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Review

A mixed treatment comparison meta-analysis of antibiotic treatments for bovine respiratory disease

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ABSTRACT

In this publication we use mixed treatment comparison meta-analysis to compare the efficacy of antibiotic treatments for bovine respiratory disease in beef cattle. Studies were eligible for the meta-analysis if they were publically available and reported the assessment of antibiotic protocols registered for use in the United States (US) for bovine respiratory disease (BRD) in beef cattle and were conducted in North America. Three electronic databases, the proceedings of two bovine specific conferences, pharmaceutical company web sites and the US Food and Drug Administration website were searched to identify relevant trials. The network of evidence used in the analysis contained 194 trial arms from 93 trials. Of the 93 trials there were 8 with three arms. The network of evidence contained information for 12 antibiotics. The output from the analysis provided information about the risk ratio comparing all possible treatments for BRD including comparisons based only on indirect data. The output also included a relative ranking of the treatments and estimates of the probability that an antibiotic protocol was the worst treatment option.

1. Introduction

Producers and veterinarians may legally choose from numerous registered antibiotics for the treatment of bovine respiratory disease (BRD). When deciding which antibiotic to use producers and veterinarians consider many factors including comparative efficacy. Ideally producers and veterinarians would conduct randomized controlled trials at the production site to compare the efficacy of the products, and make the treatment choice based on observed efficacy and cost. For owners of large feedlots and feedlot consultants this is a realistic approach to selection of treatment regimens. For other veterinarians and producers, conducting clinical trials may be difficult. In these situations, veterinarians and producers rely upon scientific literature to assess the efficacy of products. However, if the comparison of interest is not publically available veterinarians or producers must use indirect information to assess comparative efficacy. For example, if one trial compared regimen B to regimen 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 regimen C to regimen 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 vs. C. This approach to comparative efficacy is referred to as the naïve approach and can be misleading because it ignores study level factors and the unit of randomization (Glenny et al., 2005). The naïve approach also fails to empirically incorporate uncertainty about the within-trial direct estimates. For example, if the B vs. A trial used 1000 animals, while the C vs. A trial used 100 animals, the differences in uncertainty about the direct effects of B vs. A and C vs. A should be incorporated into the estimate of comparative efficacy.

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A statistical alternative to the naïve approach for comparative efficacy is called mixed treatment comparison (MTC) meta-analysis, also known as network meta-analysis (Higgins and Whitehead, 1996; Jansen et al., 2008; Lu and Ades, 2004; Lumley, 2002; Salanti et al., 2008). The principle behind MTC meta-analysis is to use evidence from the full network of trial results to make inferences about comparative efficacy while addressing many concerns associated with the naïve approach (Higgins and Whitehead, 1996). Mixed treatment comparison meta-analysis combines direct and indirect estimates of efficacy using the network of information from trials, while accounting for lack of randomization at the study level. The use of mixed treatment comparisons meta-analysis is well established in human medicine but the approach remains rare in veterinary science (Jansen et al., 2011; Nixon et al., 2007; Numthavaj et al., 2011; Piccini and Kong, 2011; Steiner et al., 2012; Van den Bruel et al., 2011; Wang et al., 2010).

Our objective was to use MTC meta-analysis to compare the efficacy of BRD antibiotic treatments. The review question was "What is the comparative efficacy of antibiotics treatments registered for use in North America for the treatment of undifferentiated bovine respiratory disease in feedlot calves?" The rationale for the project was that the information from a MTC meta-analysis would help producers and veterinarians use the full network of publically available information for decision making about BRD treatment choices.

2. Methods

2.1. The review question

Review questions are often defined in terms of the population (P), intervention (I), comparator (C) and outcome (O), i.e., a PICO question, and we elaborated each aspect of the question using this approach. The population of interest (P) was calves with undifferentiated bovine respiratory disease in North American feedlots. Therefore, studies were considered eligible if they could reasonably be expected to exclude yearling aged animals. Many studies did not provide exact information about the age or weight of cattle included in the study. Studies that reported young calves, calves <9 months of age, or less than 800 lb were considered within the scope of the review. As the review aimed to assess the efficacy of therapeutic interventions, calves in the study also had to be diagnosed with undifferentiated bovine respiratory disease as defined by the authors. The interventions (I) of interest were any injectable antibiotic registered for use in North America for the treatment of undifferentiated bovine respiratory disease. Interventions added to water or feed were no within the scope of the review. Unlike reviews about a pairwise comparison of a single intervention with a single comparator, in this review the comparator (C) was not designated as the review question was about comparative efficacy of all interventions. The outcome (O) of interest was incidence of retreatment, as defined by the authors, from undifferentiated bovine respiratory disease. We did not assess mortality or gain parameters as these were generally poorly reported in the studies. As the scope of the review was limited to studies conducted in North America, studies not published in English were not considered within the scope of the review and excluded.

2.1.1. Sources of data

Studies for the MTC meta-analysis were identified from three electronic databases. Searches of AGRICOLA, Commonwealth Agricultural Bureau abstracts, and PubMed were conducted in July 2005, January 2010, January 2012, and June 2012. All years available were searched. The searches included the "population of interest" AND "disease" AND "intervention". The full PUBMED search string was [beef OR bovine OR calf OR calves OR cattle OR cow(s) OR dairy OR Hereford OR Holstein OR ruminant(s) OR steer(s)] AND [bovine respiratory disease OR Bovine viral diarrhea OR Bovine viral diarrhea virus OR undifferentiated fever OR BRD OR BVD OR BVDV OR *Haemophilus somnus* OR Histophilus *somni* OR IBR OR Infectious bovine rhinotracheitis OR *Mannheimia hemolytica* OR *Pasteurella multocida* OR Pasteurellosis OR respiratory disease OR undifferentiated bovine respiratory disease] AND [amoxicillin OR ampicillin OR antibiotic(s) OR antimicrobial(s) OR erythromycin OR ceftiofur OR cloxacillin OR danofloxacin OR enrofloxacin OR florfenicol OR gentamycin OR lincomycin OR oxytetracycline OR penicillin OR spectinomycin OR sulfamethoxazole OR tilmicosin OR trimethoprim OR tulathromycin OR tylosin OR gamithromycin (added in January 2012) OR danofloxacin (added in January 2012) OR tildipirosin (June 2012)].

The reference lists of relevant manuscripts and the table of contents of the Proceedings of the American Association of Bovine Practitioners and the World Association for Buiatrics from 1997 to 2012 were hand searched to identify additional relevant manuscripts. Websites for companies marketing antibiotics with a label claim for BRD were searched to identify relevant controlled trials published as technical reports. The FDA website that contains the Freedom of Information New Animal Drug Approvals (NADA) summaries was searched in June and September 2010, and again in January 2012 and June 2012.[1]

2.2. Data extraction

Two reviewers read all abstracts or summaries identified by the search independently. The review team consisted of veterinary epidemiologist, undergraduate students or veterinary students working with the primary authors' research group. If deemed relevant by at least one reviewer, the full report or manuscript was acquired. Once the full manuscript or report was obtained, it was again assessed for relevance, and if still considered relevant, all data were extracted. Relevant manuscripts described trials evaluating antibiotic treatments for calves diagnosed with BRD in North American feedlots that did not receive antibiotic metaphylaxis at arrival. The definition of BRD was naturally occurring bovine respiratory disease as defined

[1] A http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/default.htm.