

Network meta-analysis

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I am planning to perform a meta-analysis to evaluate the effects of three available Covid-19 treatment options. It seems that a network meta-analysis would fit my goal, and I am wondering what the differences are between a meta-analysis and a network meta-analysis.

Network meta-analysis, which is also called mixed treatment comparison or multiple treatment comparison meta-analysis, is an analysis method for comparing multiple treatments simultaneously within a network of randomized controlled trials.^{1,2}

While a network meta-analysis and a traditional meta-analysis (pair-wise comparison) share many commonalities, including literature searches, study selection, quality evaluation, bias assessment, and sensitivity analysis, etc.,³ a network meta-analysis is a powerful extension of a traditional meta-analysis that can estimate the relative effect between any pair of treatments in the network, and usually has more precise estimates. Furthermore, a network meta-analysis allows the estimation of the ranking and hierarchy of treatments. In practice, many conditions and diseases have several or many treatment options, and a network meta-analysis provides quantitative evaluations on all the options to facilitate decision making.

1. THE NETWORK PLOT

An intuitive description of a network meta-analysis is a network plot.⁴ It consists of at least three nodes, with lines connecting to each other. The nodes represent the treatments in the network, and the lines show the direct comparisons between pairs of treatments. The thickness of the lines reflects the number of studies that compare the two connecting treatments.

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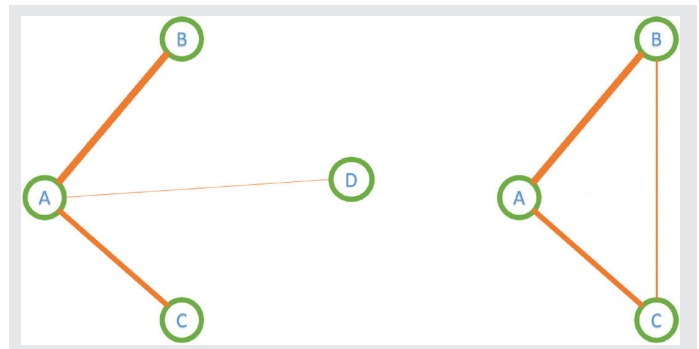


Figure 1. Network plot. Left: open loop; Right: closed loop.

For example, the line between treatments A and B is thick, reflecting a large number of studies that have direct comparisons between A and B. Meanwhile the line between treatments A and D is thin, reflecting that there are fewer studies directly comparing these two treatments (Figure 1 left). In addition, the size of the nodes can also be used to reflect the amount of available information for each treatment.

There are in general two types of loops in a network, including closed and open loops.¹ The closed loop has at least one study that compares one treatment with another and allows all the treatments to be connected to each other in the network diagram (Figure 1 right), while the open loop does not (Figure 1 left).

2. DIRECT AND INDIRECT COMPARISONS

Comparing with a traditional meta-analysis, a network meta-analysis can estimate the treatment effects, including effects between treatments that have not been directly evaluated in any existing studies, by integrating the information from both direct and indirect comparisons.⁵

To be specific, a direct comparison is the effect that have been directly compared one against the other in at least one study included in the meta-analysis,

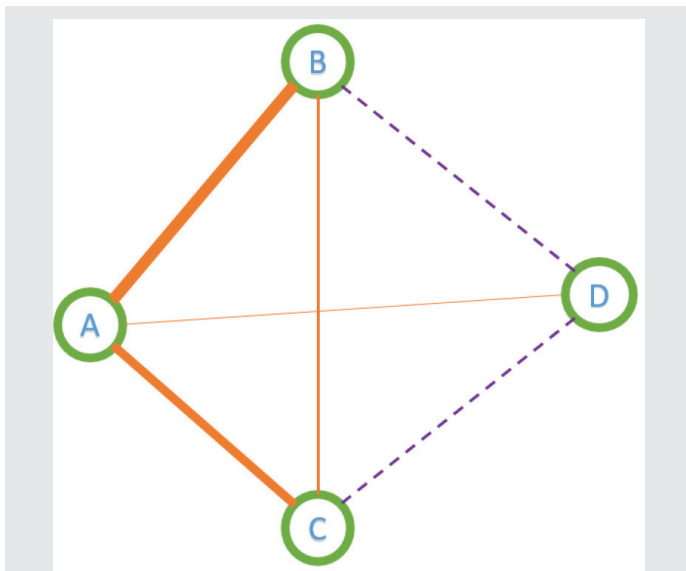


Figure 2. Network meta-analysis plot. A, B, C and D are the four treatments. The solid lines are the direct comparisons, with the thickness proportional to the number of studies. The dashed purple lines are the indirect comparisons.

e.g., the comparisons between treatments A and B, A and C, and B and C (Figure 2). On the other hand, an indirect comparison is one that has never been made directly between two treatments within any studies (dashed purple lines; Figure 2 treatments B and D, and C and D), but these two treatments can be compared against a common comparator; both can be compared against treatment A.⁶

One of the advantages of a network meta-analysis, compared to a traditional meta-analysis, is that indirect comparisons can be made between treatments with direct comparisons, e.g., between treatments A and B, A and C, and B and C. In fact, an indirect comparison complements the corresponding direct comparison, and the incorporation of results from both the direct and indirect comparisons often leads to more precise estimates. As a side note, in a closed loop model, there are two sources of information for each comparison, one from the direct comparison, the other from the indirect comparison, and thus the risk of estimation bias is smaller.

3. CONSIDERATIONS IN A NETWORK META-ANALYSIS

3.1 QUALITY EVIDENCE BASE

Many factors determine the quality of an evidence base. Internally, a systematic approach should be used to ensure that there is no selection bias in a literature search. Externally, it is important to assess whether randomization was performed appropriately, and whether blindness was enforced in the selected studies. In addition, it is important to evaluate whether publication bias exists using methods such as a funnel plot.

3.2 HOMOGENEITY

Heterogeneity reflects the underlying differences between studies that directly compare the same pair of treatments. In a network meta-analysis model, heterogeneity is often assumed to be the same for every comparison in the network. This is because one comparison can affect the estimates of many other comparisons, thus it is easier to model a common heterogeneity. In addition, with more data contributing to the estimates, the results of treatment comparisons are often more precise. Potential violation of homogeneity can be examined by using a forest plot or the I^2 statistic.⁷

3.3 TRANSITIVITY

To avoid biases caused by confounding, it is expected that all important factors other than the intervention are, on average, similar across different sets of randomized trials in a network meta-analysis. In general, transitivity should be satisfied by every possible indirect comparison, and it can be evaluated by comparing the distribution of effect modifiers across different comparisons.

3.4 CONSISTENCY (OR COHERENCE)

Consistency refers to the equivalence of direct and indirect evidence. It is required that evidence from both direct and indirect comparisons agrees, and this should be quantitatively assessed by comparing the direct and indirect estimates.

3.5 RANK PROBABILITIES

Rank probability is the probability that each treatment is the best, second best, and so on. A Bayesian approach is often used in a network meta-analysis because it is flexible to incorporate complex models and can produce estimates of rank probabilities.

3.6 SOFTWARE FOR A NETWORK META-ANALYSIS

Several statistical software packages have been developed to automate the process of a network meta-analysis. For example, the *gemtc*, *pcnetmeta*, and *netmeta* packages are all freely available in the R software (R Development Core Team). In addition, both the traditional and network meta-analyses can be performed in SAS using the *PROC BGLIMM* procedure.⁸

4. DISCUSSION

A network meta-analysis is similar to a traditional meta-analysis in many aspects. For example, many assumptions made by a traditional meta-analysis apply to a network meta-analysis. On the other hand, a network meta-analysis allows the comparisons of treatments that have not been directly compared within existing studies and produces an estimate of the relative effect between any pair of the treatments in the network.

A network meta-analysis combines estimates from both the direct and indirect comparisons into a single analysis and thus often reinforces the evaluation of the treatments. Specifically, it allows incorporating evidence from studies evaluating elements but not necessarily the entire network of relevant interventions to improve the quality of estimates. A practical consideration is that a direct estimation may come from the comparison of controlled small studies or trials with certain limitations, while the indirect estimation may come from the comparison of well-executed controlled clinical trials. It worth noting that it is a good practice that all the assumptions and requirements for performing a network meta-analysis be carefully examined.

A network meta-analysis is especially useful for evaluating the performances of all available treatment

options for a condition or disease, regardless of whether a comparison has been directly made within existing studies. In contrast to pairwise comparisons, a network meta-analysis has the potential to identify the most promising treatment and provide quantitative estimates of the relative effectiveness of the comparable treatments. In addition, a network meta-analysis does not require the combination of multiple treatments into one comparator to compare with another treatment. In fact, it allows head-to-head comparisons of multiple treatment options across trials with different designs.

Despite its advantages over traditional meta-analysis, a network meta-analysis is prone to certain limitations. For example, the estimates from indirect comparisons might not be valid due to potential violations of randomization, and ranking probability of each treatment might not be reliable if the effect modifiers are not balanced across studies. Precautions should be made to identify the most promising treatment in the network.²

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