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Health Solutions

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An Introduction to Network Meta-Analysis

The power of **knowledge.**
The value of **understanding.**

Meet Our Team

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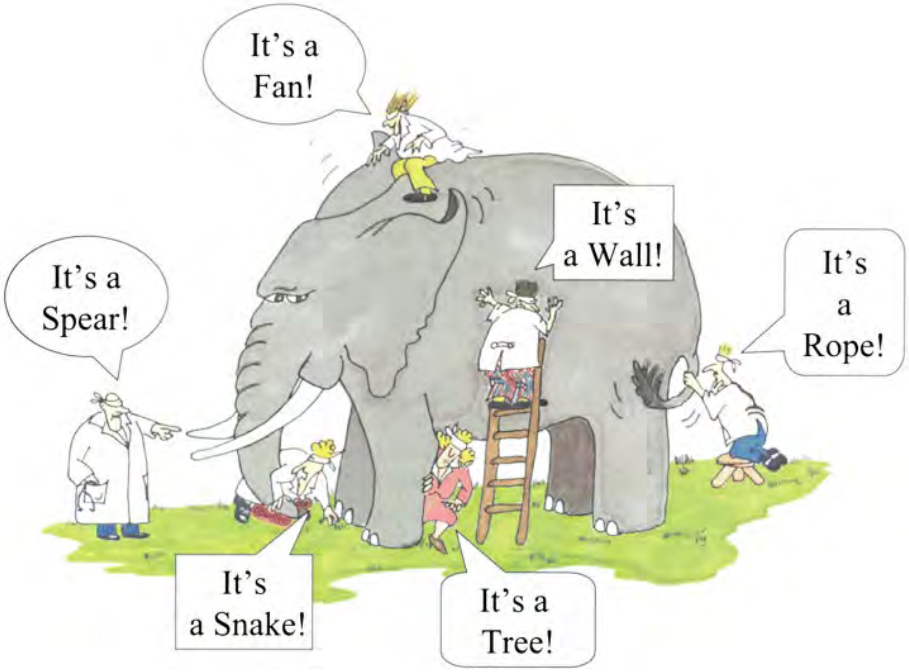
Learning Objectives

- Understand terms such as direct and indirect comparisons, mixed-treatment comparisons, and network meta analyses (NMAs) and why they are used
- Know the difference between analytic approaches such as fixed and random effects models, and frequentist and Bayesian methods
- Understand concepts, assumptions and limitations of NMAs, such as heterogeneity, inconsistency, and bias

NMA: The Big Picture!

Medicine will advance more within the next 10 years than it did in the last 100 years

- Many treatment options for the same indication
- Randomised controlled trials (RCTs) of A vs. B vs. C vs. D almost never exist
- Instead RCTs compare A vs. P, B vs. P etc.
- How do we determine which treatment is “best”?



Why Do We Conduct NMAs?

- Each year, more than 1,000,000 articles are published in more than 20,000 journals.
- In 2017, 343 publications of RCTs in schizophrenia in PubMed
  - Almost one per day!
- NMAs valuable tool for:
  - Practitioners, researchers, and decision-makers
  - Supporting all stages of a product's life cycle

What is Meta-Analysis?

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Individual study results

- Study 1
- Study 2
- Study 3
- Study 4
- Study 5

Network meta-analysis

- Of treatments and between treatments for outcomes of interest

Overall effect

- Of other characteristics on outcomes and treatment effects

What is Meta-Analysis?

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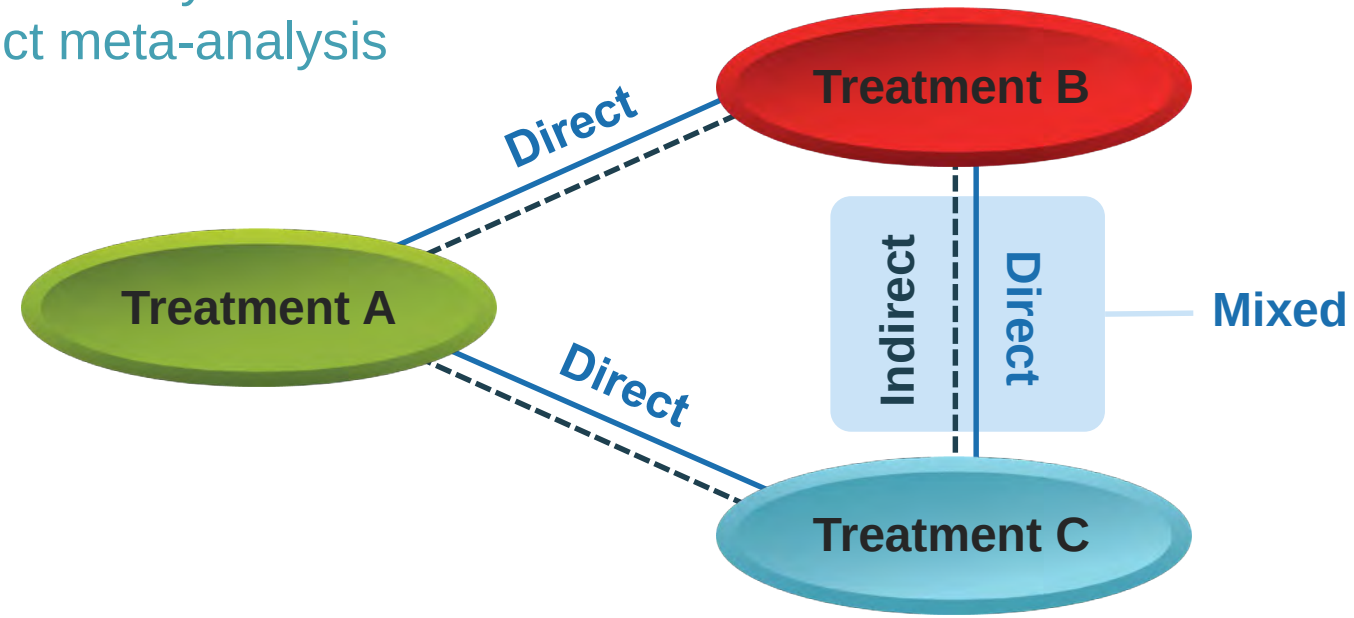
Direct meta-analysis vs. indirect meta-analysis



- **Indirect comparison**
  – when only two (or one pair of) treatments are being compared indirectly

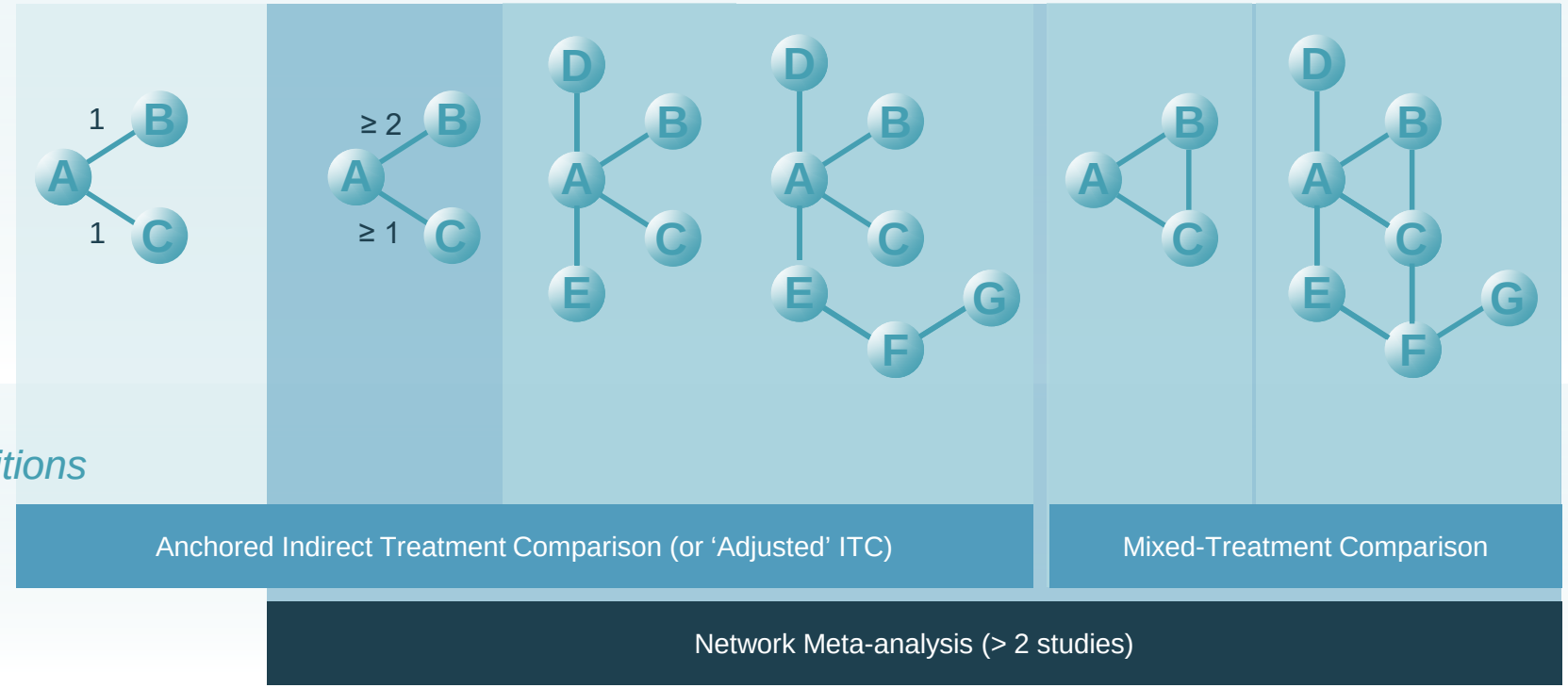
- **Mixed treatment comparisons**
  – a generalization of indirect comparisons with more than two (or multiple pairs of) treatments being compared indirectly

What Is NMA?

A systematic method for pooling the evidence from independent sources, especially randomized, controlled trials (RCTs)

Networks of evidence

Closed loops in network: combination of direct and indirect evidence



Definitions

Figure adapted from:
https://www.ispor.org/workpaper/interpreting-indirect-treatment-comparison-and-network-meta-analysis-studies-for-decision-making.pdf

Who is faster, the red or blue runner?

*The red runner finishes in **9.75** sec*

*The green runner finishes in **10.25** sec*

Tuesday afternoon

*The blue runner finishes in **10** sec*

*The green runner finishes in **10.75** sec*

Saturday morning

Conducting an NMA

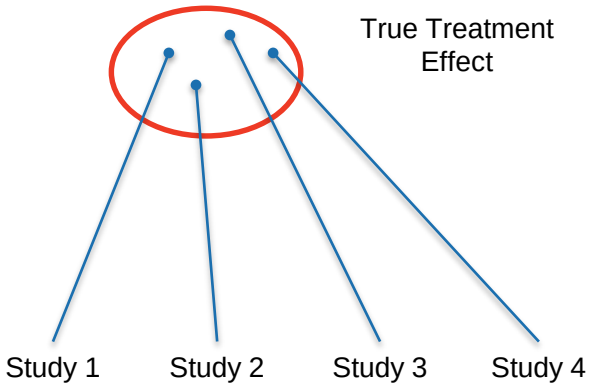
1. Develop systematic review protocol, conduct literature searches, and screen articles.
2. Extract study-level information and conduct a feasibility assessment
3. Plan the meta-analysis for each endpoint and extract arm-level data.
4. Perform heterogeneity and inconsistency analyses, perform NMA.
5. Report findings of the NMA.

Alternative Modelling Approaches

Frequentist Inference

Parameter estimates based on sample from population with assumed distribution

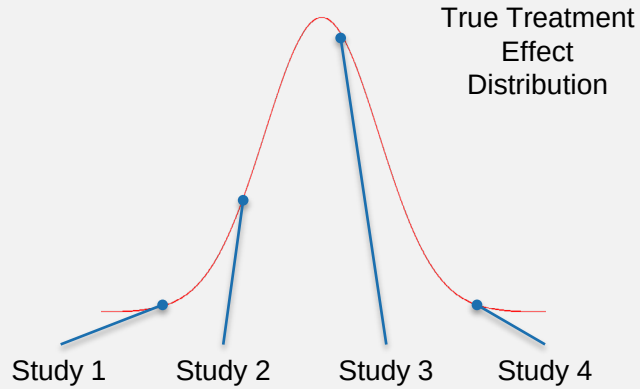
Fixed Effect



Bayesian Inference

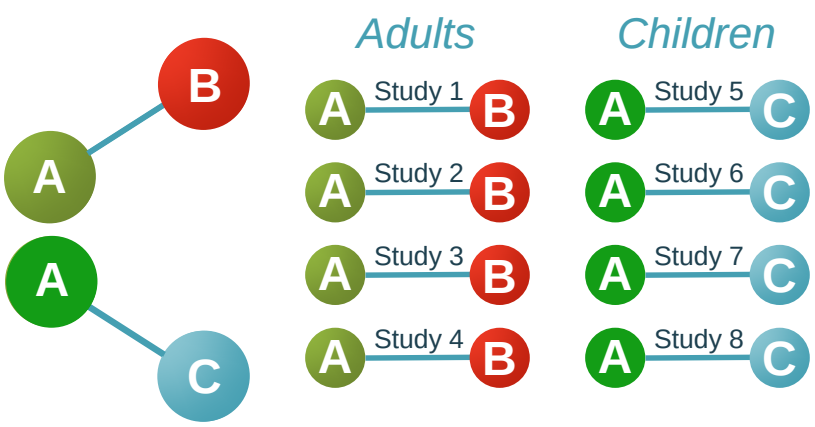
Parameter estimates drawn from posterior distribution which is product of prior and likelihood function

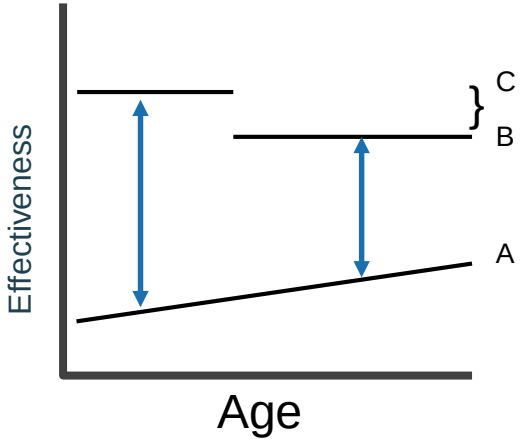
Random Effect



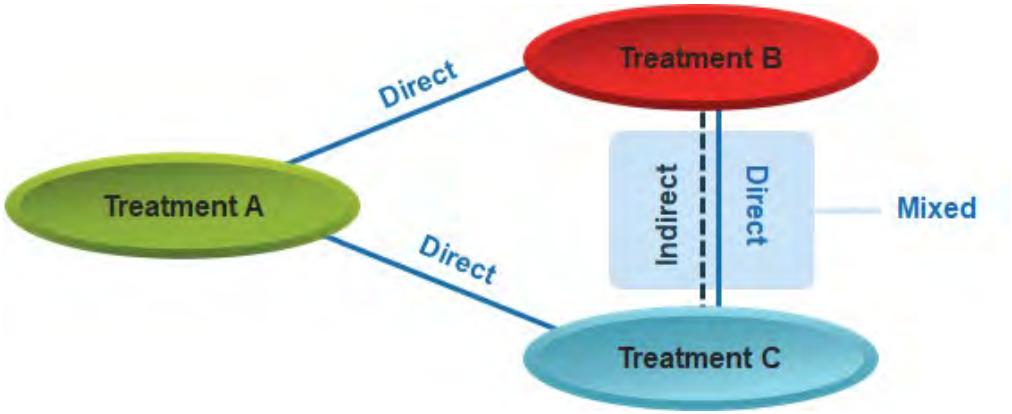
Exchangeability, heterogeneity and inconsistency

- Key assumption underlying NMA is exchangeability





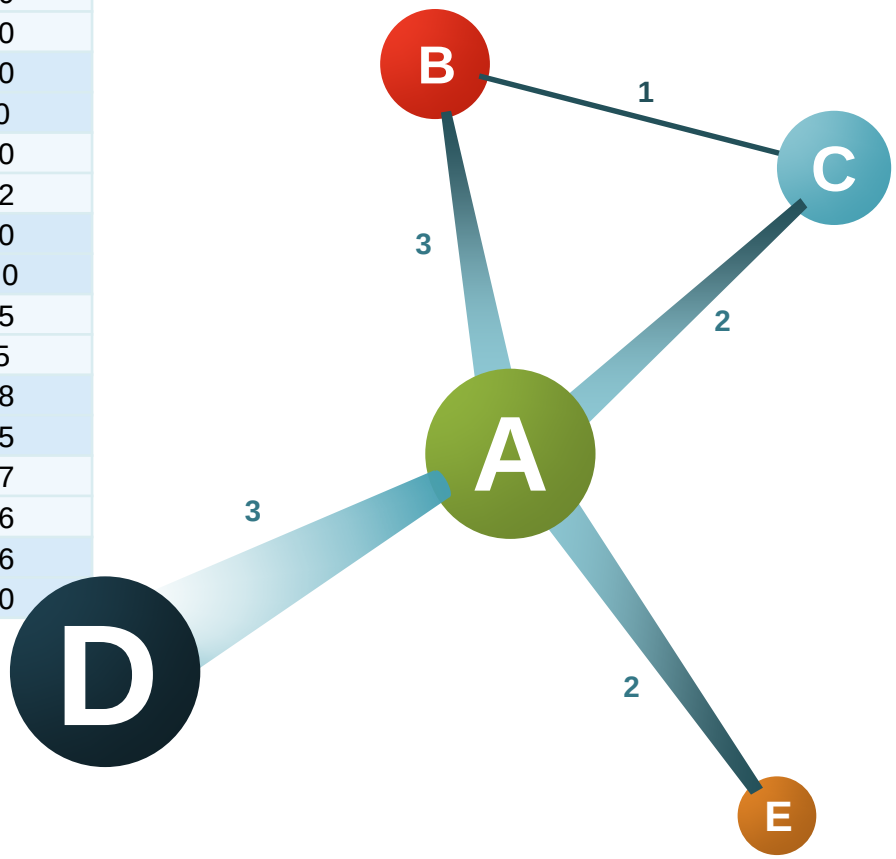
- Heterogeneity – Differences between duplicate evidence for same comparison
- Consistency – direct and indirect evidence in agreement



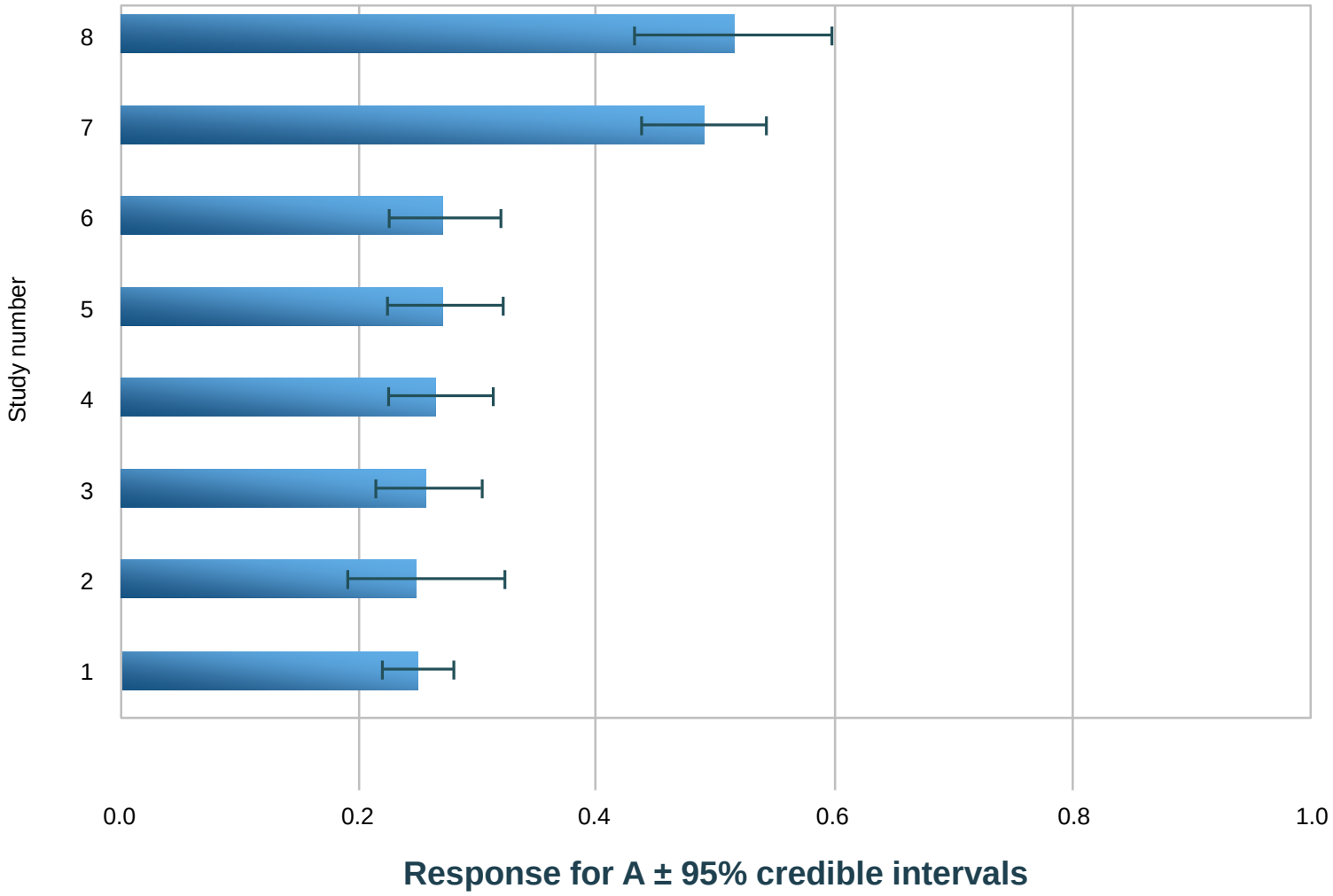
Example

Study name	Treatment	n	N
1	A	200	800
1	B	210	400
1	C	680	800
2	A	40	160
2	B	22	40
3	A	95	370
3	C	310	362
4	A	104	390
4	D	2000	3300
5	A	85	315
5	D	40	95
6	A	94	348
6	B	200	385
7	A	170	347
7	E	300	386
8	A	70	136
8	E	180	230

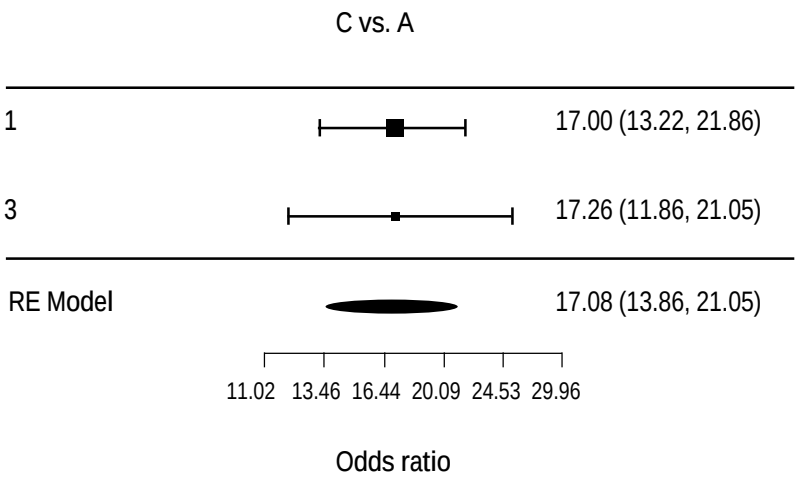
Network for response

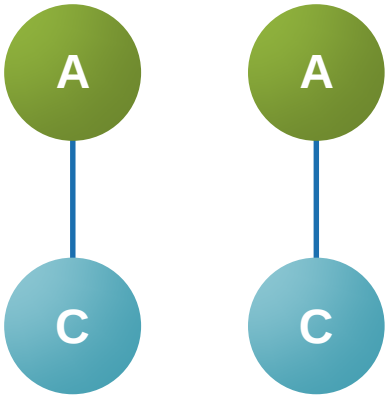


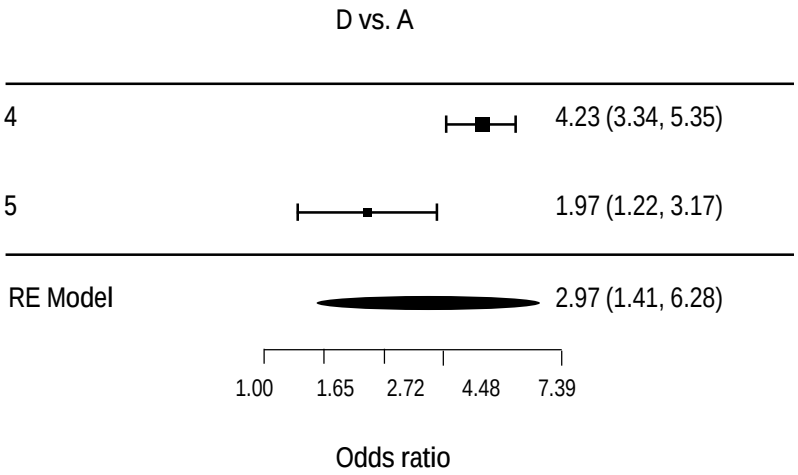
Example: Placebo response rate

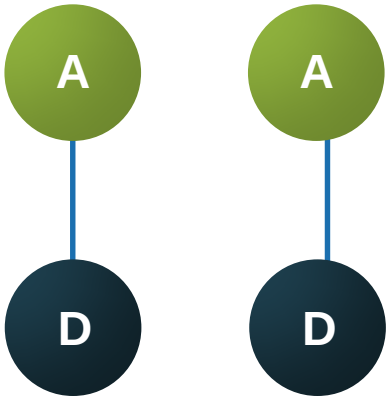


Example: Heterogeneity

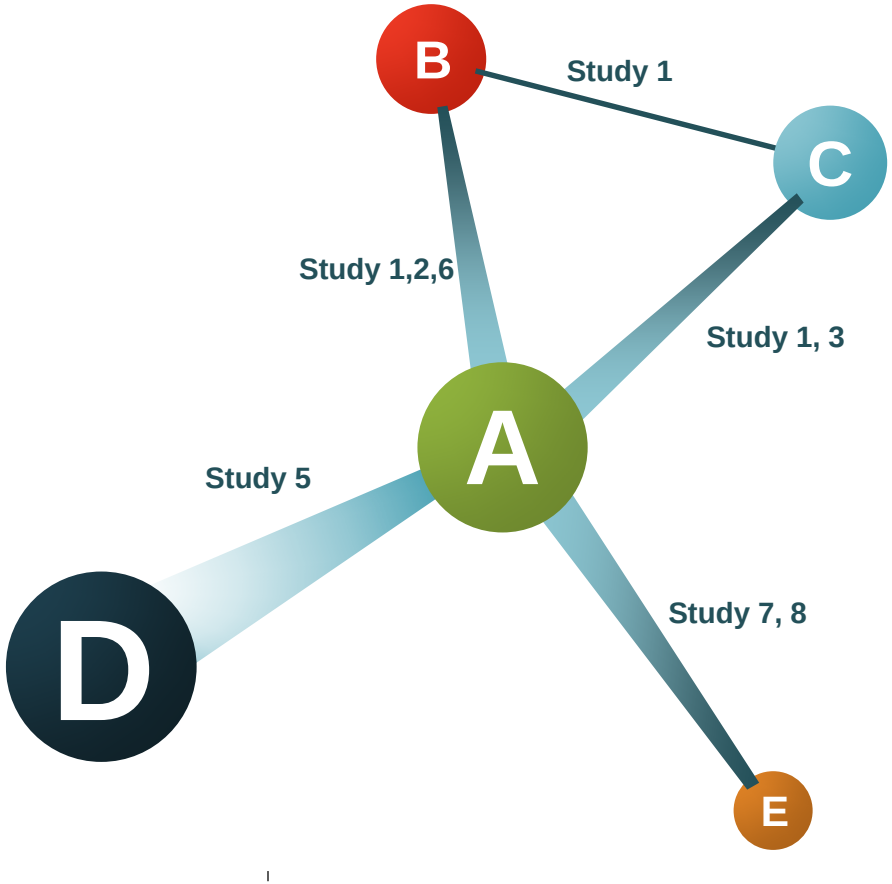


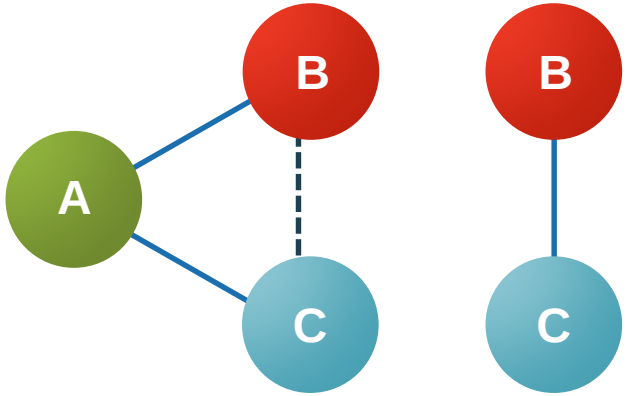




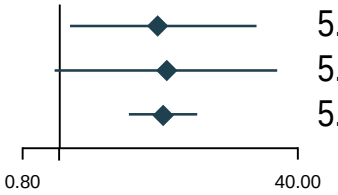


Example: Inconsistency

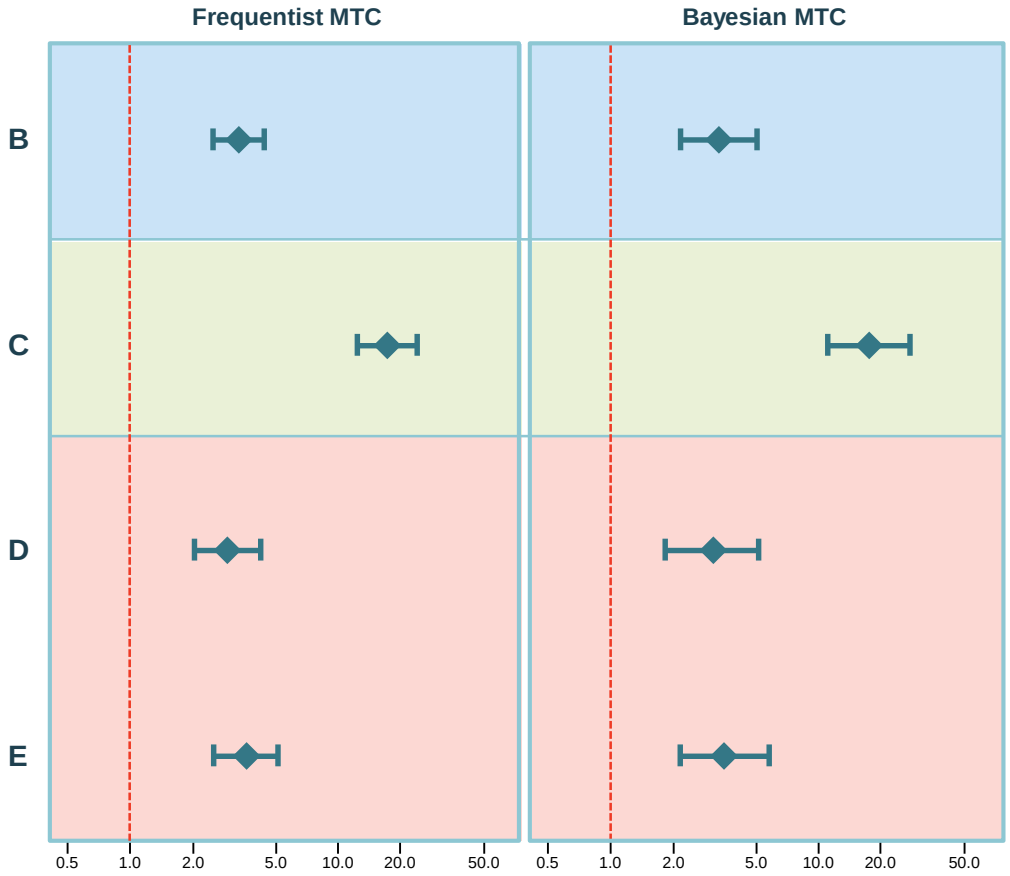




Study	P-value	Odds Ratio (95% CrI)
C vs. B		
Direct		5.1 (1.2, 21)
Indirect		5.6 (0.89, 31)
Network		5.3 (3, 8.9)



Example: Forest plot and pairwise grid



Odds ratio for response relative to A ± 95% credible intervals (log scale)

Endpoint: Response, Patient population: Overall, MTC: Random effects, Covariates: None

A	1	0.31 (0.2, 0.48)	0.06 (0.04, 0.09)	0.3 (0.2, 0.55)	0.28 (0.17, 0.46)
B	3.24 (2.15, 5.01)	1	0.19 (0.11, 0.33)	0.97 (0.55, 2.05)	0.9 (0.48, 1.75)
C	17 (11, 27)	5.3 (3.01, 9)	1	5.12 (2.78, 11)	4.77 (2.45, 9.6)
D	3.34 (1.8, 5.02)	1.04 (0.49, 1.81)	0.2 (0.09, 0.36)	1	0.93 (0.41, 1.76)
E	3.57 (2.15, 5.8)	1.11 (0.57, 2.09)	0.21 (0.1, 0.41)	1.08 (0.57, 2.42)	1
	A	**B**	**C**	**D**	**E**

Example: Predicted rates and rankogram

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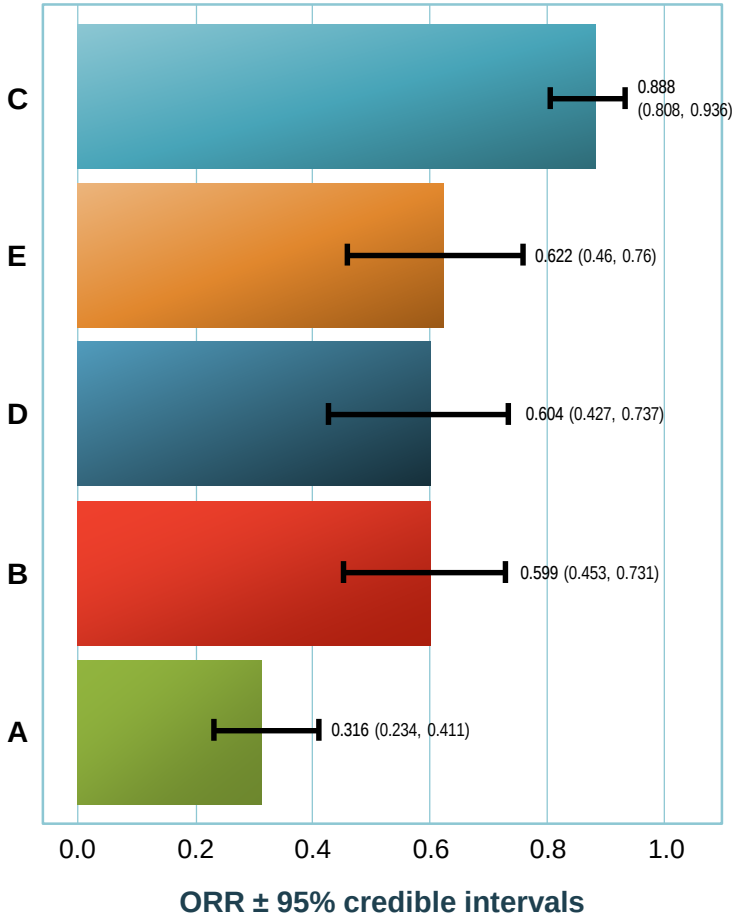
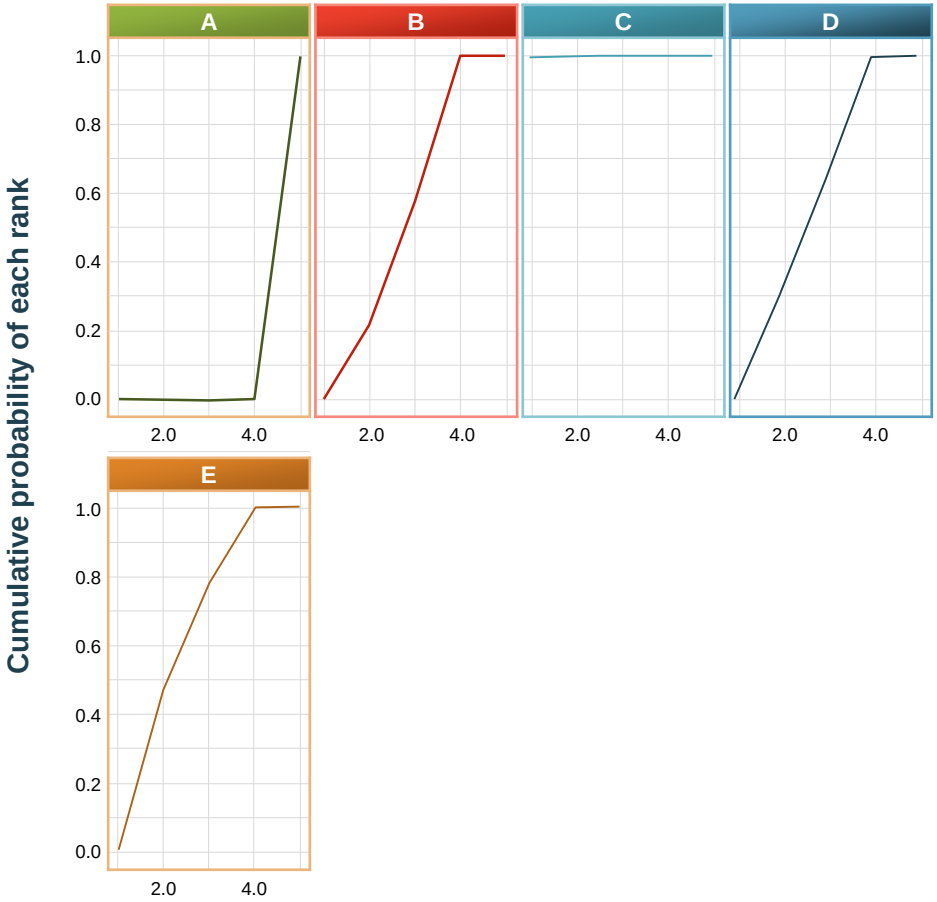
Predicted response rates from Bayesian MTC



Endpoint: Response, Patient population: Overall, MTC: Random effects, Covariates: None

Cumulative rankograms for treatment regimens from Bayesian MTC



Endpoint: Response, Patient population: Overall, MTC: Random effects, Covariates: None

Conclusion: NMAs

- Provides an approach to collectively consider available evidence and provide comparative efficacy and safety between treatments
- Important considerations
- Limitations
- Evolving field

"In our reasonings concerning matter of fact, there are all imaginable degrees of assurance, from the highest certainty to the lowest species of moral evidence. **A wise man, therefore, proportions his belief to the evidence**."
— David Hume, An Enquiry Concerning Human Understanding

Thank You

Questions?

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