Generating evidence for a guideline recommendation: systematic reviews of evidence, economic evaluation and critical appraisal

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Guideline development process

Scope the guideline

Consider logic models | Consider all relevant evidence for decision-making

Set up guideline panel and external review group

Manage declarations of interest

Formulate questions and select outcomes

Approval - Proposal

Evidence retrieval, assessment, synthesis

Appraise certainty of the body of evidence

GRADE

GRADE CERQual

Formulate recommendations

Include explicit consideration of:
- - Benefits and harms
- - Resource use/feasibility
- - Health equity/non-discrimination
- - Human rights/sociocultural acceptability

Approval - guideline

Disseminate, implement

Evaluate impact

GRC Secretariat support

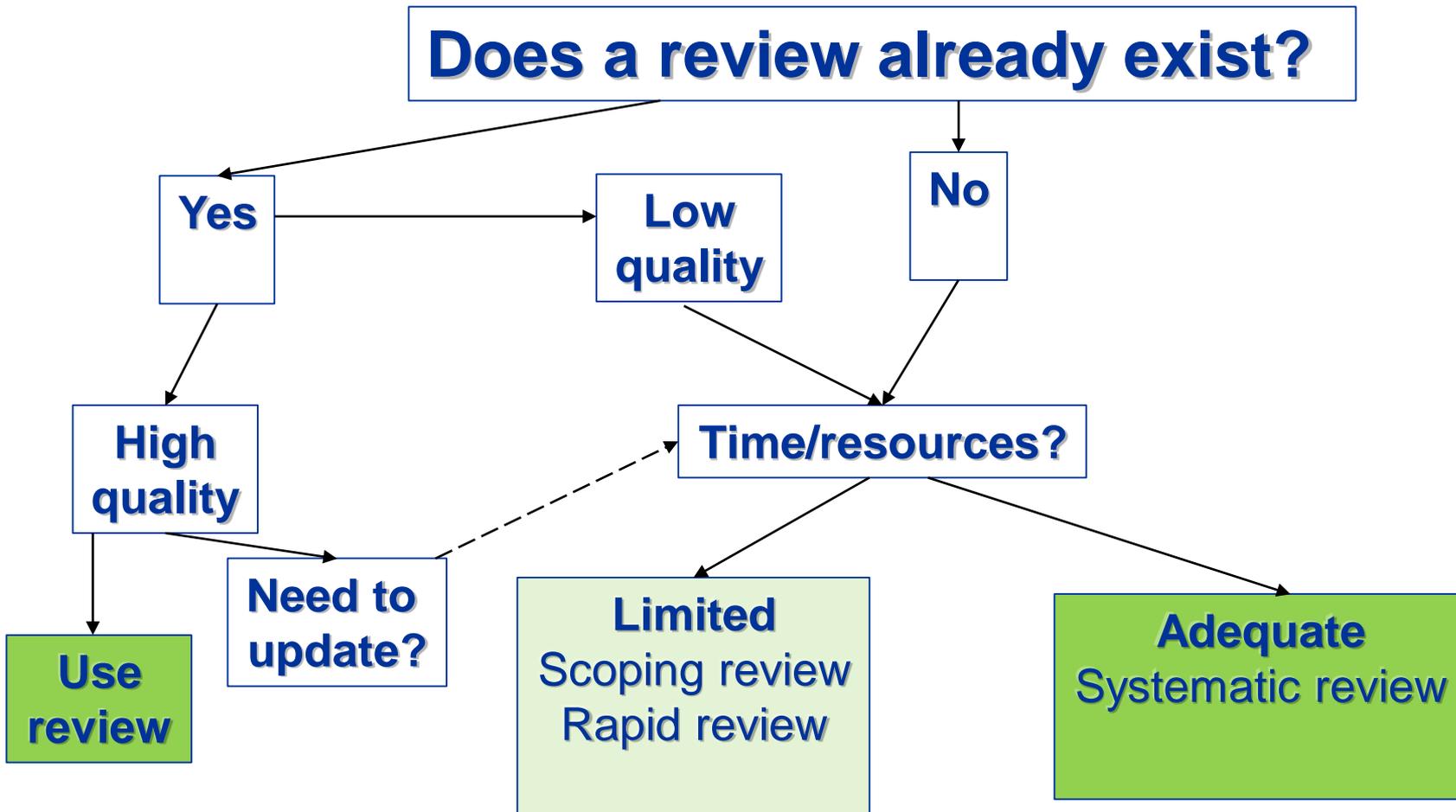# Factors affecting the strength of recommendations

- **Balance between benefits and harms**
  - The larger the relative benefit the more likely a strong recommendation
- **Certainty of the evidence**
  - Higher certainty (quality) evidence more likely to result in a strong recommendation
- **Values and preferences**
  - Decisions for which patient preferences or values are highly important or uncertain more likely to be graded as weak
- **Costs and resource allocation**
  - More costly/less cost-effective interventions less likely to receive a strong grade
- **Other factors**
  - Equity (how would recommendation impact equity)
  - Acceptability
  - Feasibility/ease of implementation

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Types of evidence reviews

Type of review	Purpose	Output	Advantages	Disadvantages
Literature review	Examine recent literature	Narrative summary	Very rapid May assess quality	Unsystematic High risk of bias
Rapid review	Assessment of what is known	Narrative and tabular	Systematic search	Time limited assessment
Scoping review	Assessment of scope of literature	Tabular, with some commentary	Systematic search used	No formal quality assessment
Systematic review	Systematic search and appraisal	Narrative and tabular	Exhaustive and comprehensive Quality assessment	Time/resource intensive
Umbrella review	Review of reviews; focus may be broad	Tabular, with some commentary	Quality assessment	Limited to existing reviews

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Evidence synthesis – how to decide

Does a review already exist?

- Yes
- No

Yes → Low quality

High quality

Low quality → Time/resources?

No → Time/resources?

High quality → Use review

High quality → Need to update? ⇢ Time/resources?

Time/resources? → Limited: Scoping review, Rapid review

Time/resources? → Adequate: Systematic review

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Key features of a systematic review

- Broad search strategy: multiple databases, grey literature

- Defined protocol

- Replicable methods

- Quality appraisal – risk of bias

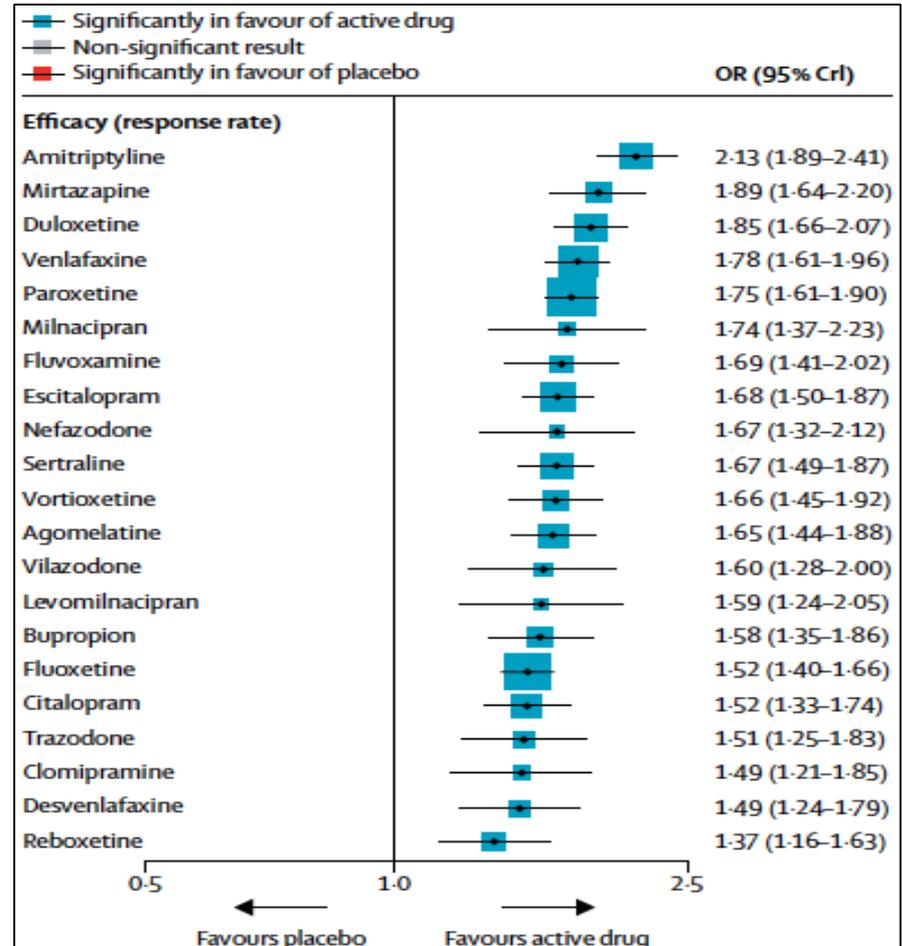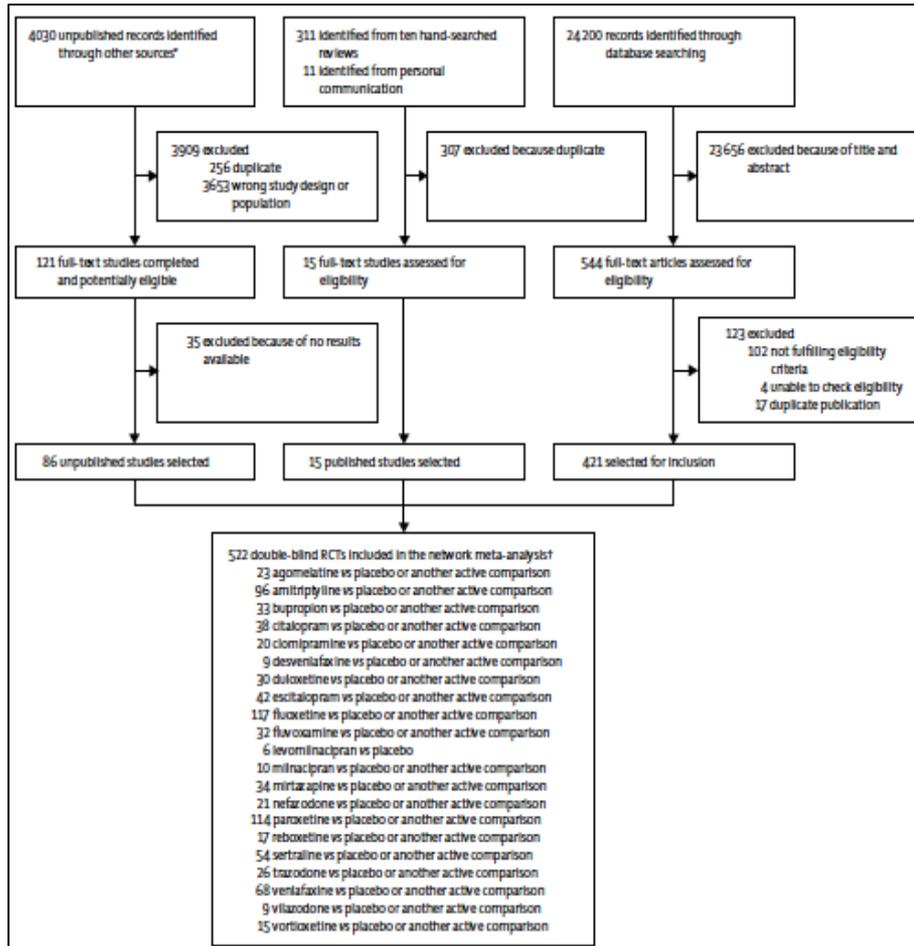- Summary/synthesis of key outcomes

May require a multidisciplinary team: review experts, clinical experts, biostatisticians
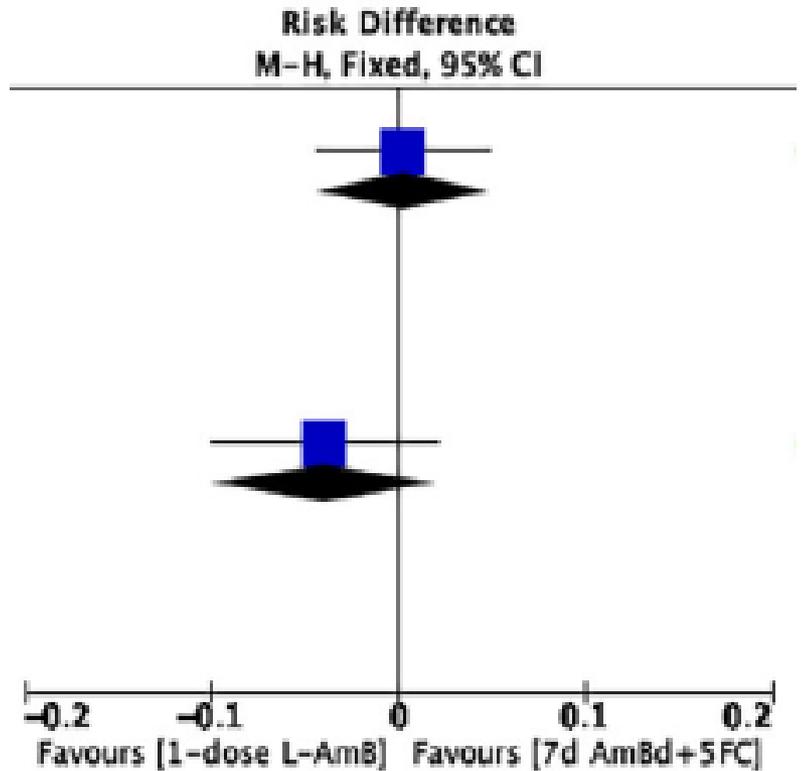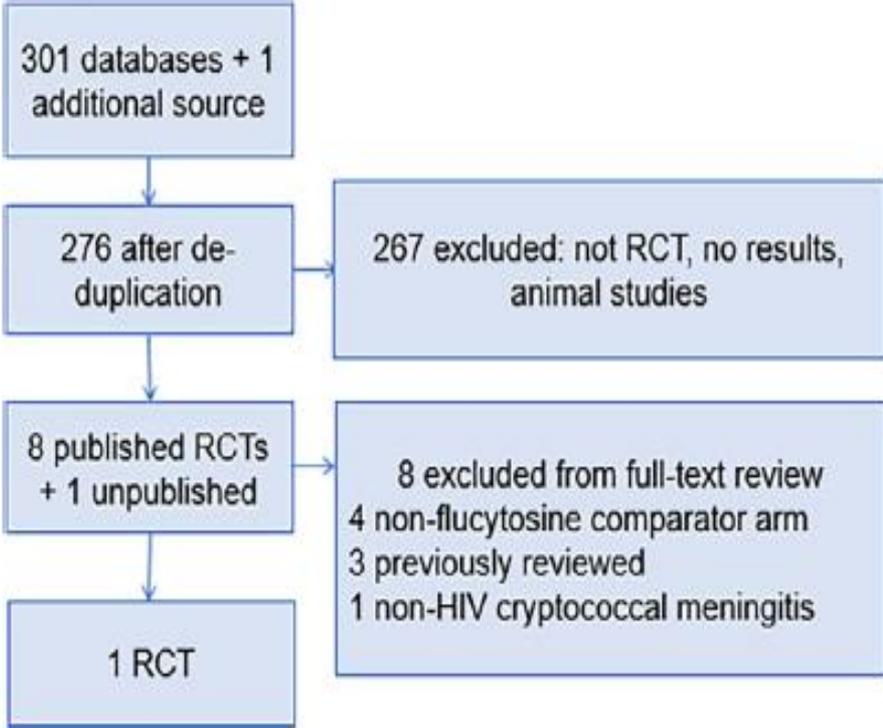
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PICO questions

Population	Who will receive the intervention? General population or a specific population (eg children) Are there sub-groups within these?
Intervention	What is the intervention? Details may include dose, duration, formulation, and delivery methods
Comparator	Would it be likely or possible to compare the intervention to a standard of care? What about different types of interventions being compared to each other?
Outcomes	What are the most important outcomes?

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Example 1: Antidepressants for major depressive disorder

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Example 2: Treatment of cryptococcal disease

301 databases + 1 additional source

→ 276 after de-duplication

→ 267 excluded: not RCT, no results, animal studies

→ 8 published RCTs + 1 unpublished

→ 8 excluded from full-text review
4 non-flucytosine comparator arm
3 previously reviewed
1 non-HIV cryptococcal meningitis

→ 1 RCT

Risk Difference
M–H, Fixed, 95% CI

−0.2   −0.1   0   0.1   0.2
Favours [1-dose L-AmB]   Favours [7d AmBd+5FC]

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Risk of bias assessment

Randomization
Allocation concealment
Blinding
Completeness of data
Completeness of
reporting
Other

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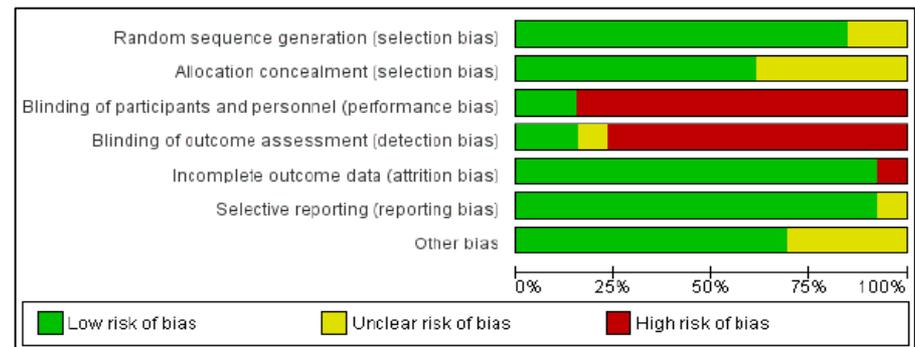
Evidence appraisal: GRADE

The quality and certainty of literature is rated using Grading of Recommendations Assessment, Development and Evaluation (GRADE)

GRADE provides a framework for

- Establishing evidence certainty
- Generating the direction and strength of recommendations
- Developing high quality and trustworthy guidelines

For more on GRADE, visit https://training.cochrane.org/grade-approach

Table: GRADE's approach to rating quality of evidence (aka confidence in effect estimates)

For each outcome based on a systematic review and across outcomes (lowest quality across the outcomes critical for decision making)

1. Establish initial level of confidence		2. Consider lowering or raising level of confidence		3. Final level of confidence rating
Study design	Initial confidence in an estimate of effect	Reasons for considering lowering or raising confidence		Confidence in an estimate of effect across those considerations
		↓ Lower if	↑ Higher if*	
Randomized trials ➔	High confidence	Risk of Bias	Large effect	High ⊕⊕⊕⊕
		Inconsistency	Dose response	
		Indirectness	All plausible confounding & bias	Moderate ⊕⊕⊕○
		Imprecision	• would reduce a demonstrated effect	
Observational studies ➔	Low confidence	Publication bias	or	Low ⊕⊕○○
			• would suggest a spurious effect if no effect was observed	Very low ⊕○○○

*upgrading criteria are usually applicable to observational studies only

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Economic Evaluations

Four main categories to consider

- Health sector costs

- Other sector costs

- Patient and family costs

- Productivity impacts

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Key questions

Is the intervention cost-effective compared to an appropriate alternative?

What will the intervention cost?

Are there necessary resources to implement it? Are there any bottlenecks?

Is this intervention going to improve equity?

What is the return on investment?

What is the opportunity cost of choosing this intervention?

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Cost effectiveness vs costing

Cost effectiveness	Costing
Provides information on the *cost per unit of health gain*	Provides information on the *financial cost of implementation*
Costing is calculated as an annual average cost of all resources used	Costing is calculated as the financial needs in the given year
E.g. multidrug therapy for CVD prevention: *ICER = $18 per HLY gained*	E.g. multidrug therapy for CVD prevention: *$1 per person per year additional to current expenditure*

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Strength of a recommendation

Strong in favour → Almost all informed patients would choose to have the intervention

Conditional in favour → A majority of informed patients would choose to have the intervention but many would not

Conditional against → A majority of informed patients would choose not to have the intervention but many would

Strong against → Almost all informed patients would choose not to have the intervention

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Making decisions

| Quality of evidence	Values and preferences	Balance benefits and harms
Resource implications	Acceptability	Feasibility

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Evidence To Decision Framework

Domain	Strong Recommendation	Conditional Recommendation
Balance of benefits to harms	Benefits highly outweigh harms	Benefits and harms more closely balanced
Quality of evidence	Higher certainty	Lower certainty
Values/preferences regarding outcomes	Benefits to harms assessment unchanged	Values/preferences influence benefits to harms assessment
Acceptability	Highly acceptable	Low or variable acceptability
Costs/resources	Cost savings/cost-effective	Costly/cost-ineffective
Feasibility	Feasible in intended settings	Varies in different settings
Equity	Increases equity	Decreases equity or effects on equity variable

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Example 2: Treatment of cryptococcal disease

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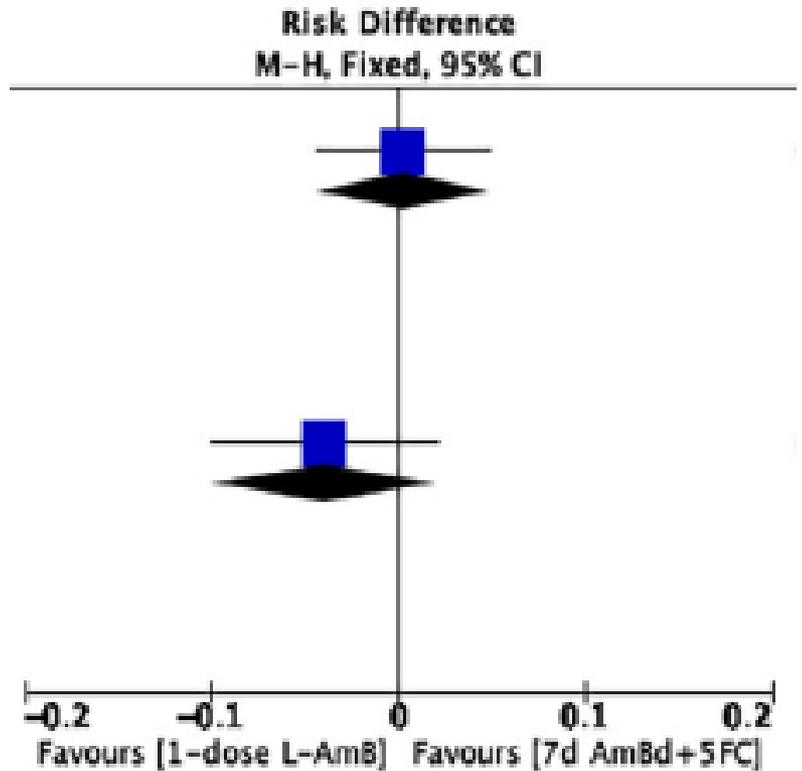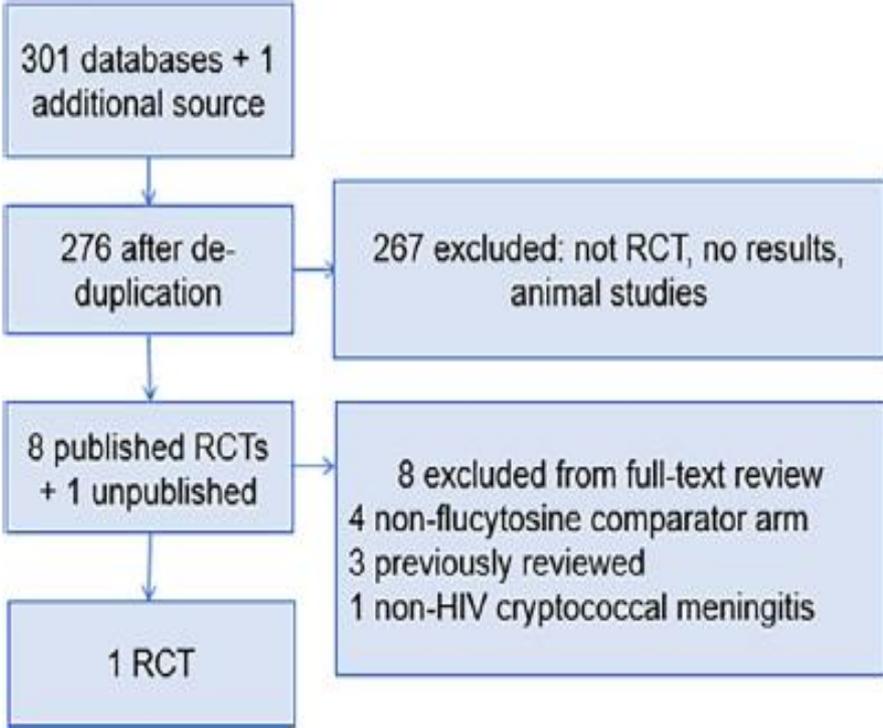
Example: cryptococcal disease

Domain	Source of evidence	Summary
Balance of benefits to harms	Multi country randomized trial	Mortality lower with new treatment Fewer adverse events
Quality of evidence	GRADE assessment	High
Values/preferences and acceptability	Qualitative study within trial	Fewer doses preferred by health workers and patients
Costs/resources	Costing and cost effectiveness	Cost/life year saved = $US80 Cost of drug variable
Feasibility	Trial data	Simpler preparation Fewer intravenous doses needed
Equity	Ethical considerations	Well tolerated/accepted = potential to increase equity
STRONG RECOMMENDATION FAVOURING NEW DRUG		

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Final guideline recommendation

A single high dose of liposomal ampho B should be used as the preferred regimen

Strong recommendation
Moderate certainty evidence