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Review

A mixed treatment meta-analysis of antibiotic treatment options for bovine respiratory disease – An update

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ABSTRACT

Bovine respiratory disease is the most economically important disease of feedlot cattle in North America. Choice of antibiotic is a critical factor for producers and veterinarians. We previously published a mixed-treatment comparison meta-analysis that combined evidence from published trials and published estimates of comparative efficacy for 12 antibiotics registered for use in the USA. Some of the comparative efficacy estimates were based only on indirect evidence. Since the original review was published, new studies that provide direct evidence of comparative efficacy have been published. We updated the original review to include the current evidence. We also compared the results from the indirect estimates from the prior model with the observed results from randomized control trials. We repeated the original search and found that five of the new studies met the criteria for inclusion in the updated review. Four of these studies provided new data on direct comparisons of active drugs. The results from one study (performed in 2002) that compared ceftiofur pinna and enrofloxacin were inconsistent with the network and were excluded from the analysis. Three new direct comparison studies examined gamithromycin compared with tulathromycin, florfenicol, and tilmicosin. The results of our analysis suggested that the indirect estimates from the prior model provided reasonable estimates of the risk ratios revealed by the primary studies. For example, for the comparison of gamithromycin (referent) with tulathromycin, the original model predicted a risk ratio of re-treatment of 0.54 (95% credible interval 0.27–0.87). The subsequent randomized controlled trial revealed that the observed risk ratio of re-treatment was 0.59 (95% confidence interval 0.45–0.78). The results of other comparisons were also similar. For the gamithromycin (referent) to florfenicol comparison, the observed randomized trial RR was 1.17 (95% confidence interval 0.83–1.64) and the indirect estimate of RR from the prior model was 0.84 (95% credibility interval 0.48–1.3). The gamithromycin to tilmicosin (referent) observed RR from the randomized trial was 0.99 (95% confidence interval 0.67–1.47) and the indirect estimate of RR from the prior model was 1.09 (95% credible interval 0.64–1.79). The results suggested that indirect estimates provided reasonable estimates of RR when direct data were not available.

Introduction

Rationale and objectives

Undifferentiated bovine respiratory disease (BRD) is the most economically important disease of feedlot cattle. Prevention using management and vaccination is the preferred approach to disease control, but it is often necessary to use antibiotics to treat animals affected by BRD. More than 16 drugs are currently registered for use for BRD treatment in the USA. Selection of antibiotic is based on several factors, including price and comparative efficacy. Comparative efficacy is often assessed using randomized controlled trials that include head-to-head direct comparisons of the antibiotics of interest. However, the results of these trials are often not publicly available. In these circumstances, meta-analytic techniques can be used to compare indirect estimates of comparative efficacy. Previously, members of our research group published the results of a mixed-treatment comparison meta-analysis (i.e., network meta-analysis) that included data from 93 publicly available trials and 194 trial arms (O'Connor et al., 2013). The analysis provided estimates of comparative efficacy for all drugs in the network, and rankings of efficacy. Some risk ratio estimates were based on

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direct head-to-head data; other estimates were obtained using only indirect data. Since the original publication, new studies that compare gamithromycin to other active drugs have been published. Our original analysis included direct data only for the comparison of gamithromycin to a non-active placebo control. Therefore, the objectives of this project were two-fold. The first objective was to include the results from these recently published studies in the network. The review question was unchanged from the question used in the prior review. It was defined using a PICOS question [population (P), intervention (I), comparator (C), outcome (O), and study (S)]. The second objective was to compare the risk ratio estimates obtained from the prior indirect meta-analysis with the subsequently published estimates of risk ratios obtained from active-to-active randomized controlled trial data.

Methods

The review approach and statistical methods used were described in detail in the original publication (O'Connor et al., 2013) and are summarized below, with modifications noted where appropriate.

Protocol and registration

No protocol was available for the original review, however the original review did serve as a protocol for the update. This report is prepared based on the PRISMA extension for network meta-analyses published in 2015 and therefore does contain items not included in the prior review (Moher et al., 2015; Shamseer et al., 2015).

Eligibility criteria

The population of interest was feedlot calves in North America with naturally occurring undifferentiated bovine respiratory disease (BRD) as defined by the individual study's authors. The interventions of interest included any injectable antibiotic using a protocol that is registered for the treatment of BRD in North America up to the end of 2015. Treatment protocols for antibiotics combined with non-steroidal anti-inflammatory drugs (NSAID), interventions added to food or water, off-label use protocols and metaphylaxis use were all considered outside the scope of the original review and the update. When an the label included multiple dose protocols, we combined these into a single treatment. The rationale for this approach was that it was assumed the protocols were therapeutically non-inferior if labeled as such. All non-active controls including placebo, saline, non-drug sterile diluent or no treatment were combined into one group defined as non-active controls. A single comparator of interest was not identified, as the purpose of the review was to compare the efficacy across all the available interventions. Incidence of re-treatment from undifferentiated bovine respiratory disease was the outcome of interest. Only studies published in English included in the analysis. This approach was unlikely to create a bias, as only studies in North America were of interest. Experimental trials, cluster-randomized trials and observational studies were not considered relevant. These eligibility criteria did not differ from the prior review. For the update, a search of Commonwealth Agricultural Bureau abstracts and PubMed were conducted on June 12, 2015. The searches were time-limited for the period from 2011 to 2015 as the last search of the original review occurred in June 2012. It was considered that a one year overlap was sufficient to capture all studies published but not indexed up to 2012. The AGRICOLA electronic database was excluded from this update, as in the prior review no relevant manuscripts were uniquely identified in that database. The exclusion of AGRICOLA as an information source is a modification from the prior review. Reference lists from newly identified relevant manuscripts were also hand searched for additional relevant manuscripts. A recently published review on a similar topic was also searched to identify any manuscripts potentially missed by our search strategy (DeDonder and Apley, 2015). The table of contents of the Proceedings of the American Association of Bovine Practitioners Conference and the World Association for Buiatrics Conferences held since 2012 were also hand searched. Pharmaceutical company websites were searched for controlled trials of BRD interventions published as technical reports. In June 2015, the Food and Drug Administration Freedom of Information New Animal Drug Approval (NADA) summaries were searched for new antibiotics registered for the treatment of BRD and for any updated substantial evidence for previously approved antibiotics. We also performed a snowball Google search to detect BRD trials. We used the search terms 'bovine respiratory disease' AND 'registered drug name' OR 'compound name'. The previous review did not include the Google search.

Search

The full search string was not modified and is described in the original review.

Study selection

Screening was conducted using systematic review management software (Distiller SR). Forms for study selection and data extraction were pretested before the analysis to ensure consistent interpretation of relevant studies and data by the two independent reviewers. The two reviewers (a veterinary epidemiologist and an epidemiology graduate student) independently assessed all abstracts for relevance based on the PICOS components. The entire article was acquired if one reviewer thought it might meet the inclusion criteria. The full text was then assessed for relevance. The data were then extracted from the eligible articles.

Data collection process

Because of the overlap in database search time periods, eligible articles were cross-referenced against previously included reports before the data extraction was performed. The data included in the original analysis were available and were reused for this analysis. For the new relevant manuscripts identified by the update, the two reviewers who performed the relevance search also extracted the data from the new articles. They used systematic review management software (Distiller SR) and independently extracted the data into pretested forms.

Data items

For each study and within each trial arm, the intervention used in each trial arm, the number enrolled in each arm, and the event occurrence for the time interval closest to 28 days post-enrollment was extracted. To be eligible for inclusion, the dose and route of the intervention had to be consistent with the manufacturer's label, so this information was not extracted. The article-authors' definition of treatment failure was used to define an event. Because the study population was narrowly defined, additional information about the study population not extracted.

Geometry of the network

Network geometry was assessed using an approach previously proposed (Salanti et al., 2008). The PIE index was calculated using custom-written R script and the C-score test was performed via R package EcoSimR version 0.1.0 *EcoSimR* version 0.1.0 (Gotelli

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