Network Meta-Analysis: A Brief Tutorial

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THE LATEST RESEARCH SHOWS THAT WE REALLY SHOULD DO SOMETHING WITH ALL THIS RESEARCH
Outline

• Introduction

• Evidence networks

• Heterogeneity, transitivity, inconsistency

• Key points
Learning Objective

• Understand the concepts and assumptions of network meta-analysis such as homogeneity, transitivity, and consistency.
Introduction
New drugs are often compared with placebo or standard care, but not against each other, in trials aimed to contribute toward obtaining approval for drug licensing.

Commercial incentive to compare the new treatment with an active control may be wanting.

Commercial incentives to compare a new treatment with an active control may be lacking
  - Constraints due to small sample sizes and short durations of follow-up.

Available treatments tend to increase over time.
Motivation

• Clinicians, patients, and health-policy makers often need to decide which treatment is “best” based on all relevant evidence.

• Unfortunately, robustly designed RCTs that simultaneously compare all interventions of interest are almost never available.

• As an alternative, indirect treatment comparisons provide useful evidence.

• Network meta-analysis is an extension of standard pairwise meta-analysis by including multiple pairwise comparisons across a range of interventions
  • It addresses the comparative effectiveness of multiple treatment alternatives.
Illustrative Rationale
**Example: Regimes for the Treatment of Children with Acute Pyelonephritis**

|       | A       | B       | C       | D       | E       | F       | G       | H       | I       | J       | K       | L       | M       | N       | O       | P       | Q       | R       | S       | T       | U       | V       | W       | X       |
|-------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| A     | CTX>TMP/SMX | 0       | 1       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       |
| B     | TMP/SMX   | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       |
| C     | CTX       | 0       | 1       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       |
| D     | Cefotaxime | 0       | 0       | 0       | 1       | 0       | 0       | 1       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       |
| E     | CTX+cefixime | 1       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       |
| F     | Gentamicin daily | 0       | 2       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       |
| G     | Gentamicin tid | 0       | 0       | 0       | 1       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       |
| H     | A/Clav    | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 1       | 0       | 0       | 0       |
| I     | CTX+netilmicin>cefixime | 0       | 1       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       |
| J     | CTX+netilmicin>CTX | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       |
| K     | Various   | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       |
| L     | Cefixime  | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       |
| M     | Cefotaxime>cefixime | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       |
| N     | Isepamicin | 0       | 1       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       |
| O     | Amikacin  | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       |
| P     | Temocillin >A or A/Clav | 1       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       |
| Q     | CTX>A/Clav | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 1       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       |
| R     | Sulfurazole | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       |
| S     | Cefepime>TMP/SMX | 0       | 1       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       |
| T     | Ceftazidime>TMP/SMX | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       |
| U     | Ceftamet  | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       |
| V     | Netilmicin daily | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       |
| W     | Netilmicin tid | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       |
| X     | CTX>ceftibuten | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       | 0       |

**Figure:** Comparisons of antibiotic regimens for acute pyelonephritis in children
Matrix shows number of available direct comparisons (0=no comparison, 1=one comparison, 2=two comparisons).

Despite mounting evidence from 18 trials spanning and evaluating 24 regimens, evidence is available only on a few direct comparisons.

## Indirect Comparisons of Multiple Treatments

<table>
<thead>
<tr>
<th>Trial</th>
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</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>B</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>B</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>A</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>A</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
</tbody>
</table>

- Want to compare A vs. B.
- Direct evidence from trials 1, 2 and 7.
- Indirect evidence from trials 3, 4, 5, 6 and 7.
- Combining all “A” arms and comparing with all “B” arms destroys randomization.
- Use indirect evidence of A vs. C and B vs. C comparisons as additional evidence to preserve randomization and within-study comparison.
12-Month Weight Reduction (Brands)

### Example: Diets

| Diet                  | 12-mo Weight Loss, kg | 4.10 (1.30 to 6.91) | 4.51 (2.37 to 6.73) | 7.19 (3.82 to 10.63) | 6.35 (3.88 to 8.89) | 5.95 (3.23 to 8.72) | 5.90 (3.88 to 8.05) | 6.55 (3.42 to 9.79) | 6.42 (3.04 to 9.70) | 5.98 (0.63 to 11.46) | 6.47 (3.56 to 9.45) | NA | NA | 4.15 (0.36 to 8.05) |
|-----------------------|-----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------| NA | NA |                   |
| No diet               | 6.02 (4.20 to 7.81)   | 0.41                 | 3.08                 | 2.27                 | 1.85                 | 1.79                 | 2.45                 | 2.34                 | 1.88                 | 2.36                 | NA | NA | 0.05               | (-4.14 to 4.30) |
| LEARN (5.79 to 9.56) | 1.65 (0.0 to 3.34)    | 2.69                 | 1.86                 | 1.45                 | 1.40                 | 2.04                 | 1.92                 | 1.48                 | 1.96                 | NA | NA | -0.36              | (-4.06 to 3.39) |
| Moderate macronutrient| 8.26 (5.87 to 10.66)  | 2.25                 | 0.59                 | Low fat              | -0.83                | -1.23                | -1.28                | -0.64                | -0.77                | -1.20                | NA | NA | -3.02              | (-7.93 to 1.87) |
| 10.14 (8.19 to 12.12)| 4.13 (2.40 to 5.88)   | 2.48                 | 1.88                 | Atkins               | -0.42                | -0.45                | 0.19                 | 0.07                 | -0.37                | 0.11                 | NA | NA | -2.22              | (-6.17 to 1.79) |
| 8.44 (6.42 to 10.44) | 2.42 (0.60 to 4.26)   | 0.77                 | 0.17                 | Zone                 | -0.05                | -2.36                | -3.39                | -0.48                | 0.04                 | 0.52                 | NA | NA | -1.80              | (-5.98 to 2.46) |
| 7.26 (5.25 to 9.27)  | 1.24 (1.08 to 3.58)   | -0.41                | -0.99                | Weight Watchers      | 0.65                 | 0.52                 | 0.08                 | 0.57                 | NA                   | -1.75                | NA | NA | -1.75              | (-5.52 to 1.96) |
| 9.03 (6.44 to 11.66) | 3.02 (0.62 to 5.45)   | 0.77                 | 0.59                 | Ornish               | -0.12                | -0.77                | -0.69                | -0.08                | NA                   | -2.39                | NA | NA | -2.39              | (-6.88 to 2.05) |
| 5.78 (3.29 to 8.29)  | -0.23 (-3.26 to 2.81) | -1.89                | -2.49                | Jenny Craig          | -0.44                | -6.76                | 0.05                 | NA                   | -2.26                | NA | NA | -2.26              | (-7.20 to 2.86) |
| 9.87 (5.54 to 14.23) | 2.20 (-0.37 to 8.11)  | 1.62                 | -1.72                | Volumetrics          | -2.21                | 0.84                 | 4.09                 | NA                   | -1.82                | NA | NA | -1.82              | (-8.08 to 4.32) |
| 6.56 (2.75 to 10.29) | 0.54 (-3.51 to 4.55)  | -1.13                | -3.60                | Rosemary Conley      | NA                   | NA                   | -3.33                | -8.87                | -1.33                | NA | NA | -3.22              | (-6.44 to 1.87) |
| 5.43 (1.50 to 9.31)  | -0.58 (-4.42 to 3.23) | -2.23                | -2.47                | Biggest Loser        | -4.42                | -1.13                | NA                   | NA                   | NA                   | NA | NA | NA                 |                   |
| 7.41 (4.63 to 10.18) | 1.40 (-1.66 to 4.43)  | -0.26                | 0.15                 | Nutrisystem          | 0.86                 | 1.97                 | NA                   | NA                   | NA                   | NA | NA | NA                 |                   |

Evidence Networks
Two Specific Types of Network 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
  • At least one pair of treatments is compared both directly and indirectly

• Extensions of standard pairwise meta-analysis of randomized control trials
  • Fixed-effect and random-effect network meta-analysis

• Relies on statistical methods that maintain benefits of randomization within each trial
Wrong: Naïve Indirect Comparison

Naïve / biased indirect comparison
Indirect Comparison

- **Trial 1**
  - B
  - A (Placebo)
  - Tx effect

- **Trial 2**
  - C
  - A (Placebo)

- **Trial 3**
  - D
  - C
  - Relative tx effect

**Delta y**
- Vs. A
- Indirect estimate of D vs. B
- Indirect estimate of C vs. B
- Indirect estimate of D vs. A

**Comparisons**
- B vs. A
- C vs. A
- D vs. C
Need for a Network

Trial 1

\[ y \]

Trial 3

Relative tx effect

\[ \text{Tx effect} \]

\[ B \]

A (Placebo)

D

C

\[ \text{delta y} \]

\[ \text{Vs. A} \]

Unknown indirect estimate of D vs. B

Unknown estimate of C vs. A

\[ ? \]

B vs. A

D vs. C
Indirect Comparison

\[ d_{BC} = d_{AC} - d_{AB} \]

Mixed Treatment Comparisons

A total of $k(k-1)/2$ contrasts

Homogeneity, Transitivity, Consistency
<table>
<thead>
<tr>
<th>Comparison</th>
<th>No of trials</th>
<th>Odds ratio (95% CI)</th>
<th>I² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion v placebo</td>
<td>9</td>
<td>0.51 (0.36 to 0.73)</td>
<td>54</td>
</tr>
<tr>
<td>NRT patch v placebo</td>
<td>19</td>
<td>0.57 (0.48 to 0.67)</td>
<td>12</td>
</tr>
<tr>
<td>Bupropion v NRT patch:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct comparison</td>
<td>1</td>
<td>0.48 (0.28 to 0.82)</td>
<td>—</td>
</tr>
<tr>
<td>Adjusted indirect comparison</td>
<td>9+19</td>
<td>0.90 (0.61 to 1.34)</td>
<td>—</td>
</tr>
<tr>
<td>Combined (direct + indirect)</td>
<td>1+(9+19)</td>
<td>0.68 (0.37 to 1.25)</td>
<td>71</td>
</tr>
</tbody>
</table>

Treatment Effects & Study Effects

- treatment effect
- study or placebo effect
- effect modifiers
- prognostic factors

Intervention      Placebo
Homogeneity

• Homogeneity occurs when the true treatment effects in a direct comparison of two treatments across studies are the same.

• Heterogeneity, the opposite of homogeneity, is the extent to which the true treatment effect varies
  • According to populations/patient characteristics, treatment characteristics (such as dose or duration), or study characteristics.

• Known as interaction by statisticians and as effect modification by epidemiologists.

• Heterogeneity is caused by variation in (un)measured effect-modifiers of the relative treatment effect.
Transitivity (Similarity)

- Transitivity requires that the distribution of patient and study characteristics that are modifiers of treatment effect be sufficiently similar in different sets of randomized controlled studies that go into an indirect comparison
  - If so, the relative effect estimated by trials of A vs. C is generalizable to patients in trials of B vs. C (and vice versa)

- In addition to clinical similarity, methodological similarity (e.g., quality, definition of outcomes) is required for valid estimates

- If there is imbalance in the distribution of effect modifiers (treatment-by-covariate interactions) between trials, then estimates become biased
Transitivity

\[ d_{bk} = d_{Ak} - d_{Ab} \]
Heterogeneity (Yes, No) and Transitivity in a Network

Without heterogeneity

- Severe/Moderate 70:30
- Severe/Moderate 70:30
- Severe/Moderate 70:30
- Pooled effect

Valid indirect estimate of C vs. B

Similar distribution of effect modifiers between AB and AC studies

With heterogeneity

- Severe/Moderate 70:30
- Severe/Moderate 50:50
- Severe/Moderate 70:30
- Pooled effect

Valid indirect estimate of C vs. B

Similar distribution of effect modifiers between AB and AC studies

0 treatment effect B vs. A

0 treatment effect C vs. A
Biased Network Meta-Analysis: Lack of Transitivity

Without heterogeneity

With heterogeneity

<table>
<thead>
<tr>
<th>Without heterogeneity</th>
<th>With heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severe/Moderate 30:70</strong></td>
<td><strong>Severe/Moderate 30:70</strong></td>
</tr>
<tr>
<td><strong>Severe/Moderate 30:70</strong></td>
<td><strong>Severe/Moderate 50:50</strong></td>
</tr>
<tr>
<td><strong>Severe/Moderate 30:70</strong></td>
<td><strong>Severe/Moderate 30:70</strong></td>
</tr>
</tbody>
</table>

**Pooled effect**

**Imbalance in distribution of effect modifiers between AB and AC studies**

**BIASED indirect estimate of C vs. B**

**treatment effect B vs. A**

**treatment effect C vs. A**
‘Trial 1: Porsche versus Golf’

Porsche - Golf = 2s

‘Trial 2: Volvo versus Golf’

Volvo - Golf = 8s

→ Volvo versus Porsche: 8-2=6s (Indirect comparison)

Is a Volvo faster than a Porsche? No, biased indirect estimate due to imbalance in treatment effect modifier (snow) across comparisons
Consistency: Agreement between Direct and Indirect Evidence for a Given Pair of Treatments
Inconsistency
Key Points
Take-Home Messages

• Randomization holds within trials and not across trials in a (network) meta-analysis.

• Homogeneity, transitivity, and consistency need to be examined.

• It all relates to the distribution of patient and study characteristics (including bias) that affect the treatment effects: effect modifiers.

• Variation in effect modifiers between studies within direct comparisons: heterogeneity.

• Variation in effect modifiers between different direct comparisons: inconsistency
  • Imbalance in effect modifiers between comparisons: transitivity violations
  • This will show as in inconsistency in the data and hence results.

• The assumption of consistency allows precision to be gained by combining direct and indirect evidence.
Additional References (beyond those given previously)


