

A Review of the Expected Effects of Antimicrobials in Bovine Respiratory Disease Treatment and Control Using Outcomes from Published Randomized Clinical Trials with Negative Controls

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KEYWORDS

- Antimicrobial drugs • Antibiotic susceptibility • Antibiotic resistance
- Bovine respiratory disease • Number needed to treat • Randomized clinical trial
- Evidence based medicine

KEY POINTS

- The randomized clinical trial (RCT) is the gold standard for efficacy determination.
- RCTs with negative (no treatment) controls are not clouded by a control group treatment effect.
- Absolute risk reduction (ARR) is the difference in the probabilities of an event in the control and treatment groups and is estimated as the corresponding difference in the event rates.
- Number needed to treat (NNT) is the reciprocal of the ARR.
- NNT is more clinically intuitive because it describes the effect in terms of the number of patients a clinician needs to treat to expect a given (typically positive) outcome.

INTRODUCTION

Bovine respiratory disease (BRD) is a multifactorial disease that has been well described by many researchers as a complex or syndrome involving an interaction of stressors, viruses, and bacteria. Despite decades of dedicated research, BRD

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remains a major disease in all types of beef and dairy production systems, with an estimated global economic impact in excess of \$3 billion per year.¹ Antimicrobial administration is a mainstay in both the control of disease in populations at high risk of BRD and in the therapeutic treatment of acute clinical disease. The pipeline of novel antimicrobial classes for therapy for BRD has remained dry, however, since the introduction of enrofloxacin (Baytril 100, Bayer Animal Health, Shawnee Mission, Kansas) in 1998. Therefore, the judicious use of antimicrobials in both human and animal health remains paramount to ensure efficacy of treatment remains acceptable.

The objective of this article is to evaluate the use of antimicrobials for therapy for BRD through the lens of a cumulative review of published RCTs investigating the effects of an antimicrobial drug for treatment or control of BRD against a negative control. The NNT is used to describe these trials.² There are many ways to express the value of an active treatment over that of its control group, such as odds ratios and risk reduction. NNT is the reciprocal of the ARR, which is the difference in the probabilities of an event in the control and treatment groups and is estimated as the corresponding difference in these event rates. The NNT statistic has the major advantage of being more straightforward to readers less versed in thinking of events (clinical outcome) in terms of probabilities. NNT is more easily interpreted by practicing clinicians and speaks in terms of number of treatments needed to make a difference in 1 patient. The use of NNT, by expressing the effect of the drug in relation to disease recovery of negative controls over the same period, also incorporates the severity of the disease challenge into the estimate of drug effect. Therefore, the use of the NNT value must be carefully relegated to the disease, regimen, animal species, and specific disease challenge.

ANCILLARY THERAPY USE IN BOVINE RESPIRATORY DISEASE

A systematic review was conducted and published in 2012 by Francoz and colleagues³ on the use of ancillary drugs in the treatment of BRD. Although finding few reliable and consistent data, they concluded that there were not enough data at that time to recommend the use of any ancillary therapy alongside antimicrobials in the treatment of BRD. Using the same search criteria as performed in that study, the authors were unable to identify any recent publications of relevance to expand that conversation; therefore, interested readers should consult that publication. Likewise, no clinical trial data addressing the use of more than 1 antimicrobial at a time versus a single antimicrobial for therapy for BRD were found. The focus of this review is, therefore, limited to the use of antimicrobials alone in the treatment of BRD.

ANTIMICROBIAL USE IN BOVINE RESPIRATORY DISEASE

The prospective, masked, RCT conducted in naturally occurring disease is the gold standard for the evaluation of efficacy for disease intervention in both human and veterinary medical clinical research. In regard to naturally occurring BRD studies of antimicrobial efficacy, the literature is divided into those using a negative control and those comparing the test article to a positive control. When using a positive control treatment, the goal of the experiment is to prove either superiority or noninferiority, either of which requires different study designs. The lack of a significant difference in treatment outcomes in a trial, which was not adequately designed to demonstrate noninferiority, cannot necessarily be interpreted as equivalence of the treatments. Analysis and interpretation of trials with positive controls provide many challenges and are beyond the scope of this article. An excellent meta-analysis was recently performed in this area and readers wishing for that scope should refer to the article by

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