Using mixed treatment comparison meta-analysis to compare interventions in bovine practice

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Abstract

Traditional meta-analysis involves a pairwise comparison of two interventions with one outcome. In this review mixed treatment comparisons (MTC) meta-analysis is discussed, which enables the comparison of multiple treatments using direct and indirect information from a network of trials. Mixed treatment comparisons meta-analysis is also known as network analysis. Although a potentially powerful tool for decision-making, several key assumptions are necessary for validity, and frequently these will not be met. As with any meta-analysis, MTC meta-analysis has the potential to propagate biases that occur at the trial level. Further, because of the assumptions necessary for MTC, bias can be introduced at the meta-analysis level, especially when trial populations compared are not comparable. In this review, we discuss how MTC meta-analysis may be used in bovine practice and raise concerns about its use.

Résumé

Les méta-analyses traditionnelles reposent sur une comparaison par paires de deux interventions donnant un même résultat. Dans cet exposé, nous parlerons d'une méta-analyse comparative de traitements mixtes, qui permet de comparer des traitements multiples au moyen d'informations directes et indirectes obtenues à partir d'un réseau d'essais. La méta-analyse comparative de traitements mixtes est également appelée analyse en réseau. Bien qu'il s'agisse d'un outil qui peut être très utile pour la prise de décision, plusieurs hypothèses clés doivent être formulées pour le valider et, souvent, il n'est pas possible de le faire. Comme pour toute méta-analyse, la méta-analyse comparative de traitements mixtes peut propager des préjugés qui se forment au stade des essais. De plus, en raison des hypothèses qui doivent être formulées pour la méta-analyse comparative de traitements mixtes, des préjugés peuvent aussi apparaître au stade de la méta-analyse, surtout quand les populations comparées lors des essais ne sont pas comparables. Dans cet exposé, nous voyons comment la méta-analyse comparative de traitements mixtes peut être utilisée dans la pratique bovine et nous nous interrogeons sur son utilisation.

Introduction to Mixed Treatment Comparisons Meta-analysis

For preventive or therapeutic interventions, well-executed randomized controlled trials directly comparing the two interventions would provide high-quality evidence for choosing between two interventions.[11,12,16,27,28] Systematic reviews that include pairwise meta-analysis of results from numerous well-executed randomized controlled trials would be even more preferable for understanding the comparison of interventions as the pairwise meta-analysis incorporates study variation into the estimate of efficacy.[11,12,16,27,28] In bovine veterinary practice there are several examples of the use of pairwise meta-analysis related to treatment interventions[7-9,14,40] and preventive interventions.[13,25] The majority of these meta-analyses are comparisons of active treatments to non-active controls. For many interventions such comparisons are of primary interest, i.e. for vaccines, often the decision being made is to use the product compared to not using the product at all. However, very frequently the question of greater interest is which of two active treatments is the most effective, i.e. the comparative efficacy.

Currently, there are few pairwise meta-analyses in veterinary science that have active-to-active comparisons because so few comparisons are available. One example is a meta-analysis of a single subcutaneous dose of tilmicosin (4.54 mg/lb; 10 mg/kg) compared with tulathromycin (1.14 mg/lb; 2.5 mg/kg) for the treatment of bovine respiratory disease (BRD).[40] Even fewer meta-analyses in bovine practice have evaluated multiple treatment options. When multiple treatment options have been compared, the resulting reviews have included only narrative summaries rather than meta-analysis,[26,29] or combined the multiple interventions into a single interventions, such as metaphylaxis.[38,41] To date, none of these approaches provides producers and veterinarians with explicit information about comparative efficacy of active products. Mixed treatment comparisons meta-analysis is a tool that can provide explicit information about comparative efficacy of active products, even when the direct trials are not available. In this review, we describe the basis for MTC meta-analysis and its possible application for assessing the comparative efficacy of interventions in bovine practice.

Applications for Mixed Treatment Comparisons Meta-Analysis

Mixed treatment comparisons meta-analysis is an approach that has been used in human medicine, but rarely in veterinary science, to provide information about comparative efficacy when multiple treatments are available. In human medicine, meta-analyses that use information from direct and indirect comparisons of treatment options are called "mixed treatment meta-analysis".[2] Such analyses are also called "network meta-analyses".[17,19,22,31] MTC meta-analysis has been used extensively to establish comparative efficacy of interventions for numerous conditions in human medicine.[1,3,4,18,23,24,33,34,36,39]

An example of where MTC meta-analysis may be helpful in bovine practice is bovine respiratory disease. BRD treatment choices represent a scenario where MTC meta-analysis could be a useful tool because producers and practitioners frequently encounter the need to make indirect comparisons about BRD therapies, as only a small number of all possible direct active-to-active comparisons are available as randomized controlled trials.

For BRD, the lack of direct active-to-active comparisons likely occurs for two primary reasons. First, many available trials conducted for US Food and Drug Administration registration employ a non-active control arm (placebo). These non-active controls provide an unrealistic comparison as producers or practitioners are rarely choosing between nothing and an active compound. The second reason direct information about active-to-active comparisons may not be available is that of changing industry perceptions about which product constitutes a standard active control. For example, in the 1980s oxytetracycline might have been considered a reasonable active control for feedlot-based BRD trials, however, in the 1990s an increasing number of trials used tilmicosin or florfenicol as the active control. This change in practice means that newer products are not compared to older products in trials.

Principles of MTC Meta-Analysis

The principle behind MTC meta-analysis is to use evidence from the full network of trials to make inferences about comparative efficacy by borrowing information from the entire network.[15] The network may be very simple or complex, as shown in Figure 1. Obviously networks can take on numerous configurations, although the networks must be connected. For example, if a dataset consists of network of AB, AC, BC, AD, EF, EG, FG pair-wise comparisons, the A, B, C, D group of treatments is not connected with the E, F, G group, and therefore A cannot be compared to E using MTC meta-analysis.
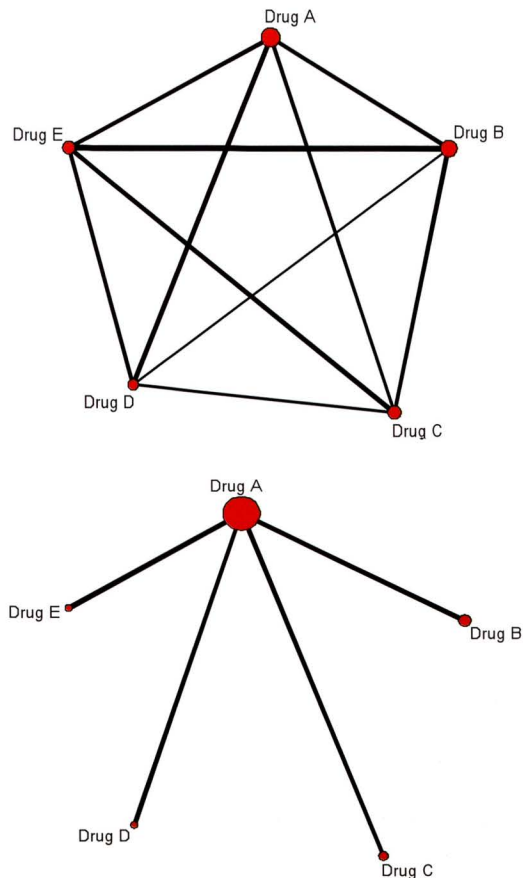

Figure 1. Two examples of networks with different conformations than can be used in mixed treatment comparisons meta-analysis.

Mixed treatment comparison meta-analysis combines direct and indirect estimates of efficacy using a network of information from trials, while accounting for lack of randomization at the study level (Figure 2). By using mixed treatment comparisons meta-analysis it is possible to:

- quantify differences between interventions where no direct comparisons exist, i.e. indirect comparisons
- borrow evidence from indirect comparison when few direct comparisons exist
- rank treatments when multiple options exist
- assess sources of bias in a network of trials.

The concept behind indirect comparisons based on MTC meta-analysis is fairly intuitive. Decision-makers, such as veterinarians or producers, likely already use indirect information to assess comparative efficacy when direct comparisons are unavailable. For example, if one trial compared treatment B to treatment A and reported a relative risk of failure of 0.5; i.e., B had half the failure rate of A, and a second trial compared treatment C to
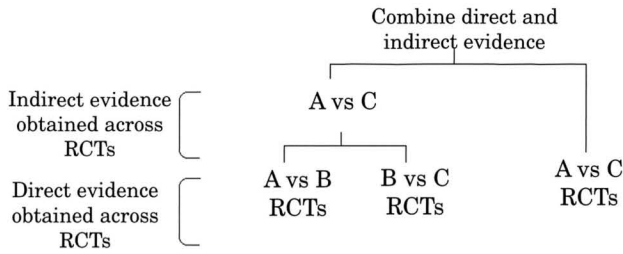
Figure 2. Illustration of how a mixed treatment comparison meta-analysis enables indirect and mixed comparisons of treatment options. The direct comparisons of A versus B and B versus C are combined to create an indirect comparison of A versus C. For the mixed comparison, the indirect A versus C is combined with the direct A versus V.

treatment A and reported a relative risk of failure of 0.25, many would conclude that C was twice as effective as B based on the indirect comparison of B versus C. This approach to comparison is referred to as the naïve or unadjusted approach to mixed treatment comparisons; naïve, because it ignores study level factors and the unit of randomization.[10] This naïve approach also fails to empirically incorporate the uncertainty about the within-trial direct estimates. For example, if the first trial comparing A to B used 1,000 animals, while the second trial used 100 animals, the uncertainty about the comparative efficacy of A versus B and A versus C varies and should be incorporated into the estimate of relative efficacy. Figure 1 illustrates how MTC meta-analysis uses indirect information. There are other approaches to indirect comparisons, MTC meta-analysis being just one.[10]

BRD has many examples where direct pairwise comparisons between antibiotics are not available. This use of MTC meta-analysis relates directly to the principle that "claims of advantages of new treatments should consider the full range of alternatives rather than those selected by the industry".[32] For example, at the time this paper was written, publicly available studies of danofloxacin only compared it to a non-active control, although the treatment decision between a non-active control and danofloxacin is unlikely one that many producers would seriously consider. More realistically, decision-makers may be interested in the comparative efficacy of danofloxacin versus a product such as tulathromycin, two of the newer products on the market. Also, both drugs are marketed by the same pharmaceutical company, therefore funding for a direct comparison trial would be less likely as it might not benefit the company to document that one product is superior to the other. MTC analysis could provide these data.

Another application of MTC meta-analysis is to borrow evidence from indirect comparisons and add those data to direct comparisons. One rationale for this is to narrow the confidence interval for estimates, especially when there are few direct comparisons and many indirect comparisons, however, indirect comparisons only contribute about one-quarter of the information of direct comparisons.[31]

Another rationale for MTC meta-analysis is perhaps to identify and adjust for publication bias or other sources of bias. For example, for some products all or the majority of direct comparisons available may be published by one sponsor, and despite attempts to limit within-trial bias with design features such as randomization and blinding, the potential for particular findings to be preferentially published still exists. However, indirect comparisons may be published by different sponsors with competing publication biases. Therefore, combining indirect and direct comparisons may reveal inconsistencies between direct and indirect comparisons. This use of MTC meta-analyses is sometimes seen as a particular advantage of MTC. Sources of inconsistencies between direct, indirect and mixed comparisons (mixed being a form of weighted average of the direct and indirect) can be useful for identifying biases. When inconsistencies are identified, these should become a topic for exploration in much the same manner than heterogeneity is explored in pairwise meta-analysis using meta-regression.

Another motivation for using MTC may be to choose the best treatment among a variety of treatments.[30,37] MTC meta-analysis can be used to rank the treatments or to provide evidence of which treatment has the highest or lowest probability of being the best or worst, depending upon how the data are organized. Of course, such an approach is controversial. Some comparisons are based on substantially more information than others. Likely, such ranking will only affirm those who hold the same belief before the ranking was conducted, rather than sway the opinions of people who have different rankings in mind, who will be more likely to emphasize the limitations of the approach. However, the advantage of the MTC meta-analysis approach is that it can be used to provide bounds of uncertainty around questions that many decision-makers are already making without viewing all the data.

Mixed Treatment Comparisons Statistical Framework

There are numerous approaches to obtaining indirect comparisons, and MTC meta-analysis is one usually implemented in a Bayesian framework.[5,6,17] MTC meta-analyses are frequently used for categorical and continuous outcomes; methods also exist for time-to-event data. Excellent tutorial examples are provided by the UK-based National Institute for Health and Clinical Excellence (NICE) decision support unit.[b] Further nu-

merous excellent and detailed statistical publications are available on MTC meta-analysis.[5,15,20,22,31] Here, we give a very brief introduction to the statistical framework for Bayesian MTC meta-analysis.

The underlying statistical model here for the MTC meta-analysis was that described by Dias *et al*,[5] which was itself based upon the Higgins and Whitehead[15] model for discrete outcomes :

Where θ_{jk} is the logit (p_{jk}), where p_{jk} is the probability of the event in trial *j* under treatment *k* and δ_{jbk} is the trial-specific log odds ratio of treatment *k* relative to the baseline treatment *b* in trial *j*. Study effects μ_{jb} are unrelated nuisance parameters.

Dias *et al* indicate that the study effects are treated as unrelated nuisance parameters with priors: $\mu_{jb} \sim N(0,10000)$.[5] The treatment effect A (such as the non-active control effect) and the treatment effects of B, C, and D relative to treatment A are referred to as *basic* parameters with vague priors: $d_{AB}, d_{AC}, d_{AD} \sim N(0,10000)$. The remaining contrasts, referred to as *functional* parameters, are expressed in terms of the basic parameters: $d_{BC} = d_{AC}\text{-}d_{AB}$; $d_{BD} = d_{AD}\text{-}d_{AB}$; $d_{CD} = d_{AD}\text{-}d_{AC}$. The baseline treatment can be any treatment, and is frequently the standard treatment or a non-active control. For example, in a BRD example the comparison between ceftiofur pinna versus tilmicosin would be given by the difference between the other comparisons i.e., d$_{\text{ceftiofur pinna versus tilmiconsin}}$ = d$_{\text{placebo versus tilmiconsin}}$ - d$_{\text{placebo versus ceftiofur pinna}}$. Note that the choice of baseline does not affect the analysis, but choosing one that is intuitive to end-users is sensible.

The trial-specific treatments are drawn from one of the random effects distributions that result from the analysis: $\delta_{jbk} \sim N(d_{bk}, \sigma^2_{bk})$. As a random effects model is used, it is necessary to make an assumption about the variance, i.e. the assumption of homogeneous variance: $\sigma^2_{XY} = \sigma^2$. A vague prior can be provided for the common variance term. For multi-arm trials on treatments A,B,C which induce a covariance between δ_{jAB} and δ_{jAC}, again an assumption of homogeneous variance is necessary, i.e. the covariance is often set at $\sigma^2/2$.[15,19]

Checking consistency assumption between direct and indirect estimates

One of the major assumptions for mixed treatment comparisons is consistency of the direct comparisons with indirect comparisons. By definition, consistency can only be checked for comparisons where a direct comparison exists. Several approaches to assessing the consistency assumption are available.[5,21,22,31] Regardless of the statistical approach used, the concept behind checking the consistency assumption is similar. For a pair of treatments *XY,* an estimate of the XY comparison calculated from direct information ($\hat{d}^{Dir}_{XY}$) is compared to an estimate derived from only indirect evidence $\hat{d}^{Ind}_{XY}$.

If the difference between the estimates is zero, this suggests consistency. For the back calculation method, when the trials represent a simple loop rather than a network of trials, the difference between the direct estimate ($\hat{d}^{Dir}_{XY}$) and the indirect estimate ($\hat{d}^{Ind}_{XY}$) is represented by $\hat{\omega}_{XY} = \hat{d}^{Dir}_{XY} - \hat{d}^{Ind}_{XY}$. The variance of $\hat{\omega}_{XY}$ is given by $Var(\hat{\omega}_{XY}) = Var^{Dir}_{XY} + Var^{Ind}_{XY}$ and used to create the test statistic $Z_{XY} = \hat{\omega}_{XY} \Big/ \sqrt{Var(\hat{\omega}_{XY})}$ which is reasonably assumed to be normally distributed and used to test the null hypothesis that $\hat{\omega}_{XY} = 0$. The consistency assumption can be tested by asking if $\hat{\omega}_{XY} = 0$ using the test statistic above. Details of the estimate of the variance $Var(\hat{\omega}_{XY})$ in a mixed treatment comparison meta-analysis are available.[5]

Assessing the impact sources of bias

MTC meta-analysis can also be used to assess the potential for systematic bias by using an indicator variable for a bias factor.[6] An indicator can be used for any source of heterogeneity of interest, clinical or methodological. The indicator may identify the study was blinded, or randomized or pen level versus individual allocation. However, as with all subgroup analysis, the basis for the heterogeneity should be established *a priori* rather than exploring numerous subgroups for statistical significance. For each indicator, the null hypothesis is that the beta estimate of the indicator is equal to zero ($\beta_{indicator} = 0$). The null hypothesis is rejected if the p value for the $\beta_{indicator}$ is less than a predetermined level of significance, such as $P < 0.1$ or $P < 0.05$. As a confidence interval (or credibility interval) can be computed for an indicator variable, it would be more meaningful if these are presented rather than the results of statistical significance testing.

The Assumptions for Mixed Treatment Comparisons Meta-Analysis and Criticisms

The aim of this review is not to provide a comprehensive review or tutorial on mixed treatment comparisons, as there is an enormous amount of theoretical and applied literature available on the topic in human medicine that can be readily extrapolated to veterinary science. However, it is worthwhile to mention some of the key assumptions employed for MTC meta-analysis and which should be considered before using the approach.

The first assumption is the same as standard meta-analysis, i.e. homogeneity – that the different trials are testing homogeneous effects, a single treated effect for a fixed-effect model, and a distribution of effects for a random model. As a practical example, for BRD this would mean that one would be comfortable conducting a pairwise meta-analysis where possible to calculate a summary effect measure. Of course, the reviewer

must decide what constitutes a population that can be combined.

One practical way to think about homogeneity of effect is, "Are all the trials of the same comparison (A versus B) estimating the same effect?" An example where this may not be a valid assumption in BRD may be a group of trials that assessed antibiotic efficacy with or without metaphylaxis. To illustrate, if a pairwise meta-analysis was conducted comparing treatment A versus treatment B, and in some trials treatment A was also used as a metaphylactic treatment upon arrival. In this situation we would not expect the comparative effect of treatments A and B to be the same in both sets of trials, so these should likely not be combined in a meta-analysis as they are not estimating the same effect. The failure to meet this assumption would be the same for either a pairwise or MTC meta-analysis. Decisions about what should and should not be combined in a pairwise or MCT meta-analysis are often difficult to judge.

The second assumption is that the trial populations are similar clinically and methodologically. That is, the result from a comparison of treatment A versus treatment C would be applicable to the population in which Treatment A versus Treatment B was studied. This assumption is akin to imagining that each trial actually used all possible interventions, but those not observed are simply missing at random. The concern with this assumption is that it may be invalid. For example; perhaps trials of treatment A *versus* treatment B and treatment A *versus* treatment C are conducted in populations that are systematically different from trials of B *versus* C, in which case the assumption is invalid and the observed associations are confounded. For example, perhaps B is a surgical treatment option that is only conducted in animals without concurrent disease, whereas Treatment A is a medical option for animals that are not candidates for surgery. In this situation, the populations are different and should likely not be combined in meta-analysis. Such assumptions are unlikely to be assessed or validated statistically, but are routinely based on experience of decision-makers.

A third unique assumption for mixed treatment comparison meta-analysis is the assumption of consistency, i.e., that the direct and indirect estimates of efficacy are consistent. This assumption can be subjected to statistical tests (which themselves have assumptions). An example of a source of inconsistency may occur in MTC meta-analyses that combine data from older trials with newer trials where there is a difference in the underlying baseline level of disease and, most importantly, efficiency of the intervention depends upon the baseline level of disease. For example, treatment A might be only twice as good as treatment B when animals are treated early in the disease process, and such a difference decreases as the disease severity of enrolled animals increases. This might occur if animals were routinely treated later in the disease process in older trials, than in more recent trials. This issue is extremely difficult to assess, but should be incorporated into the decision to conduct a mixed treatment comparison analysis. For an infectious disease such as BRD, where the method of diagnosis has not changed noticeably for 40 years, i.e., cowboy observation, this may be less critical. In human medicine, and perhaps companion animal medicine, where diagnostic methods such as ultrasound have led to earlier detection of disease, this issue may be very relevant.

Finally, all research synthesis approaches are only as unbiased as the availability of good quality data. The conclusions of any research synthesis approach – naïve, risk assessment, narrative review, systematic review, pairwise meta-analysis or MTC meta-analysis – are subject to publication bias and selective reporting if the only information available is a distortion of the evidence base. For this reason, any research synthesis approach should endeavor to find as broad an information base as possible. MTA meta-analysis is susceptible to publication and selective reporting bias like other forms of research synthesis.[35] Unfortunately, or fortunately, because meta-analyses lend themselves to graphic presentations of the results; they may be more appealing to end users than a 20-page-long narrative review, and therefore they have the potential to propagate bias faster.

Conclusions

MTC meta-analysis is a statistical tool not yet used frequently in bovine practice. It is an appealing tool with the potential to provide estimates of active-to-active comparisons using indirect information from the network of trials. MTC, however, is unlikely to be preferable to pairwise meta-analysis of active-to-active treatments. Nevertheless, in lieu of no information, provided there is reasonable agreement that the assumptions for MTC have been met, MTC may be a useful decision support tool for bovine practitioners.

Endnotes

[a]http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm
[b]http://www.nicedsu.org.uk/Evidence-Synthesis-TSD-series%282391675%29.htm

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