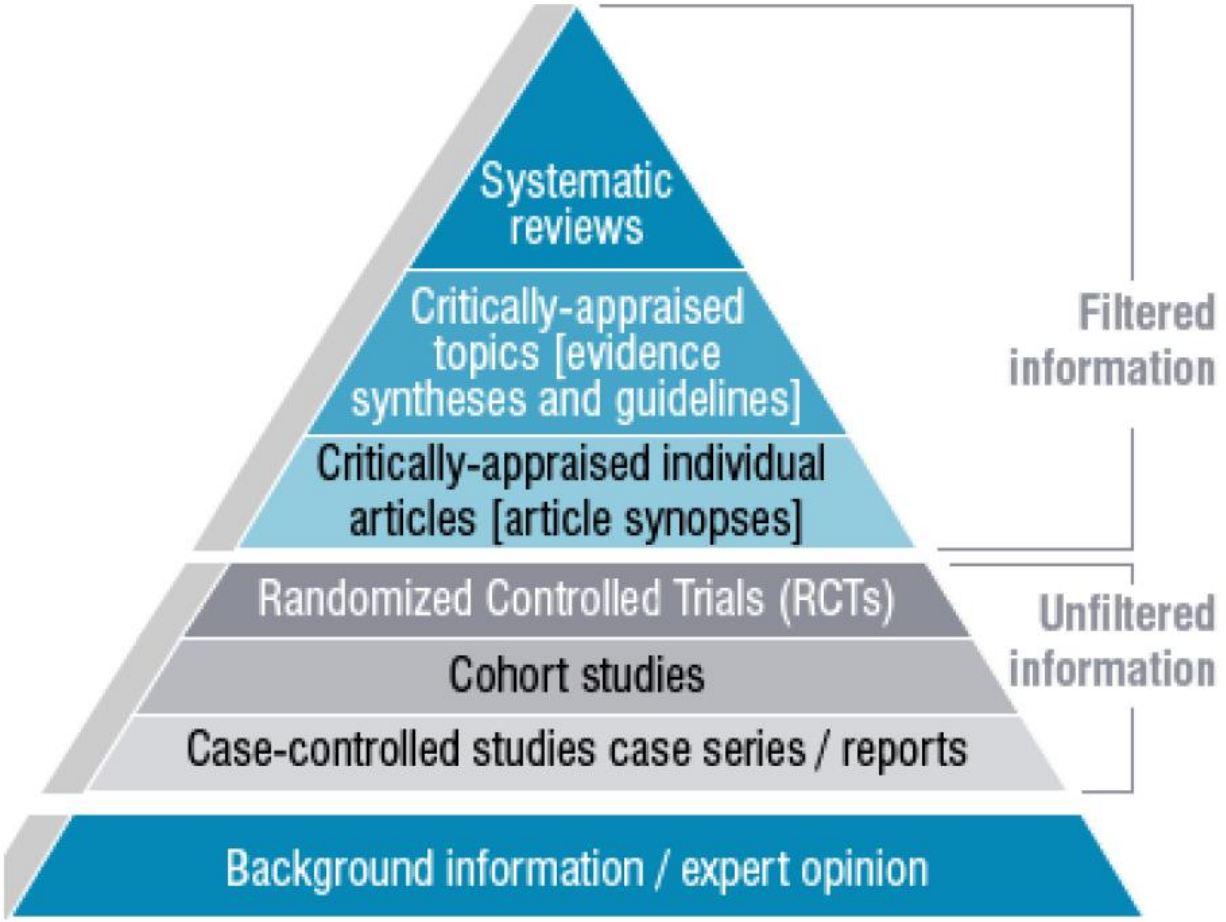
NOT ALL EVIDENCE IS THE SAME

HIERARCHY OF EVIDENCE: THE EVIDENCE PYRAMID



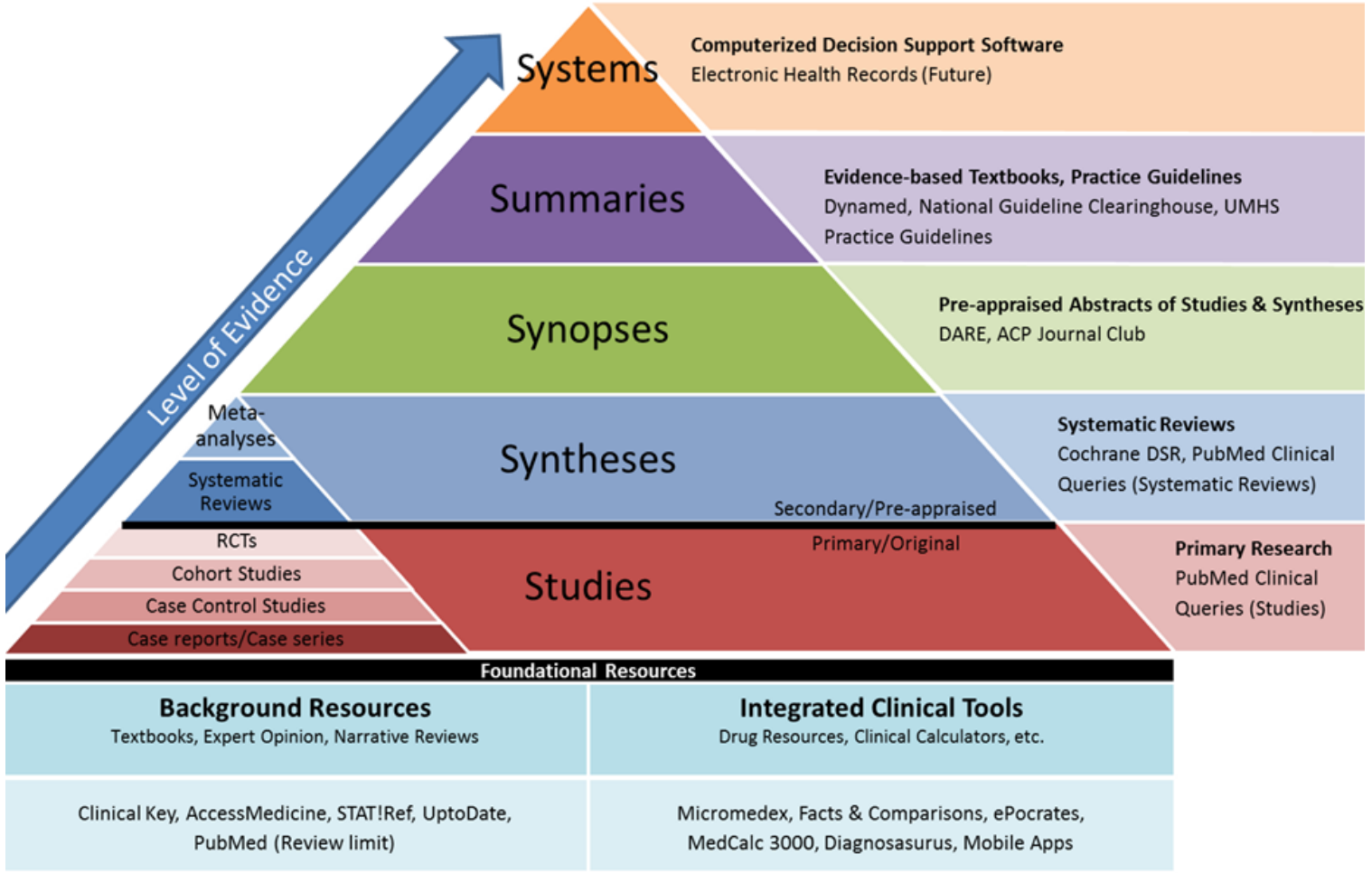
Am J Clin Nutr doi: 10.3945/ajcn.116.139097

VARIATIONS OF THE EVIDENCE PYRAMID



National Health and Medical Research Council. (2009). *[Hierarchy of Evidence]*.https://www.nhmrc.gov.au/

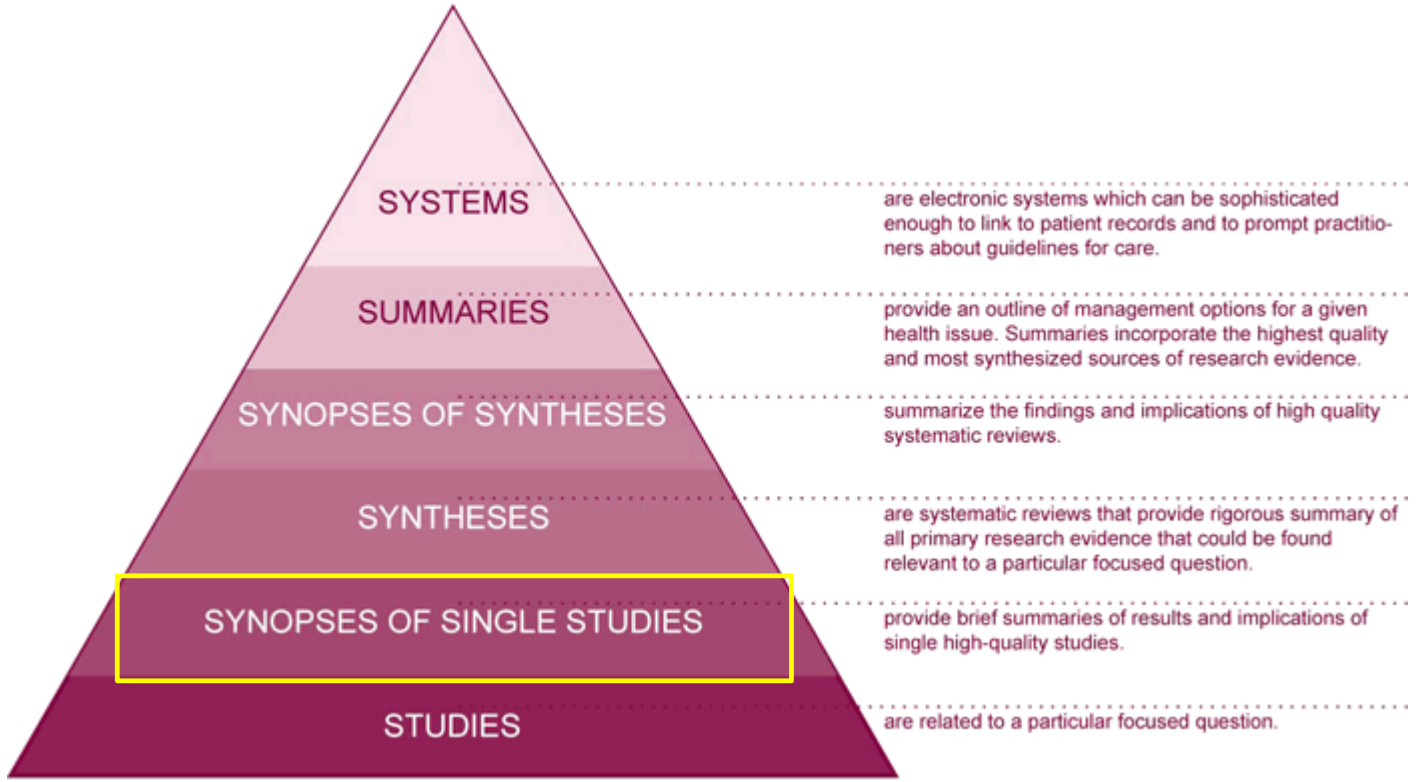
VARIATIONS OF THE EVIDENCE PYRAMID



The 5S pyramid

Haynes RB. Of studies, syntheses, synopses, summaries and systems: the “5S" evolution of services for evidence-based health care decisions. ACP J Club. 2006 Nov-Dec;145(3):A8-9.

VARIATIONS OF THE EVIDENCE PYRAMID



The 6S pyramid

from: https://www.nccmt.ca/tools/6s-search-pyramid

LEVELS OF EVIDENCE

Level of Evidence	Type of Study
1a	Systematic reviews of randomized controlled trials (RCTs)
1b	Individual RCTs with narrow confidence interval
2a	Systematic reviews of cohort studies
2b	Individual cohort studies and low-quality RCTs
3a	Systematic reviews of case-control studies
3b	Case-controlled studies
4	Case series and poor-quality cohort and case-control studies
5	Expert opinion

Sackett DL, Straus SE, Richardson WS, et al. Evidence-Based Medicine: How to Practice and Teach EBM. 2nd ed. Edinburgh, Scotland:Churchill Livingstone Inc; 2000:173-177.

ISSUES WITH THESE EARLY HIERARCHIES OF EVIDENCE

- They were meant for evidence about therapy
- Other kinds of evidence is also needed in clinical practice and for health decisions
- Each kind of clinical/research question is best answered by specific study designs
- Not all studies of the same design on the same topic provide reliable estimates
- Evidence from the best primary design may not always be available nor provide the best evidence
- Mainly addressed internal validity; largely ignored external validity
- Provided levels of evidence based on strength of the research design (Hierarchies of methods)

TYPES OF QUESTIONS, STUDY DESIGNS AND LEVELS OF EVIDENCE (OCEBM)

Level of evidence	Intervention	Prognosis	Diagnosis	Etiology
Least biased **I**	Systematic Review of RCTs	Systematic Review of inception cohort studies	Systematic Review of Cross sectional studies	Systematic Review of prospective cohort studies
II **(Appropriate primary study design)**	**RCT**	**Inception cohort study**	**Cross sectional study among consecutive patients**	**Prospective cohort study**
III	•Non-randomized controlled clinical trial •Controlled before and after study •Interrupted time series •Cohort study •Case control study	•Untreated controls in an RCT •Retrospectively assembled cohort study	•Cross sectional study among non-consecutive patients •Case control study	•Retrospective cohort study •Case control study
Most biased **IV**	Case series	Case series	Case series Cohort of patients at different stages of disease	Cross sectional study

Least bias ← Most bias

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

GRADES OF EVIDENCE FOR RECOMMENDATIONS

Grades of Recommendation		Strength of Evidence
A	Strong Evidence	A preponderance of level I and/or level II studies support the recommendation. This must include at least 1 level I study.
B	Moderate Evidence	A single high-quality randomized controlled trial or a preponderance of level II studies support the recommendation
C	Weak Evidence	A single level II study or a preponderance of level III and IV studies including statements of consensus by content experts support the recommendation
D	Conflicting Evidence	Higher-quality studies conducted on this topic disagree with respect to their conclusions. The recommendation is based on these conflicting studies
E	Theoretical/ Foundational Evidence	A preponderance of evidence from animal or cadaver studies, from conceptual models/principles, or from basic sciences/bench research support this conclusion
F	Expert Opinion	Best practice based on the clinical experience of the guidelines development team

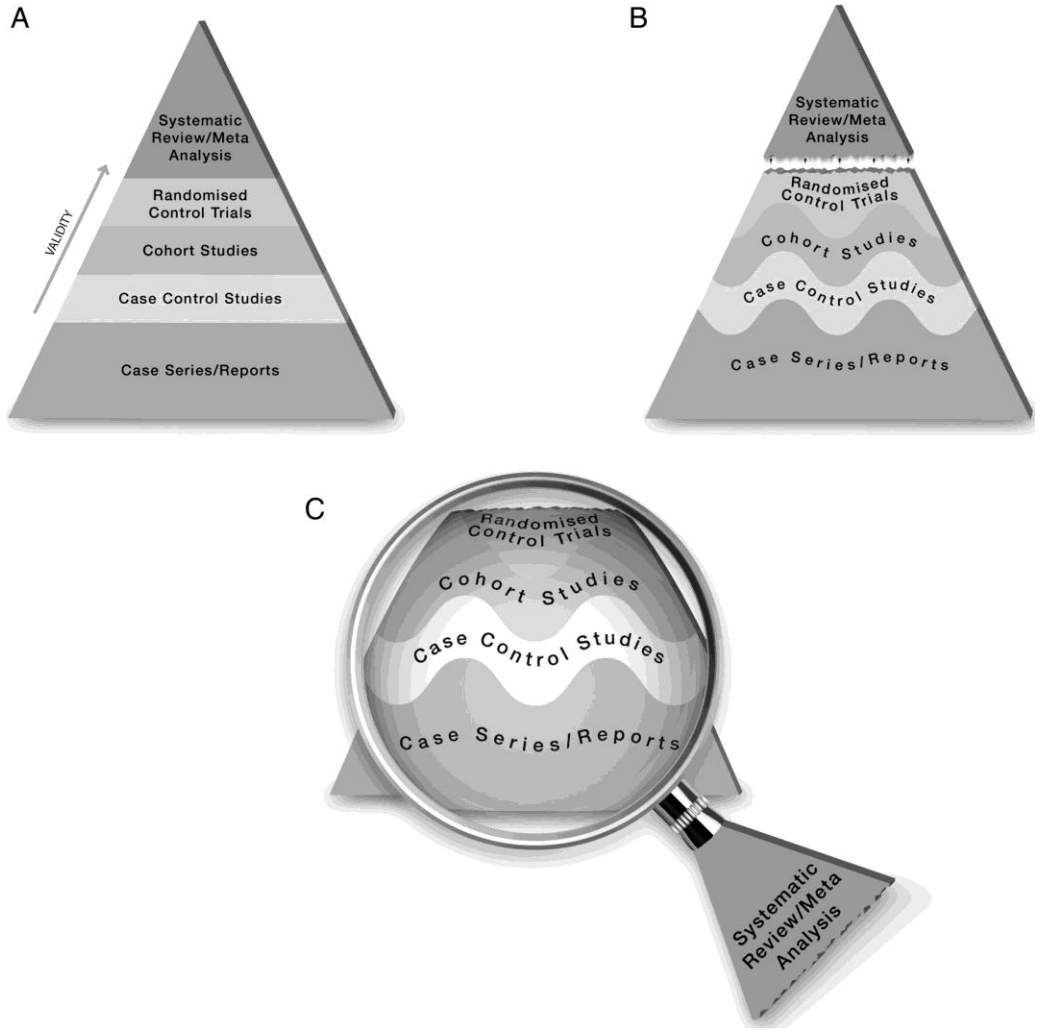
Guyatt GH, Sackett DL, Sinclair JC, et al. Users' guides to the medical literature. IX. A method for grading health care recommendations. Evidence-Based Medicine Working Group. JAMA. 1995;274(22):1800-1804.

Two issues identified here: Hierarchies in the Strength of the Evidence and the Hierarchies in the Strength of Recommendations

CURRENT APPROACHES TO ADDRESS THESE ISSUES

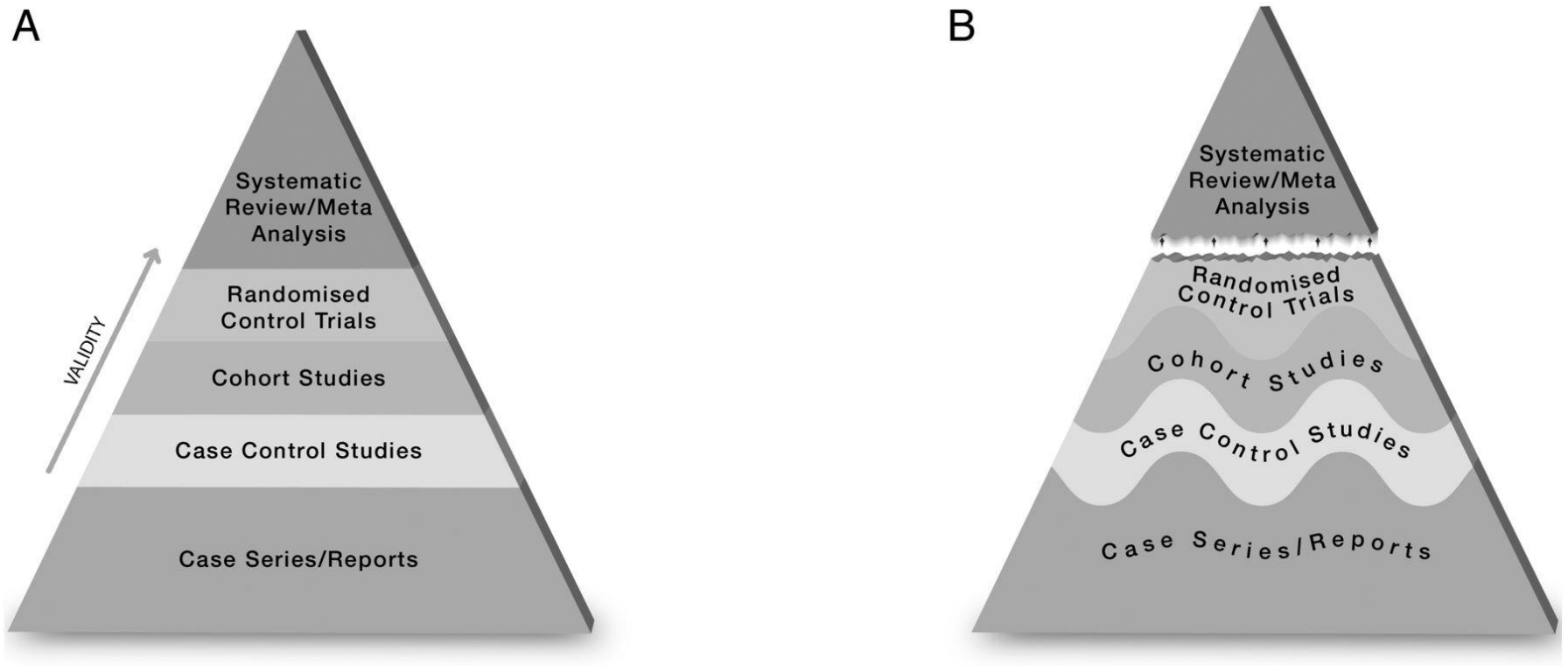
Conditional Hierarchies as opposed to **Absolute Hierarchies**

The proposed new evidence-based medicine pyramid.



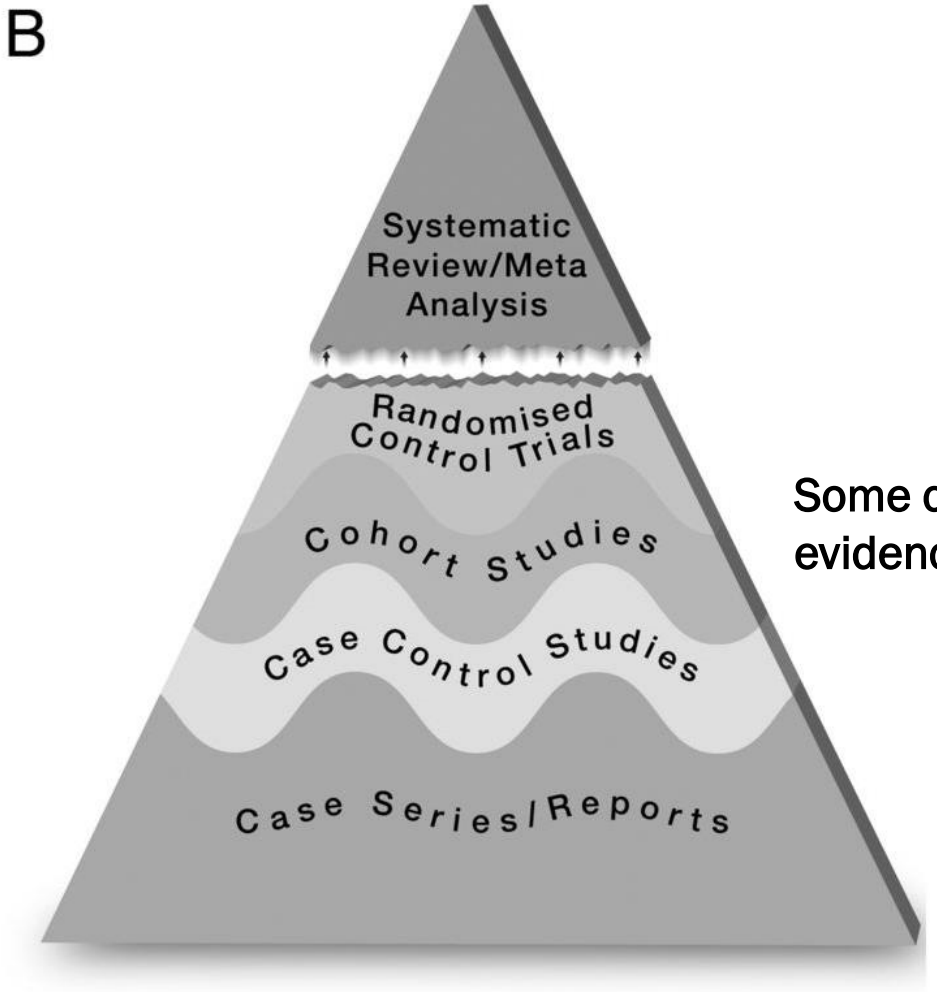
M Hassan Murad et al. Evid Based Med 2016;21:125-127

The proposed new evidence-based medicine pyramid.



M Hassan Murad et al. Evid Based Med 2016;21:125-127

The proposed new evidence-based medicine pyramid.



Some cohort studies may provide better evidence than some RCTs

M Hassan Murad et al. Evid Based Med 2016;21:125-127

The proposed new evidence-based medicine pyramid.



- Systematic reviews (and meta-analyses) are the tools used to appraise the evidence
- Conditional Hierarchies for the Certainty in the Evidence and the Strength of Recommendations

M Hassan Murad et al. Evid Based Med 2016;21:125-127

MOVING FROM EVIDENCE TO POLICY & PRACTICE

GRADE

GRADE Summary of Findings (SoF) Tables (Evidence Summaries) from Systematic Reviews

GRADE Evidence to Policy framework for guideline developers

Research



Evidence



Practice

Getting the evidence right

Getting the evidence used

GRADEpro GDT

EVALUATING THE RESULTS OF A SYSTEMATIC REVIEW:

- In order to be confident about the results of a systematic review to inform policy decisions, we need to know:

1. **Does the systematic review suffer from any critical flaws in its methods so that its results are unreliable?**

RESEARCH METHODS AND REPORTING

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

Beverley J Shea,[1,2,3] Barnaby C Reeves,[4] George Wells,[3,5] Micere Thuku1,[2] Candyce Hamel,[1] Julian Moran,[6] David Moher,[1,3] Peter Tugwell1,[2,3,7] Vivian Welch,[2,3] Elizabeth Kristjansson,[8] David A Henry[9,10,11]

Box 1: AMSTAR 2 critical domains

- Protocol registered before commencement of the review (item 2)
- Adequacy of the literature search (item 4)
- Justification for excluding individual studies (item 7)
- Risk of bias from individual studies being included in the review (item 9)
- Appropriateness of meta-analytical methods (item 11)
- Consideration of risk of bias when interpreting the results of the review (item 13)
- Assessment of presence and likely impact of publication bias (item 15)

AMSTAR 2 has 16 items assessing potential weaknesses in the review

7 items are considered critical flaws and 9 items are considered non-critical

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

Box 2: Rating overall confidence in the results of the review

- **High**
- *No or one non-critical weakness*: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest
- **Moderate**
- *More than one non-critical weakness**: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review
- **Low**
- *One critical flaw with or without non-critical weaknesses*: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest
- **Critically low**
- *More than one critical flaw with or without non-critical weaknesses*: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence.

EVALUATING THE RESULTS OF A SYSTEMATIC REVIEW:

- In order to be confident about the results of a systematic review to inform policy decisions, we need to know:

2. **What do the results tell us?**

   A. **Do the pooled effect estimates (with 95% CIs) for each clinically important outcome indicate appreciable advantages?**

      - Efficacy | Safety | Adherence | Costs | Quality of life | Other

   B. **How confident are we that:**

      a) **these estimates are likely to be the true ?**

      b) **these effects are likely to be seen in actual practice?**

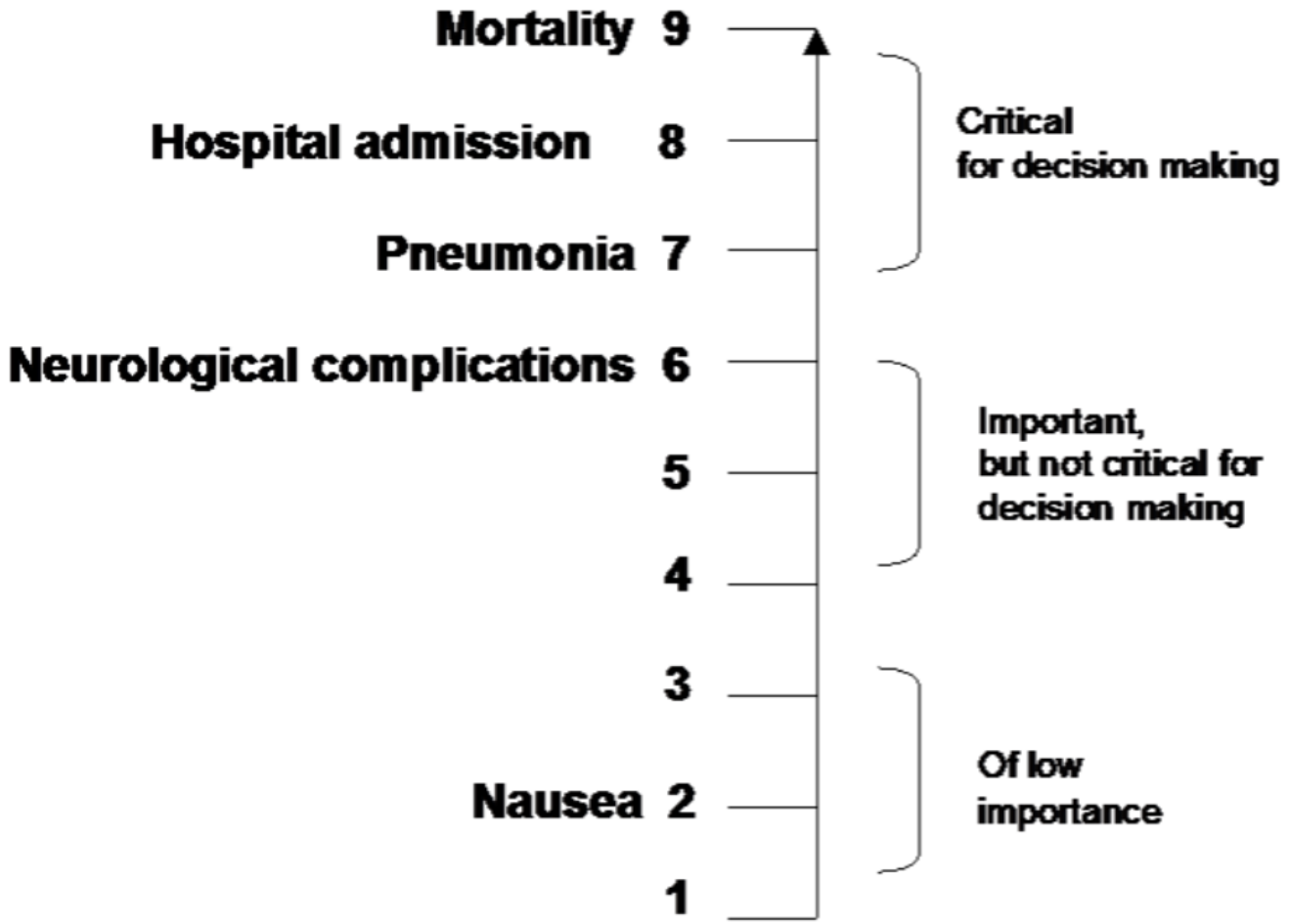
      c) **that further research will not change these estimates?**

GRADE IS APPLIED TO OUTCOMES:
SELECT OUTCOMES THAT ARE CRITICALLY IMPORTANT/IMPORTANT

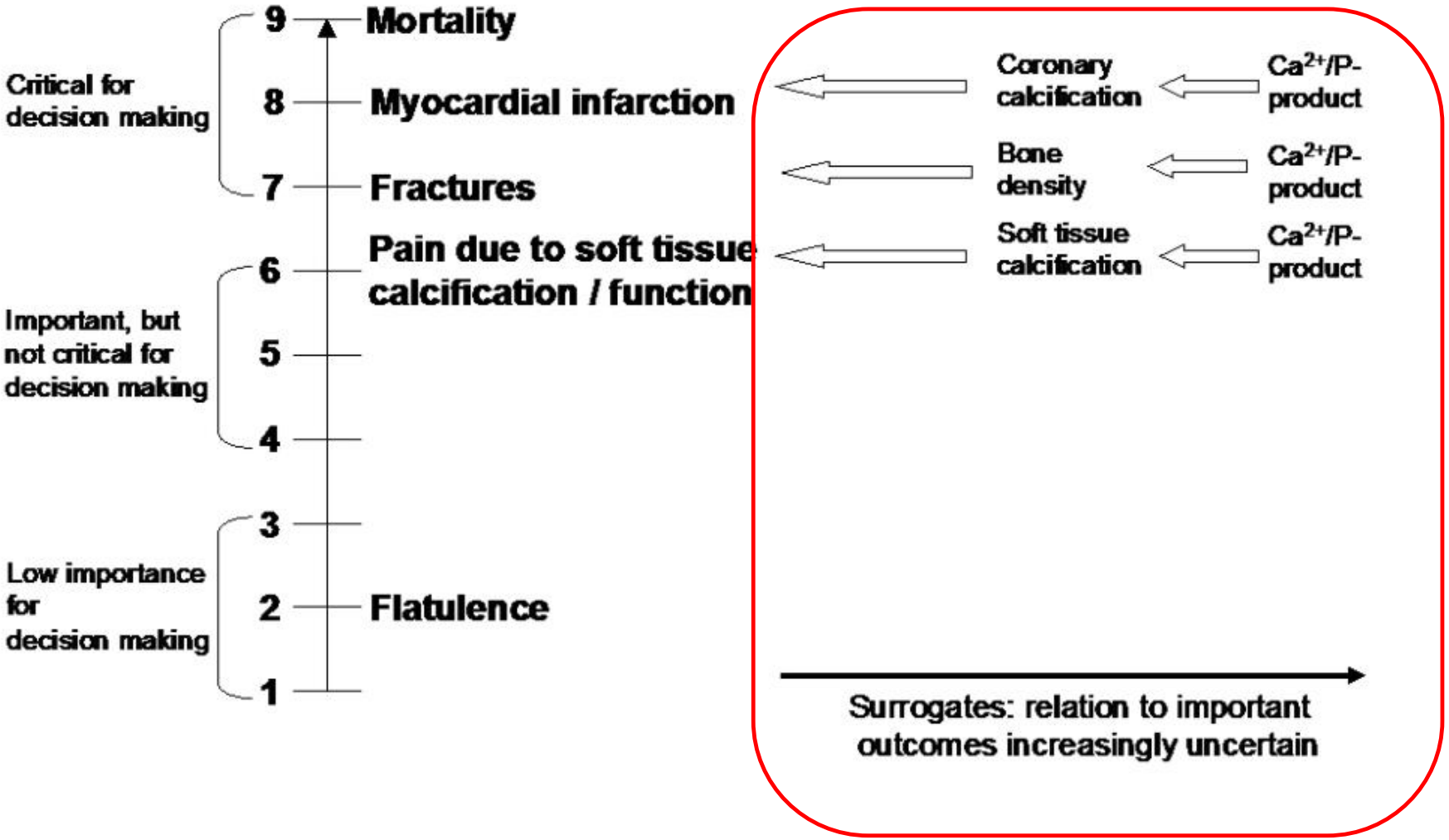
rating scale:								
1	2	3	4	5	6	7	8	9
of **least** importance								of **most** importance
of limited importance for making a decision (not included in evidence profile)			important, but not critical for making a decision (included in evidence profile)			Critical for making a decision (included in evidence profile)		

- A separate summary of findings table is created for each comparison (if more than one)
- For each comparison, clinically important outcomes (maximum of 7) are presented with the relative effect estimates and the absolute difference (with 95% CIs)
- For each outcome the GRADE quality (confidence/ certainty) judgement is also presented reflecting the confidence one has in that estimate

VIRAL PNEUMONIA WITH HIGH MORTALITY



PHOSPHATE LOWERING DRUGS IN PEOPLE WITH RENAL FAILURE AND INCREASED PHOSPHATE LEVELS



CONFIDENCE IN THE EVIDENCE FROM SYSTEMATIC REVIEWS IS CONDITIONAL

- **Can we trust the evidence?**
  - The risk of bias of the included trials: (**Study Limitations)**
- **Does the evidence apply to my setting?**
  - The characteristics of the individual trials: Population/comparisons/outcomes/health systems **(Directness)**
- **Are the results consistent in all the trials?**
  - If not, can heterogeneity be explained? **(Inconsistency)**
- **Are the results precise?**
  - Do the upper and lower limits of the 95% CIs show clinically appreciable effects? Are the data sufficient based on the number of participants and number of events? **(Imprecision)**
- **Is there evidence complete?**
  - Did the review include all relevant trials or only easily accessed ones? **(Publication bias)**

Formulate question

Select outcomes

Rate importance

Outcomes across studies

P
I
C
O

Outcome Critical

Outcome Critical

Outcome Important

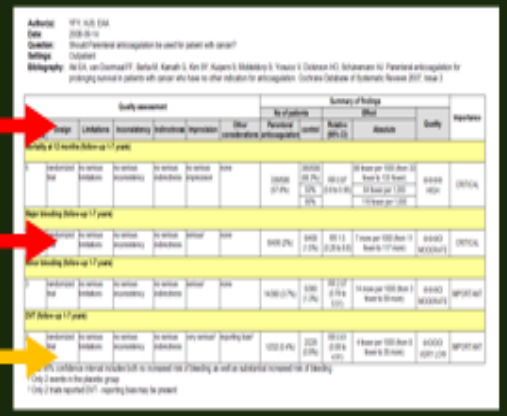
Outcome Not important



Systematic review

Create evidence profile with GRADEpro

Rate quality of evidence for each outcome



Summary of findings & estimate of effect for each outcome

High

Moderate

Low

Very low

RCT start high, obs. data start low

Grade down

1. Risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias

Grade up

1. Large effect
2. Dose response
3. Confounders

GRADE

RCTs HIGH

Observational

Very Low

Factors that can reduce the quality of evidence

- Study limitations [⬇1 or 2 levels]
- Inconsistency of results [⬇1 or 2 levels]
- Indirectness of evidence [⬇1 or 2 levels]
- Imprecision [⬇1 or 2 levels]
- Reporting bias [⬇1 or 2 levels]

Factors that can increase the quality of evidence

- Large magnitude of effect [⬆1 or 2 levels]
- All plausible confounding would reduce observed effect [⬆1 level]
- Dose-response gradient [⬆1 level]

Final level of certainty rating

Certainty in the evidence across those considerations
High ⊕⊕⊕⊕
Moderate ⊕⊕⊕◯
Low ⊕⊕◯◯
Very low ⊕◯◯◯

GRADE

LEVELS OF CERTAINTY OR CONFIDENCE IN THE EFFECT ESTIMATES FOR EACH OUTCOME

Certainty in the evidence across the five domains	*Interpretation*	*Terminology*
⨁⨁⨁⨁ High	We are very confident that the true effect lies close to that of the estimate of the effect; further research is unlikely to change this estimate	It will
⨁⨁⨁◯ Moderate	We are moderately confident that the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different; further research may change this estimate	It probably, or likely, will
⨁⨁◯◯ Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect; further research is likely to change this estimate	It may
⨁◯◯◯ Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect; further research is needed and is very likely to alter these estimates	We are very uncertain

SUMMARY OF FINDINGS

Population: People with confirmed or suspected COVID-19 infection (critical, severe, non-severe)
Setting: At home or in hospital
Intervention: Intervention X, any dose or duration
Comparison: Usual care/ Placebo

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Usual care/placebo	Intervention X				
Death due to any cause	22 per 1000	**84 fewer per 1000 (from 56 fewer to 109 fewer)**	**RR 0.62 (0.51 to 0.75)**	1938 (6 RCTs)	⨁⨁⨁⨁ **HIGH** [1,2]	Intervention X **substantially reduces** the risk of death
Progression to mechanical ventilation	270 per 1000	**146 fewer per 1000 (from 35 fewer to 202 fewer)**	**RR 0.46 (0.25 to 0.87)**	185 (2 RCTs)	⨁⨁⨁⨀ **LOW**[3,4] Due to indirectness and inconsistency	Intervention X **may reduce** the need for ventilation **to moderate extent**
Negative PCR by day 7	300 per 1000	**110 more per 1000 (from 50 fewer to 210 more)**	**RR 1.40 (0.82 to 2.13)**	684 (6 RCTs)	⨁⨀⨀⨀ **VERY LOW** [5,6,7] Due to indirectness, inconsistency and imprecision	**The evidence is very uncertain** about the effects of Intervention X on negative PCR by day 7
Adverse events	420 per 1000	**198 more per 1000 (from 220 fewer to 200**	**RR 0.46 (0.25 to 1.28)**	1485 (5 RCTs)	⨁⨁⨁⨀ **MODERATE** [7]	Intervention X probably does not differ in

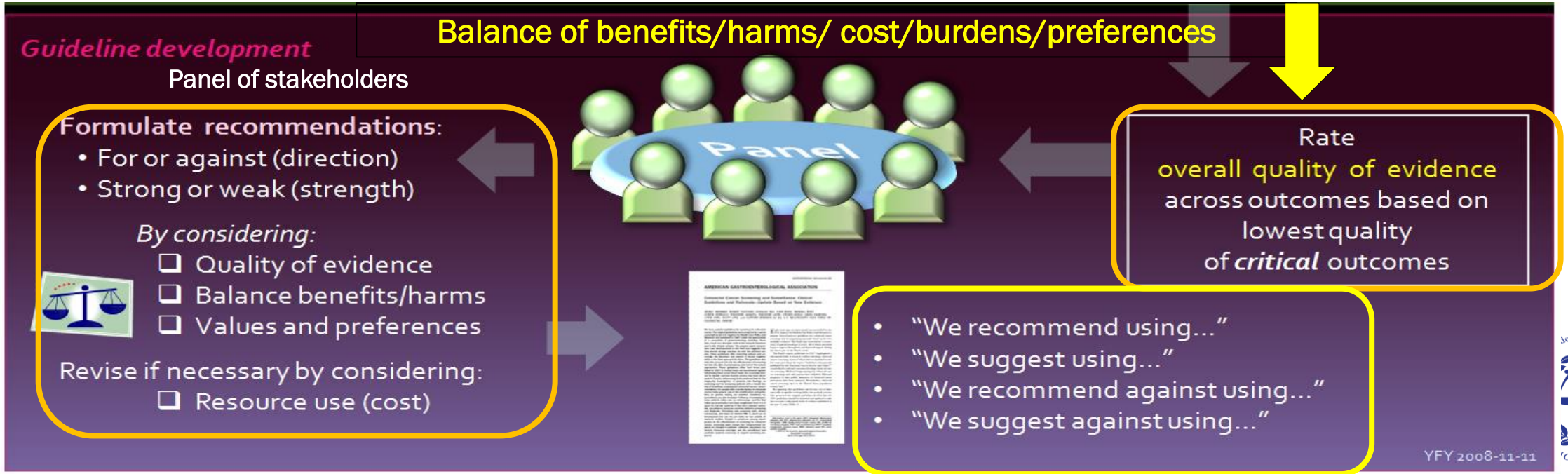
GRADE

Strength of the recommendations

- **Strong recommendation:** most informed patients would choose the recommended management
- **Conditional recommendation:** patients' choices will vary according to their values and preferences

The overall confidence in the result

⊕⊕⊕⊕ High	Further research is very unlikely to change our confidence in the estimate of effect.
⊕⊕⊕◯ Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
⊕⊕◯◯ Low	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	We are very uncertain about the estimate.



THE ROLE OF EVIDENCE IN POLICY IS ALSO CONDITIONAL

Systematic reviews
Judgements about the impact of policies

Local evidence
Judgements about modifying factors, needs, values, resources

Judgements about the expected benefits, harms, and opportunity costs of policies

Judgements about trade-offs



Desirable impacts
- Health benefits
- Less burdens'
- Savings

Undesirable impacts
- Harms
- More burdens
- Costs

Good health policy

Support tools for Evidence Based Decision Making: *Health Research Policy and Systems 2009, **7(Suppl 1):***

FINAL CAVEAT

- **No fixed hierarchies exist that are valid and useful for the process of health decision-making.**
- The **process is always conditional** on the methods used in research synthesis, the certainty in the evidence for clinically important outcomes, and the context in which the evidence is to be used.
- **Evidence is cumulative;** as new evidence accrues, the numerical estimates and the certainty in the evidence could change
- The certainty of evidence **applies to the population in the studies** providing data for outcomes
- This does not account for **individual variations** and the **"unknown unknowns"**

“If you look at the ending as the beginning and the beginning as the ending, then there is no ending and there is no beginning!”

— Mehmet Murat Ildan (contemporary Turkish playwright)

THANK YOU AND BE SAFE



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