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Title

A Systematic Review and Network Meta-Analysis of Antibiotic Interventions of Liver Abscess in Feedlot Cattle

Registration:

The protocol for the systematic review will be made available on the Systematic Reviews of Animals and Food (SYREAF – http://www.syreaf.org/protocol/) website.

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Contributions

PM conceived the idea and provided guidance on eligibility, AOC and CW provided guidance on the approach to review and analysis and AF and ST provided additional critique and protocol preparation.

Rationale

Liver abscesses (LAs) are one of the most common and costly health problems in the beef industry, and there has been a significantly increased prevalence identified in the past decade. Supplementing diets with tylosin phosphate is currently the most efficacious prevention method, but currently, approved labeling requires continuous supplementation and the inability to use alternative regimens that reduce antimicrobial drug (AMD) exposures hampers our ability to fulfill ethical obligations to promote antimicrobial stewardship. As a consequence, we are working with FDA to conduct a trial assessing alternative durations of antibiotic feeding for feedlot cattle. We intend to combine the results from that study with the results from other studies to understand the comparative efficacy of antibiotics and non-antibiotic treatments for liver abscesses in feedlot cattle in the USA. For this topic we propose to approach to the conduct of the systematic reviews will follow internationally recognized standards [1-5].

Objective:

What is the comparative efficacy of currently licenced and experimental antibiotic treatments designed to prevent liver abscesses (category A and A+) (not due to parasitic infection) in North American feedlot cattle?

PICOD Question

The specific PICOD elements, which will define the eligibility criteria, are as follows:

- Population: Feedlot cattle in United State of America or Canada
- Intervention: Any preventive interventions for liver abscess not due to parasitic infection
- Comparator: Placebo, or any treatment
- Outcomes: Liver abscess at slaughter scored on any combination of the Liver Scoring System (A+ or A+/A or A+/A/A-). (https://www.elanco.us/liver-check-service)
- Design: Controlled trial with random allocation of animals to the intervention in either groups or individually.

Eligibility criteria:

In addition to the PICOD criteria described above, eligibility criteria will include a full text in English. Both published and non-published studies are eligible, provided they report a primary research study with a concurrent comparison group using an eligible study design. Eligible study designs will be controlled trials with natural disease exposure.

Information sources:

The search will be conducted using multiple electronic databases using the MSU Web of Science license (CAB abstracts® and Medline®). Additional sources will be the reference lists of relevant manuscripts, Proceedings of the American Association of Bovine Practitioners, Proceedings of the American Society of Animal Sciences, Proceedings of the Plains Nutrition Conference, and the FDA Freedom of Information New Animal Drug Approvals (NADA) summaries. Further we will access reports of studies conducted by private companies we work with and team members will approach industry groups for proprietory trial protocols and results We will also search the websites of companies that have products registered for the prevention of liver abscess for additional technical reports. At the search level, no restrictions on date or language will be applied.

Search strategy:

The search terms for the electronic databases will be a combination of terms that capture the population and the outcome. Search terms will be created for some or all of the key elements for each question. The proposed search strategy for Medline® is provided in Table 1.

Table 1: Medline® search strings

Terms	Search #	String
Population	1	MH=(Cattle OR Cattle Diseases)
	2	TS=(cow or cows or cattle or heifer$ or steer or steers or bull or bulls or calf or calves or youngstock$ or young-stock$ or beef or veal or bovine$ or bovinae or buiatric$)
	3	1 or 2
Outcome	4	TS=(liver or hepat$)

	5	TS=Abscess
Combined	6	4 AND 5
	7	3 AND 6

Data management and selection process:

Citations identified will be uploaded into the reference management software EndNote® and de-duplicated. The resulting citations then will be managed in DistillerSR® (Evidence Partners, Ottawa). Forms for eligibility screening, data extraction, and risk of bias will be created in DistillerSR®. Two reviewers working independently will screen titles/abstracts records for eligibility. The title/abstract form will be piloted using 30 citations for each question, and the full-text screening form will be piloted on 8 citations. We anticipate using the built-in machine-assisted citation prioritization in DistillerSR®. This citation prioritization allows citations to be automatically reordered such that more likely relevant references are presented to the reviewer sooner, which allows the collection of full texts and full-text screening to begin sooner. Publications must be more than 500 words to be considered a full text. Michigan State University has license agreements for all the major journals and acquisition will be through the MSU licenses and interlibrary loans if needed. The full-text screening will be conducted by two reviewers working independently.

Data collection process

Two experienced reviewers working independently will extract data with disagreements resolved by consensus. The forms will be pre-tested on three full-text publications to ensure clarity and consistency.

Data items

Study-level data will be extracted on the population (state/province, year, animal characteristics (breed, weight, sex)) and details of the intervention and comparator groups (e.g. antibiotic, route, dose, frequency, duration) and whether the study was sponsored by the manufacturer of the intervention. Data will be extracted for each of the outcomes with the presence of liver abscess considered the event. Where relevant information is reported, data from the supplemental materials of studies will also be extracted.

Data outcomes and prioritization

Only binary outcomes will be extracted i.e., (A+) vs (A/A-/0), (A+/A) vs (A-/0), (A+/A/A-) vs (0). Results for each of the outcomes will be extracted, including sample sizes, losses to follow-up, raw data for events in each arm, the number enrolled in arm and the number analyzed or relative measure (RR, OR), measures of variation, and other variables controlled in the analysis. The study populations we are working with are invariable have populations of non-independent study subjects, therefore it is very common for authors to use mixed model methods to adjust for non-independence. Therefore, the effect sizes extracted from the studies were prioritized as follows:

- First prioritymetric:Estimates of efficacy that adjusted for the clustering of feedlot populations, such as adjusted risk ratios, adjusted odds ratios, or the arm-level probability of an event obtained by transformation of the adjusted odds ratio. If the study was conducted in only one pen, the adjustment would not be considered necessary.
- Second priority metric: Estimates of efficacy that did not adjust for the clustering of feedlot populations, such as unadjusted risk ratios, unadjusted odds ratios, or the arm-level probability of an event obtained by transformation of the unadjusted odds ratio.
- Third priority metric: Raw arm-level data, such as the number of animals with liver abscesses and the number of animals allocated and analyzed in the group.

If the first priority metric was reported, the lower priority metrics will not be extracted. Our rationale for the prioritization is that the meta-analysis should use an adjusted summary effect, as most relevant studies are randomized trials conducted in clustered populations[6].

Risk-of-bias assessment

We will use a modified risk-of-bias tool for randomized trials in clustered populations. This is based on the Cochrane ROB 2 tool but places less emphasis on allocation concealment. (https://www.bmj.com/content/366/bmj.l4898)

Data Analysis

Hypothesis tested

The hypothesis of interest is that the new treatments (-56d removal periods and -84d removal periods) are non-inferior to continuous feeding of tylosin phosphate supplementation. To test this assumption, we will use a one-sided 95% credible intervals for the log odds ratios of treatment -56d to the positive control and treatment -84d to positive control from the random effects NMA model. Since the goal is to determine whether either of the new treatments can be equivalent or better than the positive control, the upper limit of the credible intervals should be less than or equal to 0.2. Use an 0-1 indicator to denote if the upper limit of the 95% credible interval of log odds ratio is less than or equal to 0.2. If less than 5% of the estimates in the posterior distribution of the log odds ratio are greater than 0.2, then we would reject the null hypothesis and conclude that the new treatment (either -56d removal periods and -84d removal periods) is non-inferior to the continuous feeding of tylosin phosphate supplementation

Overview of the approach to analysis

The extracted outcome data for systematic review will be combined with the estimate from the clinical trial and synthesized using random effects network meta-analysis. A Bayesian hierarchical model approach, previously published, will be used to obtain the estimates [6-15]. The basic of the NMA model and the outputs are described below. The arrangement of data and all the R scripts, JAGS scripts and BUGS required for the analysis of the data are available online at GitHub (https://github.com/a-oconnor/NETWORK_MA_FRONTIERS_TUTORIAL).

Planned method of statistical analysis

We will use a random-effects Bayesian model for continuous outcomes to obtain the posterior distribution of the effects of interest. Let b denote the baseline treatment of the whole network (usually placebo), and let b_i denote the trial-specific baseline treatment of trial i. It could be the case that $b \neq b_i$. Suppose there are L treatments in a network. Assume a normal distribution for the continuous measure of the treatment effects of arm k relative to the trial-specific baseline arm b_i in trial i, y_{ib_ik}, with variance V_{ib_ik}, such that

$$y_{ib_ik} \sim N(\theta_{ib_ik},\ V_{ib_ik}),$$

and

$$\theta_{ib_ik} \sim \begin{cases} N(d_{b_ik},\ \sigma^2_{b_ik}), & \text{for } b_i = b, \\ N(d_{bk} - d_{bb_i},\ \sigma^2_{b_ik}), & \text{for } b_i \neq b, \end{cases}$$

where d bk is the treatment effects of k relative to the network baseline treatment b and $\sigma^2_{b_ik}$ is the between-trial variance. The priors of d bk and σ_{b_ik} are

$d_{bk} \sim N(0,\ 10000)$, and there is a homogeneous variance assumption that $\sigma^2_{b_ik} = \sigma^2$, where σ ~ U(0, 5). Thus, for L treatments, we have L − 1 priors for dbl, l ∈ {1, …, L}, l ≠ b. For l = b, we have d bb = 0.

Handling of multi-arm trials

For multi-arm trials, we will assume that the co-variance between θ_{jb_jk} and $\theta_{jb_jk'}$ was $\sigma^2/2$ (Higgins and Whitehead, 1996; Lu and Ades, 2004). The likelihood of a trial i with a_i arms will be defined as multivariate normal:

$$\begin{pmatrix} y_{i,1,2} \\ y_{i,1,3} \\ \vdots \\ y_{i,1,a_i} \end{pmatrix} \sim N_{a_i-1}\left(\begin{pmatrix} \theta_{i,1,2} \\ \theta_{i,1,3} \\ \vdots \\ \theta_{i,1,a_i} \end{pmatrix}, \begin{bmatrix} V_{i,1,2} & se^2_{i1} & \cdots & se^2_{i1} \\ se^2_{i1} & V_{i,1,3} & \cdots & se^2_{i1} \\ \vdots & \vdots & \ddots & \vdots \\ se^2_{i1} & se^2_{i1} & \cdots & V_{i,1,a_i} \end{bmatrix} \right),$$

where the diagonal elements in the variance–covariance matrix represent the variances of the treatment differences, and the off-diagonal elements represent the observed variance in the control arm in trial i, denoted by se^2_{i1}. For all studies, the results will be converted to log odds ratios for analysis. If the study authors reported a risk ratio, that was converted back to the log odds ratio using the reported risk of disease in the placebo group. When the authors reported the probability of liver abscess in each treatment arm on the basis of a model, then that probability was converted back to the logs odds ratio using a method described elsewhere {Hu, 2020 #139}

Selection of prior distributions in the Bayesian analysis

As in previous models, we will assess $\sigma \sim U(0, 2)$ and $\sigma \sim U(0, 5)$, and determine which is preferred.

Implementation and output

All posterior samples will be generated using a Markov Chain Monte Carlo (MCMC) simulation implemented with the Just Another Gibbs Sampler (JAGS) software. All statistical analyses will be performed using R software. We will fit the model using JAGS, an MCMC sampler, by calling JAGS from R through the rjags package (version 4-8). Three chains will be simulated, and the convergence will assessed using Gelman–Rubin diagnostics. We will discard 5000 'burn-in' iterations based on our inferences from a further 10,000 iterations. The model output included all possible pairwise comparisons of the log odds ratios (for inconsistency assessment), risk ratios (used for comparative efficacy reporting), and treatment failure rankings (for comparative efficacy reporting).

Assessment of the model fit

The fit of the model will be assessed on the basis on the log odds ratios by examining the residual deviance between the predicted values from the NMA model and the observed values from each study.

Assessment of inconsistency

Network meta-analysis relies on an assumption of consistency between direct and indirect intervention effects that are distinct from the usual variation that stems from a random effects meta-analysis model. For example, if one study compares the direct effect of treatment A with the effect of treatment B, and another study compares the efficacies of treatments B and C, then the (indirect) effect of treatment A relative to the efficacy of treatment C can be inferred. We will use the back calculation method to assess the consistency assumption. We will not rely only on the P-values for the consistency evaluation; instead, we will compare the direction and magnitude of the estimates. We will also compare the estimates from the direct and indirect models and consider the standard deviation of each estimate. Comparisons in which the direct and indirect estimates have different signs will be further evaluated and discussed.

1. O'Connor AM, Anderson KM, Goodell CK, Sargeant JM: **Conducting systematic reviews of intervention questions I: Writing the review protocol, formulating the question and searching the literature**. *Zoonoses Public Health* 2014, **61 Suppl 1**:28-38.
2. O'Connor AM, Sargeant JM, Wang C: **Conducting systematic reviews of intervention questions III: Synthesizing data from intervention studies using meta-analysis**. *Zoonoses Public Health* 2014, **61 Suppl 1**:52-63.
3. Sargeant JM, Kelton DF, O'Connor AM: **Randomized controlled trials and challenge trials: design and criterion for validity**. *Zoonoses Public Health* 2014, **61 Suppl 1**:18-27.

4. Sargeant JM, Kelton DF, O'Connor AM: **Study designs and systematic reviews of interventions: building evidence across study designs**. *Zoonoses Public Health* 2014, **61 Suppl 1**:10-17.
5. Sargeant JM, O'Connor AM: **Conducting systematic reviews of intervention questions II: Relevance screening, data extraction, assessing risk of bias, presenting the results and interpreting the findings**. *Zoonoses Public Health* 2014, **61 Suppl 1**:39-51.
6. Hu D, Wang C, O'Connor AM: **A method of back-calculating the log odds ratio and standard error of the log odds ratio from the reported group-level risk of disease**. *PLoS One* 2020, **15**(3):e0222690.
7. Hu D, O'Connor AM, Wang C, Sargeant JM, Winder CB: **How to Conduct a Bayesian Network Meta-Analysis**. *Front Vet Sci* 2020, **7**:271.
8. Winder CB, Sargeant JM, Hu D, Wang C, Kelton DF, Leblanc SJ, Duffield TF, Glanville J, Wood H, Churchill KJ *et al*: **Comparative efficacy of antimicrobial treatments in dairy cows at dry-off to prevent new intramammary infections during the dry period or clinical mastitis during early lactation: a systematic review and network meta-analysis**. *Anim Health Res Rev* 2019, **20**(2):199-216.
9. Winder CB, Sargeant JM, Hu D, Wang C, Kelton DF, Leblanc SJ, Duffield TF, Glanville J, Wood H, Churchill KJ *et al*: **Comparative efficacy of teat sealants given prepartum for prevention of intramammary infections and clinical mastitis: a systematic review and network meta-analysis**. *Anim Health Res Rev* 2019, **20**(2):182-198.
10. Winder CB, Sargeant JM, Hu D, Wang C, Kelton DF, Godkin MA, Churchill KJ, O'Connor AM: **Comparative efficacy of antimicrobials for treatment of clinical mastitis in lactating dairy cattle: a systematic review and network meta-analysis**. *Anim Health Res Rev* 2019, **20**(2):229-246.
11. Sargeant JM, Deb B, Bergevin MD, Churchill K, Dawkins K, Dunn J, Hu D, Moody C, O'Connor AM, O'Sullivan TL *et al*: **Efficacy of bacterial vaccines to prevent respiratory disease in swine: a systematic review and network meta-analysis**. *Anim Health Res Rev* 2019, **20**(2):274-290.
12. O'Connor AM, Hu D, Totton SC, Scott N, Winder CB, Wang B, Wang C, Glanville J, Wood H, White B *et al*: **A systematic review and network meta-analysis of injectable antibiotic options for the control of bovine respiratory disease in the first 45 days post arrival at the feedlot**. *Anim Health Res Rev* 2019, **20**(2):163-181.
13. O'Connor AM, Hu D, Totton SC, Scott N, Winder CB, Wang B, Wang C, Glanville J, Wood H, White B *et al*: **A systematic review and network meta-analysis of bacterial and viral vaccines, administered at or near arrival at the feedlot, for control of bovine respiratory disease in beef cattle**. *Anim Health Res Rev* 2019, **20**(2):143-162.
14. Hu D, O'Connor AM, Winder CB, Sargeant JM, Wang C: **How to read and interpret the results of a Bayesian network meta-analysis: a short tutorial**. *Anim Health Res Rev* 2019, **20**(2):106-115.
15. Dias S, Caldwell DM: **Network meta-analysis explained**. *Arch Dis Child Fetal Neonatal Ed* 2019, **104**(1):F8-F12.