



Evaluating the quality of evidence from a network meta-analysis

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Overview

- Evidence network
 - e.g. topical antibiotics for chronically discharging ears
- GRADE
- Network meta-analysis
- Application of GRADE to network meta-analysis
- Particular attention to
 - transitivity of effects (indirect comparison)
 - contributions of different bits of evidence

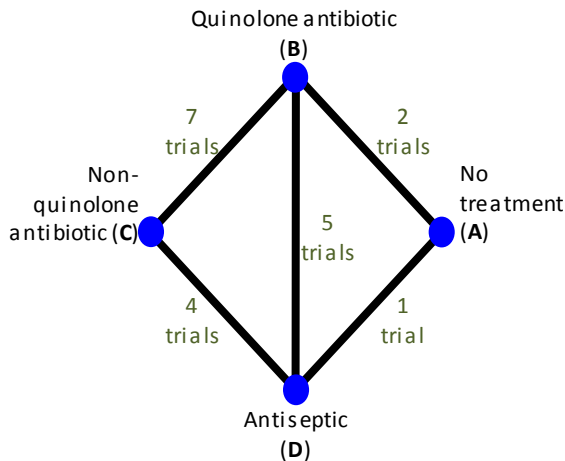


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Evidence network: topical antibiotics for chronically discharging ears



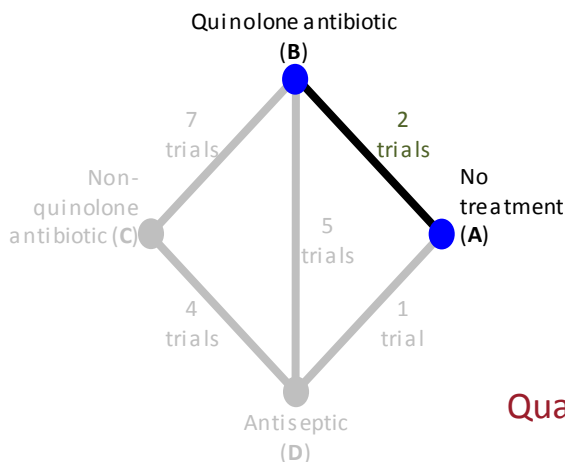
	No. studies	Direct evidence OR (95%CI)	I^2 (P value); τ^2
AB	2	0.09 (0.01, 0.51)	69% (0.07); 1.22
AD	1	1.42 (0.65, 3.09)	N/A; N/A
BC	7	1.46 (0.80, 2.67)	48% (0.07); 0.31
BD	5	3.47 (1.71, 7.07)	66% (0.02); 0.39
CD	4	1.69 (0.59, 4.83)	67% (0.03); 0.75

Outcome: persistent discharge from the ear after 1 week

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Evidence network: topical antibiotics for chronically discharging ears



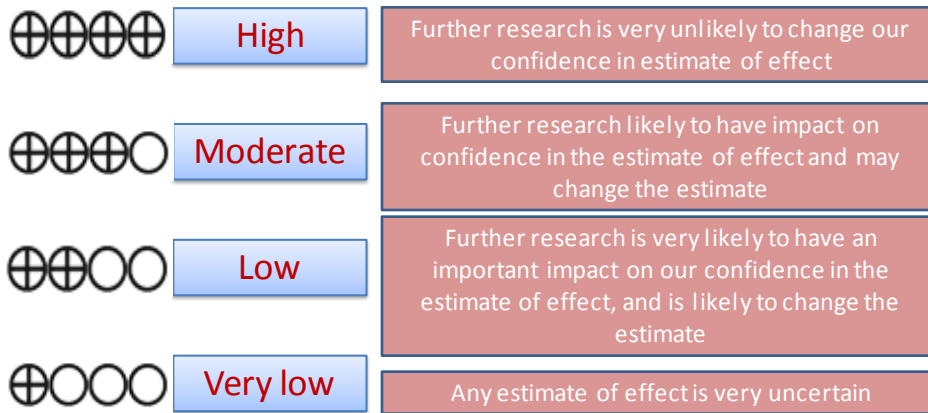
	No. studies	Direct evidence OR (95%CI)	I^2 (P value); τ^2
AB	2	0.09 (0.01, 0.51)	69% (0.07); 1.22

Quality of this evidence?

Outcome: persistent discharge from the ear after 1 week

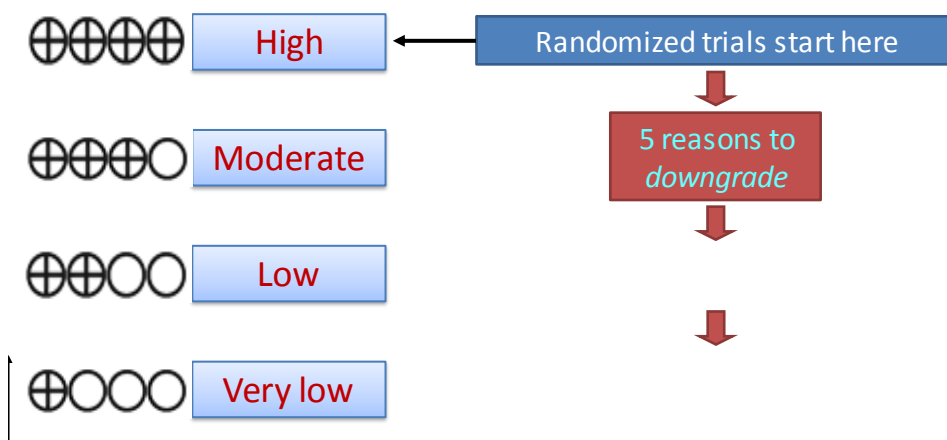
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GRADE in a nutshell



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GRADE in a nutshell



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What might decrease quality of evidence

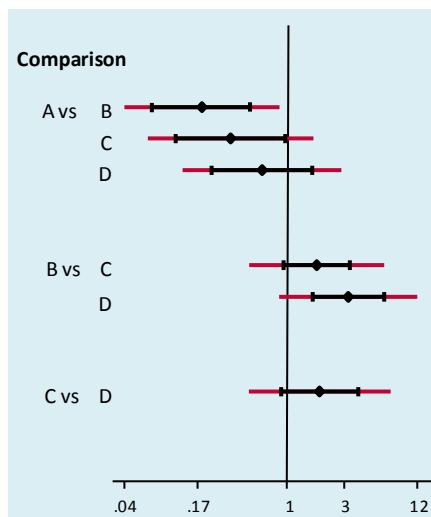
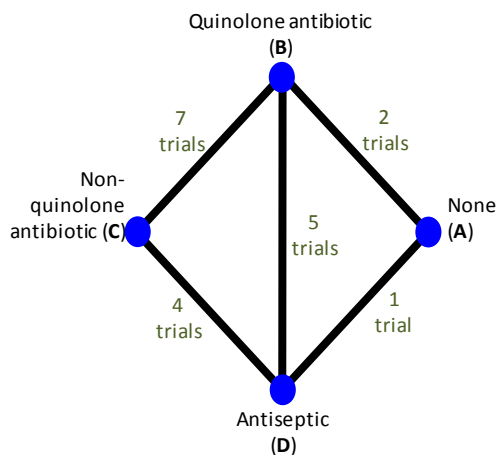
1. Risk of bias
2. Indirectness of evidence
3. Inconsistency of results
4. Imprecision
5. Publication bias



- For each category, 3 scoring options:
 - No concerns
 - Serious -1 level
 - Very serious -2 levels

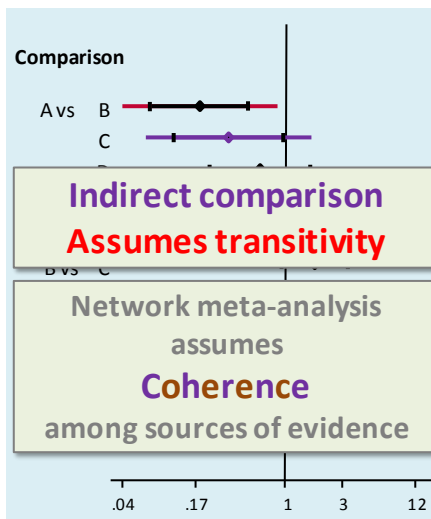
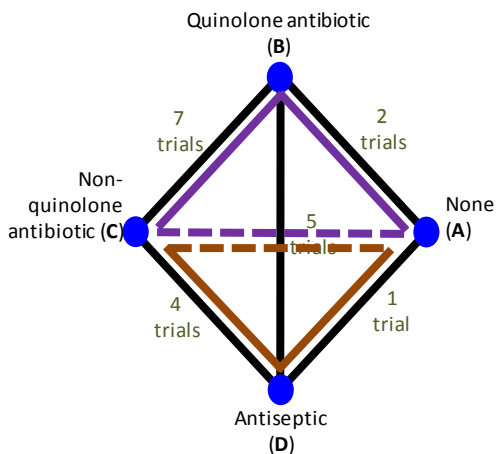
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Network meta-analysis: simultaneous analysis of all the evidence





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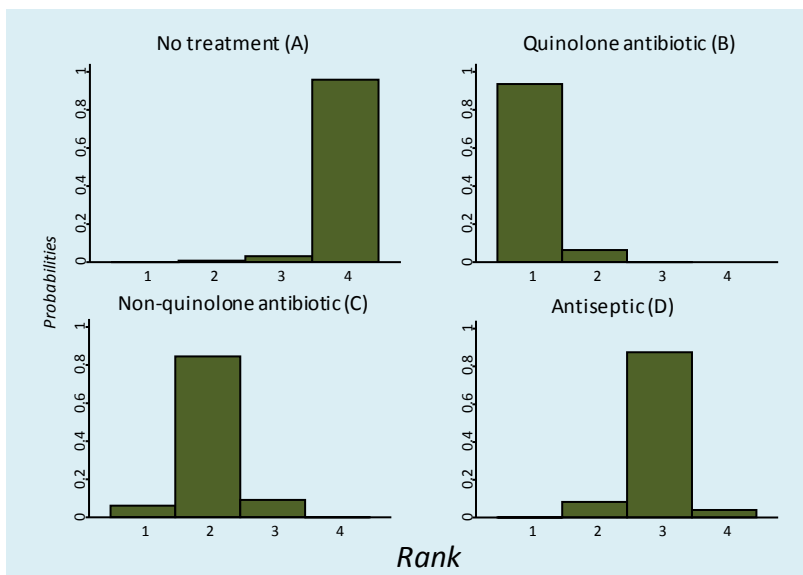


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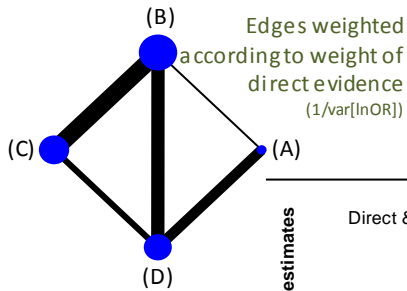
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Network meta-analysis: treatment rankings



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Contributions to the analysis

		Direct comparisons in the network				
		AB	AD	BC	BD	CD
Network meta-analysis estimates	Direct & Indirect					
	AB	12.0	39.0	10.0	29.0	10.0
	AD	12.3	72.3	3.1	9.1	3.2
	BC	1.9	1.9	66.6	13.9	15.8
	BD	6.8	6.8	17.6	51.2	17.6
	CD	4.1	4.1	35.0	30.9	25.9
	Indirect only					
	AC	8.9	32.8	25.5	16.7	16.1
Entire network		8.0	26.6	25.3	25.0	15.1
Included studies		2	1	7	5	4

Lu et al 2011
Krahn et al 2013

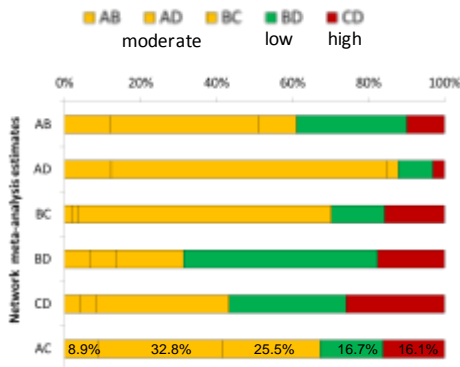
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1. Evaluating risk of bias

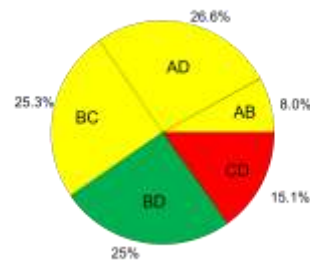
Pairwise estimates

Risk of Bias (RoB) judgments for each direct estimate (as in GRADE)



- For each pairwise comparison, integrate the RoB assessments and the respective contributions

Ranking



- Integrate the RoB assessments and the contribution of each direct evidence to the network as a whole

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2. Evaluating indirectness

Pairwise estimates

Ranking

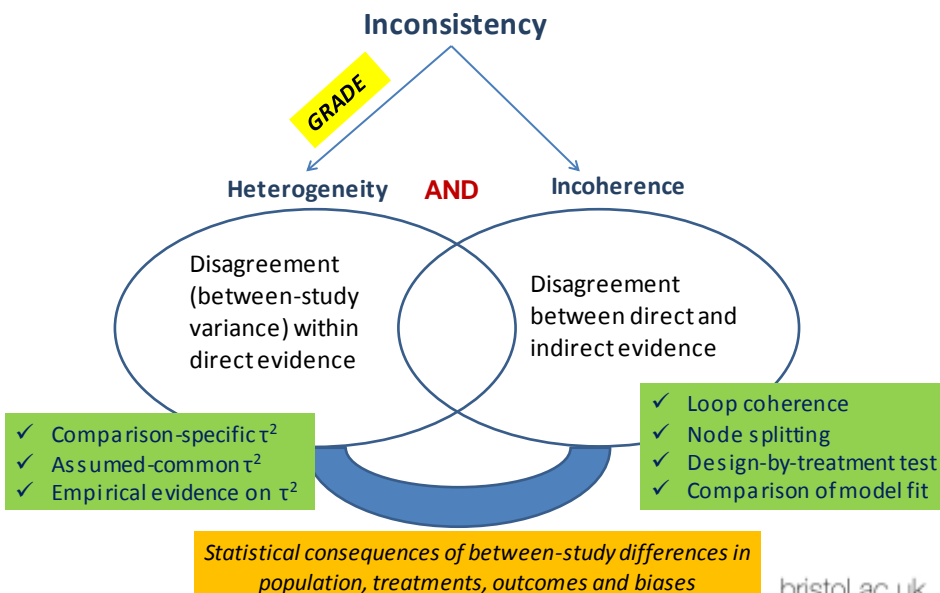
Consider populations, treatments and outcomes (as in GRADE)

Examine similarity of *effects modifiers* across sources of direct evidence

- **transitivity assumption**
- consider contributions of direct evidence to each pairwise network estimates
- consider whole network

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3. Evaluating inconsistency





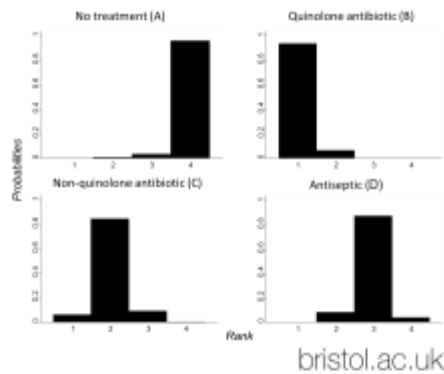
4. Evaluating imprecision

Pairwise estimates

- Examine the width of the confidence intervals (as in GRADE)
- Exclude clinically relevant effect sizes?

Ranking

- Visually examine whole range of probabilities for overlap to assess precision of treatments rankings



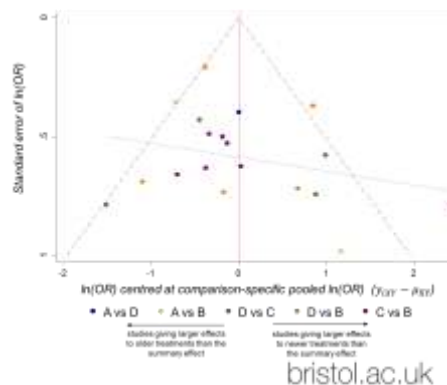
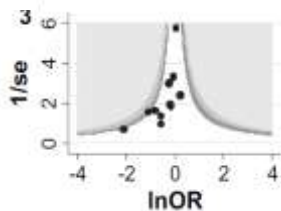
5. Evaluating publication bias

Pairwise estimates

- Use GRADE criteria
- Non-statistical consideration of likelihood of non-publication of evidence
- Could consider a symmetry in *contour-enhanced funnel plots* for each pair-wise comparison

Ranking

- Could consider *comparison-adjusted funnel plot* for the network



- Take into account the contributions of each direct piece of evidence

Summary of confidence in effect estimates

Comparison	Nature of the evidence	Confidence	Downgrading due to
AB: Quinolone antibiotic vs no treatment	Mixed	Low	Study limitations ¹ ; Indirectness ²
AC: Non-quinolone antibiotic vs no treatment	Indirect only	Low	Study limitations ¹ ; Inconsistency ³
AD: Antiseptic vs no treatment	Mixed	Very low	Study limitations ¹ ; Imprecision ⁴ ; Indirectness ³
BC: Non-quinolone antibiotic vs quinolone antibiotic	Mixed	Very low	Study limitations ¹ ; Imprecision ⁴ ; Indirectness ³
BD: Antiseptic vs quinolone antibiotic	Mixed	Moderate	Inconsistency ³
CD: Antiseptic vs non-quinolone antibiotic	Mixed	Very low	Study limitations ¹ ; Imprecision ⁴ ; Indirectness ³
<i>Ranking of treatments</i>		<i>Low</i>	<i>Study limitations⁵; Inconsistency⁶</i>

¹Dominated by evidence at high or moderate risk of bias.

²No convincing evidence for the plausibility of the transitivity assumption.

³Predictive intervals include effects with different interpretations (also no convincing evidence for plausibility of transitivity assumption).

⁴Confidence intervals include values favouring either treatment.

⁵60% of the information is from studies at moderate risk of bias.

⁶Moderate level of heterogeneity, and some evidence of incoherence in the network.

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Concluding remarks

- Confidence in findings of network meta-analysis should consider **both pair-wise estimates and any ranking** of treatments
- Key issues in addition to pair-wise meta-analysis are
 - **transitivity assumption** required for indirect comparisons
 - extension of 'directness' in GRADE
 - **coherence** between direct and indirect evidence
 - extension to 'inconsistency' in GRADE
- Our suggestions are workable but subjective
- We encourage use of the **contributions of direct evidence** to the network estimates and the network as whole

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References

- Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JPT. Evaluating the quality of evidence from a network meta-analysis. *PLoS One* 2014; 9: e99682. doi: 10.1371/journal.pone.0099682.

Example:

- Macfadyen CA, Acuin JM, Gamble C. Topical antibiotics without steroids for chronically discharging ears with underlying eardrum perforations. *Cochrane Database Syst Rev* 2005; CD004618.

Contributions of direct evidence:

- Krahn U, Binder H, König J. A graphical tool for locating inconsistency in network meta-analyses. *BMC Med Res Methodol* 2013; 13: 35.
- Lu G, Welton NJ, Higgins JPT, White IR, Ades AE. Linear inference for mixed treatment comparison meta-analysis: a two-stage approach. *Research Synthesis Methods* 2011; 2: 43-60.

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