

# Applying lessons from veterinary clinical trials to antimicrobial stewardship

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## Abstract

Antimicrobial stewardship has been one of the largest buzzwords in veterinary and human medicine for several years. The American Veterinary Medical Association (AVMA) defines antimicrobial stewardship as: "...the actions veterinarians take to preserve the success and availability of antimicrobial drugs through conscientious oversight and responsible medical decision-making while safeguarding animal, public, and environmental health." Definitions for antimicrobial stewardships are used repetitively throughout the veterinary profession with varying interpretations. This can cause difficulties for veterinarians "in the trenches" as decisions must be made daily on how to best support stewardship for the veterinarian, client, and the rest of the population. Livestock veterinarians have a unique role in antimicrobial stewardship, with their decisions on antimicrobial usage having potential effects on the foodstuffs that the public consumes. It is partly due to this reason that the usage of antimicrobials in veterinary livestock medicine have been under ever-increasing scrutiny over the last decade. An overwhelming number of different metrics have been developed and discussed over the last several years to measure and monitor usage patterns of antimicrobials in livestock systems. These metrics are beyond the scope of this discussion, but are noted here because it is likely that the veterinary livestock practitioner and their clients need to be prepared to justify and document antimicrobial treatments at some point in the future. The veterinarian and producer must continue to challenge themselves to improve preventative and management practices in order to minimize the need for therapeutic interventions in the first place. The veterinarian must work with producers to ensure that a stewardship plan is in place and also to identify ways to monitor the outcomes of treatment to be able to adjust antimicrobial usage as necessary.

**Key words:** veterinary clinical trial, antimicrobial stewardship, bovine respiratory disease, BRD

## Antimicrobial Stewardship and Bovine Respiratory Disease

Antimicrobial stewardship has been one of the largest buzzwords in veterinary and human medicine for several years. The American Veterinary Medical Association (AVMA) defines antimicrobial stewardship as: "...the actions veterinarians take to preserve the success and availability of antimicro-

bial drugs through conscientious oversight and responsible medical decision-making while safeguarding animal, public, and environmental health."<sup>1</sup> Definitions for antimicrobial stewardships are used repetitively throughout the veterinary profession with varying interpretations. This can cause difficulties for veterinarians "in the trenches", as decisions must be made daily on how to best support stewardship for the veterinarian, client, and the rest of the population. Livestock veterinarians have a unique role in antimicrobial stewardship, with their decisions on antimicrobial usage having potential effects on the foodstuffs that the public consumes. It is partly due to this reason that the usage of antimicrobials in veterinary livestock medicine have been under ever-increasing scrutiny over the last decade. An overwhelming number of different metrics have been developed and discussed over the last several years to measure and monitor usage patterns of antimicrobials in livestock systems.<sup>2</sup> These metrics are beyond the scope of this discussion, but are noted here because it is likely that veterinary livestock practitioners and their clients need to be prepared to justify and document antimicrobial treatments at some point in the future.

The number of publications stating bovine respiratory disease (BRD) as the largest threat to cattle health and well-being, the number 1 most economically devastating disease in the cattle industry, and providing statistics to show that this has remained the same, if not worsened, over the last several decades are far too numerous to count. Further, many authors have continued to share very similar potential causes for BRD's devastating effects. These commonly include various viral and bacterial components, physiological aspects of the bovine that predispose it to pneumonia, and stressors (e.g. long transport, weaning practices, procurement practices, cattle management shortcomings, etc.). Despite advancement of vaccines and supplements available, the negative economic and animal welfare effects of BRD have not lessened. The published reports of antimicrobial resistance for pathogens associated with BRD in the literature have shown an alarming trend towards resistance to all of the antimicrobials available for BRD treatment and control. To date, the research available on non-antimicrobial alternatives to treat and/or control BRD has not been promising. One of the key concepts related to antimicrobial alternatives is that we should not expect such alternatives to have the disease prevention, control, or treatment impact of a properly selected antimicrobial used against a susceptible pathogen.

One of the main pillars of antimicrobial stewardship is ensuring an accurate diagnosis of disease such that the

correct treatment can be applied. It is well accepted that the correct diagnosis of BRD is 1 of the most challenging aspects of the disease because the clinical signs are generally subjective and non-specific. The clinical signs of BRD can look like many other diseases, and the industry would benefit greatly from an objective diagnostic test to aid in the early accurate diagnosis of BRD. However, research in this area has also been largely unrewarding to date.

### **Veterinary Clinical Trials**

The gold standard for evaluation and efficacy testing in the support of a new animal drug application (NADA) with the Food and Drug Administration Center for Veterinary Medicine (FDA CVM) is the use of a naturally occurring disease model in a prospective, masked, randomized clinical trial. These clinical trials are typically designed with a negative control treatment group. A negative control study is where the investigational product is compared to either no treatment at all, or more commonly, a placebo treatment is used. A negative control study offers a unique insight into the true value of a treatment as the comparison is not to another product, but to not treating the disease condition at all.

### **Comparison of Antimicrobial Treatment to Negative Controls**

In 2015, DeDonder and Apley performed a literature review where all published data met certain criteria, namely, the studies had to have been prospective, masked, randomized clinical trials with a negative control.<sup>3</sup> The data were assimilated and presented to show the differences between the antimicrobial product being tested vs a negative control group. In that literature review publication, Freedom of Information (FOI) data and independently published data were extracted and all subjected to the same statistical procedures. Most useful to the current discussion, the authors of that publication used the extracted data to calculate the absolute risk reduction (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. To put that in more clinically understandable terms, the authors presented what is termed the number needed to treat (NNT), calculated as the reciprocal of ARR. The NNT is the number of treatments needed to be administered in order to make a difference in 1 patient. For example, if a hypothetical drug has a NNT of 3, 3 patients would need to be treated for the disease in order for the drug to make a clinical difference in 1 patient.

As pointed out by the authors, there are 2 major caveats that must be kept in mind when interpreting this publication. First, the use of the NNT value must be carefully relegated to the disease, regimen, animal species, and the specific disease challenge. Second, these data are not meant to be used to directly compare the NNT of 1 antimicrobial to another due

to differences in trial design, sample size, class of cattle (risk profile), resultant spontaneous recovery rates, and potential differences in case definition and success/failure outcome between trials.

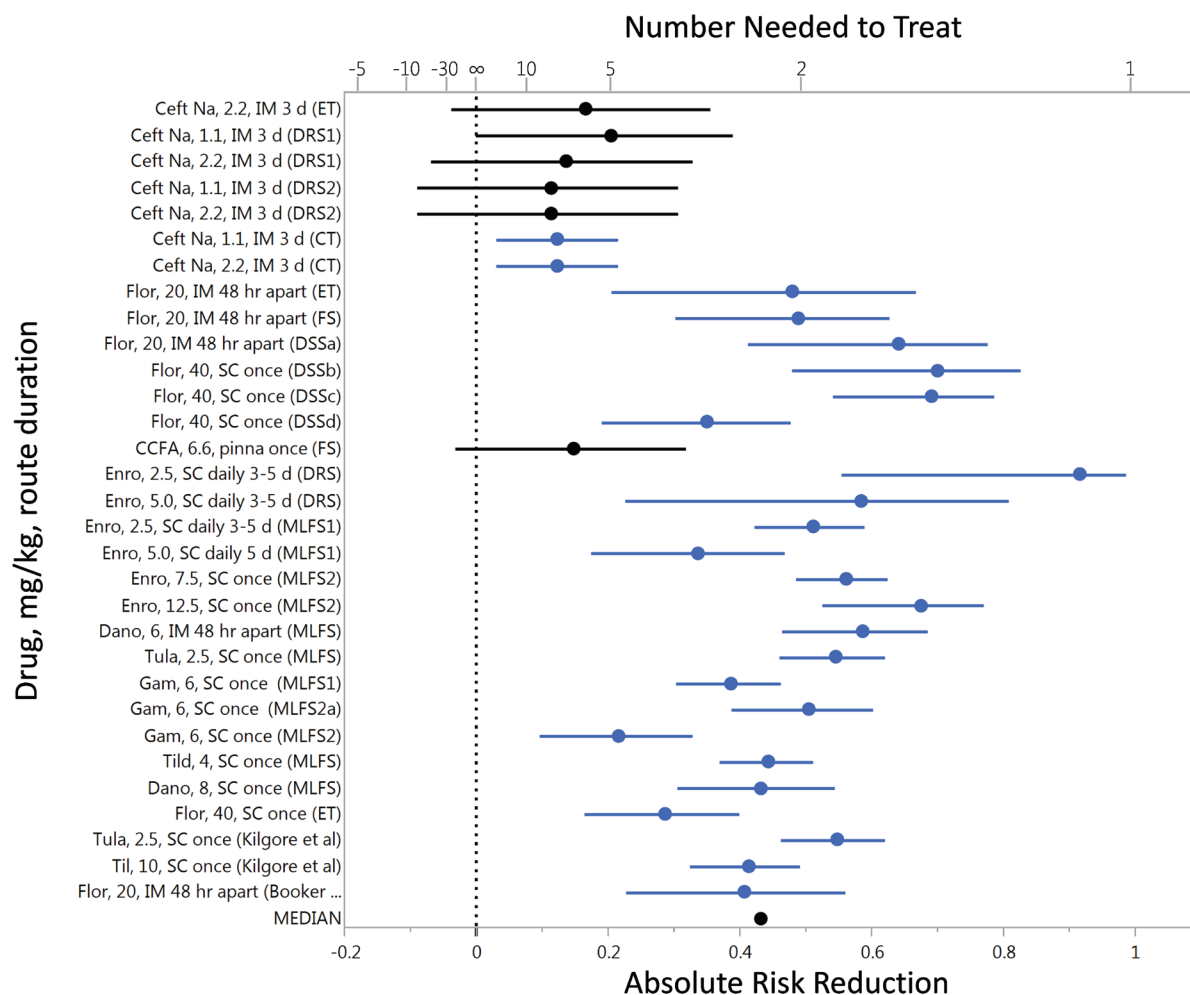
With that said, a partial reproduction of the results of analysis from the publication can be found in Figures 1 (morbidity) and 2 (mortality) with the antimicrobial listed on the y-axis, the ARR on the bottom x-axis, and the NNT on the top x-axis. The data points that have 95% confidence intervals crossing the null axis (dashed line at 0 and  $\infty$ ) display insignificant results by the analysis that the authors performed. Meaning that in the analysis, it cannot be stated with 95% confidence that the use of that particular antimicrobial, in that group of cattle, had a positive effect compared to treatment with saline placebo injection. As stated by the authors, the overwhelming majority of trials show a positive effect on case outcome in the therapy of BRD. The median NNT in therapeutic trials involving negative controls is 2. Therefore, for every 2 animals treated for BRD in the overall population of these studies, 1 case was a treatment success, seen in the last row of Figure 1 (labeled Median). The median NNT for preventing 1 mortality due to BRD in the trials reviewed is 6; for every 6 animals treated, therapeutically, 1 BRD death is prevented as displayed in Figure 2.

The concept of NNT applies to antimicrobial stewardship through considering the effect the antimicrobials are able to produce in naturally occurring BRD. In these studies, these differences were observed when antimicrobials were administered using case definitions based on a combination of subjective and objective criteria, as imperfect as they are. The majority of these definitions were utilized in pivotal clinical studies where the success/failure definitions tend to bias towards more failures than might be observed in normal practice in order to minimize false success classifications; nevertheless, these values give us an insight into when results may be “too good” (e.g., a 95% success rate) and serve as a basis to investigate whether antimicrobials are being applied indiscriminately.

External validity of all studies must be carefully evaluated. In the case of the NNT values presented here, these were primarily in high-risk calves selected in studies to maximize the effect of the treatment in comparison to untreated controls. In the case of backgrounded calves or low-risk yearlings, it is reasonable to hypothesize that the drug effect would be less, due to a higher rate of spontaneous recoveries in the untreated controls. It should also be noted that these success/failure definitions are only based on the success/failure criteria used in each study and do not include treatment effects on subsequent average daily gain or feed conversion.

### **Case Definition**

One of the cornerstones of a properly designed veterinary clinical trial is the selection of a well thought-out case



**Figure 1.** Forest plot of point estimates and 95% confidence intervals of the Absolute Risk Reduction of morbidity (bottom x-axis) and the corresponding Number Needed to Treat (top x-axis) found from analysis of the therapeutic studies. Studies listed on the y-axis are listed by active ingredient, dose (mg/kg), route of administration, and duration of therapy. (ET = efficacy trial, DRS = dose response study, CT = clinical trial, FS = field study, DSS = dose selection study, MLFS = multi-location field study) (Reproduced from DeDonder and Apley, 2015)

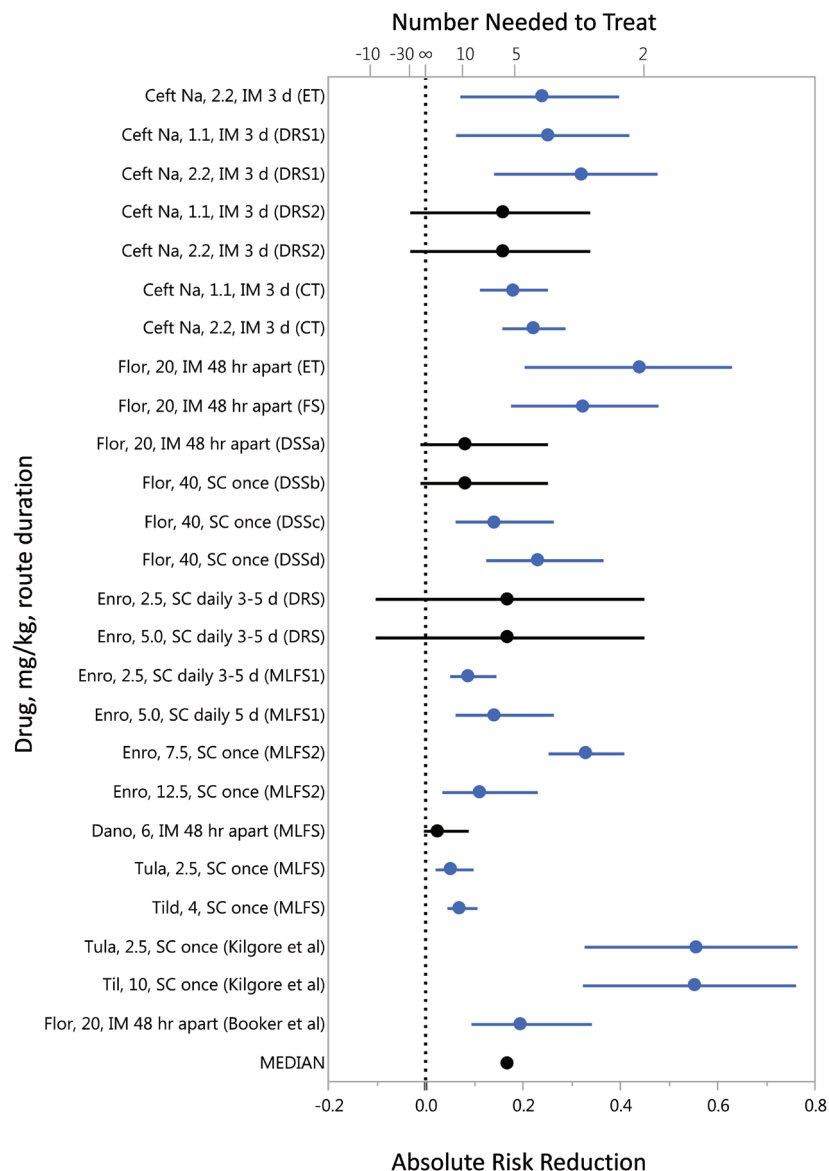
definition. A case definition is a specific set of criteria that an animal must meet, with no exceptions, to be qualified as sick with BRD for enrollment into a study. These can vary between each study depending on the objectives of the individual investigator, but the most important attribute is that they are defined ahead of time in the protocol, and there are no allowable excursions from the case definition. The adherence to the definition described in the study protocol assures that all cattle enrolled in the study have at least exceeded a minimum threshold of criteria (e.g. specific clinical signs coupled with a minimum rectal temperature) to be enrolled in the study. This enrollment criteria, when combined with proper randomization techniques, ensures that an equal distribution of sick cattle will be enrolled in both the treatment group and the negative control group of the veterinary clinical trial. These procedures ensure that both the antimicrobial drug being investigated and the negative control have an

equal distribution of severity of diseased animals, and thus the comparison between the 2 is unbiased.

These case definitions are not only important in clinical trials. Case definitions are the basis for antimicrobial stewardship by properly selecting cases where antimicrobials have the potential to make a difference. We have long struggled to make sure we don't miss an animal that might benefit from antimicrobials. Antimicrobial stewardship requires that we also spend time assuring we don't administer antimicrobials to animals that won't benefit from that treatment.

### Case Outcome

As efficacy determination depends on treatment success/failure, the criteria that determine case outcome (also termed success/failure criteria) are just as important in the evaluation of an antimicrobial treatment as the case defini-



**Figure 2.** Forest plot of point estimates and 95% confidence intervals of the Absolute Risk Reduction of mortality (bottom x-axis) and the corresponding Number Needed to Treat (top x-axis) found from analysis of the therapeutic studies. Studies listed on the y-axis are listed by active ingredient, dose (mg/kg), route of administration, and duration of therapy. (ET = efficacy trial, DRS = dose response study, CT = clinical trial, FS = field study, DSS = dose selection study, MLFS = multi-location field study) (Reproduced from DeDonder and Apley, 2015).

tion. In properly conducted veterinary clinical trials, the case outcome is also defined in the protocol ahead of time, and is very strictly adhered to as well. Well defined and adhered to definitions of outcome are important to avoid bias during analysis and will lead to results that are more easily interpreted by the end user. Likewise, a well-thought-out case outcome definition in production systems allows for much more meaningful data in terms of monitoring treatment response for the practitioner and producer alike.

Antimicrobial stewardship not only includes the initial decision to treat an animal or group of animals, but also when we should stop. Although second and third treatments for

BRD make up a smaller portion of total antimicrobial use than initial treatment, they result in additional antimicrobial exposure and should be justified through well characterized case selection criteria.

### Clinical Application

An important piece of the puzzle that is antimicrobial stewardship is making an accurate diagnosis such that a proper therapeutic regimen can be prescribed. Making an accurate diagnosis of BRD is 1 of the more challenging and frustrating parts of BRD management. However, through the

development of consistent case definitions and case outcome definitions, there can at least be consistency to how BRD is diagnosed and treated. The veterinarian should work with producers to define criteria specific for each individual production system.

The take-home message of all of the information on antimicrobial stewardship is that our first obligation as veterinarians is to assure we are accurately identifying the disease challenge. Then, we must apply all reasonable strategies to prevent the challenge, followed by instituting procedures to properly apply antimicrobials for prevention, control, or treatment of the associated pathogens. If our only approach is to utilize antimicrobials whenever there could be a potential benefit, or liability in not doing so, then our claims to antimicrobial stewardship are unfounded.

It is very unlikely that regulatory oversight is going to lessen at any point in the future, therefore, antimicrobial usage monitoring is much more likely to continue to increase in livestock production systems. The veterinarian and producer must continue to challenge themselves to improve preventative and management practices in order to minimize the need for therapeutic interventions in the first place. The veterinarian must work with producers to ensure

that a stewardship plan is in place, and also to identify ways to monitor the outcomes of treatment to be able to adjust antimicrobial usage as necessary.

### Acknowledgement

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