A randomized trial comparing the effects of tulathromycin, tildipirosin and gamithromycin used as first treatment for clinical bovine respiratory disease in commercial feedlot steers

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Abstract

Our objective was to compare effects of 3 macrolide antibiotics used as first-time bovine respiratory disease (BRD) treatment on primary health outcomes (retreatment, removal and mortality) in feedlot steers. Secondary outcomes included days-on-feed, rectal temperature and weight at the time of event occurrences. Crossbred beef steers (n = 978; average body weight [± SD] 655 ± 84.0 lb [297 ± 38.1 kg]) were enrolled across 2 commercial feedlots in the U.S. High Plains in a randomized complete block design. Steers were eligible for inclusion if they were exhibiting clinical BRD symptoms from natural exposure and had not been previously treated with an antimicrobial drug for any reason including metaphylaxis. Treatment was administration of tulathromycin, tildipirosin or gamithromycin, at the time of first BRD diagnosis. Linear and generalized linear mixed models were used for statistical analyses with significance threshold α = 0.05. At enrollment, animal weight ($P = 0.98$), rectal temperature ($P = 0.58$), and days-on-feed ($P = 0.28$) did not differ significantly between treatments. There was no evidence of differences for any health outcome ($P \geq 0.30$), nor for any cattle characteristics at the time of retreatment, removal, or mortality ($P \geq 0.15$). Treatment success (steers that were never retreated, removed, and/or were a BRD case fatality) ranged from 62.7 to 64.8% between treatments ($P = 0.87$). There was no evidence to reject the null hypothesis of similar effectiveness between these macrolides when administered to similar steer populations as first-time clinical BRD treatments.

Key words: antibiotic, bovine respiratory disease, feedlot cattle, macrolide, steers

Introduction

Bovine respiratory disease (BRD) complex is a syndrome that has troubled the beef industry for decades. It is well established as the predominant cause of morbidity and mortality in the feedlot, as well as having a substantial economic burden on the industry.[1,2] In addition to negative impacts on animal well-being, the disease also adversely affects beef production through reduced cattle performance, poorer carcass characteristics, and the associated costs of prevention, treatment, and control.[2–6] It has also been estimated that when BRD incidence is reduced, environmental sustainability may be improved through the reduction of greenhouse gas emissions due to healthier cattle populations with reduced mortality and improved feedlot performance.[7] Although the importance of BRD cannot be overstated, and advancements have been made, it remains a challenging disease to control due to its multifactorial nature involving the environment, pathogens and host.[8]

Antimicrobial metaphylaxis has been a successful tool for controlling BRD incidence, particularly in high-risk cattle populations,[9–11] for which the macrolide class of antibiotics has been implied to be superior compared to others.[9] The 2011 National Animal Health Monitoring System survey of health and management on U.S. feedlots found that approximately 21.3% of cattle placed in feedlots were administered antimicrobial metaphylaxis.[12] In typical commercial cattle feeding operations, cattle that do not receive metaphylaxis upon feedlot arrival can generally be presumed to fall into low- to medium-risk categories for development of BRD; still, proportions of these cattle will be afflicted and require clinical treatment. Antimicrobial treatment options for animals with clinical BRD have been summarized in a systematic review and meta-analyses.[13] This can be a valuable resource for researchers, bovine practitioners and producers for the consideration of antimicrobial regimens and comparative efficacy. Notably however, specific macrolides of interest, particularly tildipirosin and gamithromycin, have few direct comparisons from single clinical trials.

The success rate and reduction of retreatment (cattle requiring sequential BRD treatments after an initial treatment failure) is critical when selecting a specific antibiotic for use; animals requiring multiple treatments will not only have increased drug and processing costs, their performance and production efficiency also suffer.[5] To the knowledge of the authors, there are no peer-reviewed publications with a head-to-head comparison of tulathromycin, tildipirosin and gamithromycin when used as a first-time treatment option for clinical BRD. The molecular composition and ring structures of tulathromycin,[14] tildipirosin[15] and gamithromycin,[16] differ. As these macrolides have been implicated to be in the top-tier for the control of BRD,[9] it was of interest to evaluate this comparison in a randomized clinical trial. Therefore, our primary objective was to compare the effects of tulathromycin, tildipirosin and gamithromycin when administered for first-time clinical BRD treatment in feedlot steers on cattle health – namely the probability of treatment success, which encompasses retreatment, removal and mortality. Secondary

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objectives were to characterize potential differences in cattle characteristics pertaining to animal weight, rectal temperature and days-on-feed (DOF), at the time of primary outcome occurrence.

Materials and methods

This trial was approved through the Boehringer Ingelheim Animal Health Institutional Animal Care and Use Committee, approval number APS-20-128.

Cattle population

A total of 978 crossbred beef steers with an average initial body weight (BW ± 1 SD) of 655 ± 84.0 lb (297 ± 38.1 kg) were selected for trial inclusion beginning in February 2021 through March 2022. Steers were housed at one of 2 commercial feedlots in Kansas and Oklahoma. The specific feedlots were chosen out of convenience and history with research conduct. Cattle selected for trial inclusion were similar between the feedlots and were of typical type (excluding dairy-influenced cattle), age and origin for steers commonly fed at the locations. Steers were eligible for inclusion in the trial if they required a first-time treatment for clinical BRD, and the following conditions were met: 1) there was no history of prior treatment (for any reason) or antimicrobial metaphylaxis at initial processing; 2) clinical symptoms for BRD were displayed, including: depression, anorexia, labored breathing, coughing and nasal discharge; 3) rectal temperature was 104 °F (40 °C) or greater; 4) there was no known or evident concurrent disease (e.g., lameness); and 5) the animal's weight was between 400 and 850 lb (181 to 386 kg).

Treatment structure and experimental design

A one-way factorial treatment structure in a randomized complete block design was implemented. Experimental treatments consisted of tulathromycin[a] (TUL), tildipirosin[b] (TILD) or gamithromycin[c] (GAM) administered as the first treatment regimen for clinical BRD (see Table 1 for regimens). A randomization table generated using commercial software (Proc FACTEX, SAS 9.4[d]) was used for random allocation to treatment within blocks. Blocks consisted of 3 animals which were assigned to one of the 3 experimental treatments determined by their order through the hospital chute and the corresponding randomization sequence for the current block. Blocks were filled by 3 animals (meeting all trial inclusion criteria) that required treatment for first-time clinical BRD on the same day and time. No incomplete blocks were used (e.g., if 5 animals met all inclusion criteria on a given day, only the first 3 through the chute were enrolled in a block, and the remaining 2 would have been excluded from the trial). Hospital personnel were blinded to treatment when moving cattle through the chute and evaluating eligibility criteria for enrollment; personnel were not blinded when physically administering experimental treatments to enrolled steers. All antibiotics were administered subcutaneously in the lateral neck according to manufacturer labels and following Beef Quality Assurance[e] (BQA) guidelines using syringes fitted with 16-gauge × 5/8 in. (15.88 mm) needles. A seven-day post-treatment interval was required before animals were eligible to be re-treated for BRD if clinical signs persisted. Table 1 outlines the experimental treatments with additional detail. A priori sample size calculations using $\alpha = 0.05$ and $\beta = 0.20$ estimated that a total of 3,000 steers (1,000 per treatment) would be required to detect a difference in BRD retreatment risk of 30.0 vs 24.4%, and it was estimated that it would take approximately 1 year to enroll this number of steers. Fewer than expected BRD cases occurred after 1 year of enrollment; it was decided to cease trial continuation, resulting in a smaller effective sample size and reduced statistical power to detect differences (additional rationale described later).

Cattle management and stewardship

Upon feedlot arrival, cattle were given ad libitum access to long-stemmed forages and water, and were allowed a 1- to 3-day rest-period prior to initial processing. Cattle were then processed as a lot (cohort) per feedlot standard operating procedures. This included administration of a trivalent modified live respiratory vaccine[f], a multivalent clostridial vaccine[g], an injectable parasiticide (1% ivermectin[h]), an oral anthelmintic[i], and a growth promotant implant[j]. Specific products used were consistent within blocks, but variable between blocks, as this included all steer-lots received within (and some before) the trial enrollment timeframe. Steers were housed in dirt-surfaced pens with ad libitum water access provided from automatic fountains. Cattle were gradually transitioned (over at least 21 days) to a high-concentrate finishing diet formulated to meet or exceed animal maintenance and growth requirements.[17] Cattle were fed 2 times daily to provide nominal ad libitum access.

Table 1: Characteristics of macrolide antimicrobial drugs used as the first treatment regimen for clinical bovine respiratory disease (BRD) in beef steers in a randomized clinical trial conducted at 2 U.S. High Plains feedlots.

	Treatment		
Item	**TUL[†]**	**TILD[‡]**	**GAM[§]**
Dosage, mL/100 lb	1.1	1.0	1.8
Post-treatment-interval[‖], days	7	7	7
Pre-harvest withdrawal[¶], days	18	21	35

[†] Tulathromycin (Draxxin®; Zoetis Animal Health, Parsippany, NJ) administered subcutaneously.

[‡] Tildipirosin (Zuprevo®; Merck Animal Health, De Soto, KS) administered subcutaneously.

[§] Gamithromycin (Zactran®; Boehringer Ingelheim, Duluth, GA) administered subcutaneously.

[‖] Time between when the antibiotic was administered and when an animal would be eligible to be re-treated if clinical signs of BRD persisted or returned.

[¶] Time between when the antibiotic was administered and when the animal could be harvested for consumption.

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The primary outcomes of interest were health related, namely, BRD retreatment, removal (animals removed from the trial for health reasons) and mortality. Treatment success was defined as steers that were never retreated for BRD, removed for BRD, and/or were a BRD case fatality. Pens were monitored daily by trained animal caretakers who evaluated these health outcomes. Steers could be retreated for BRD if clinical signs (previously described) persisted; retreatment could occur at any time following the initial BRD case enrollment so long as steers were outside of the 7-day post-treatment interval. Rectal temperature was recorded, but not factored into the decision to re-treat, as BRD retreatments were treated solely on clinical symptoms. Additionally, animal DOF and BW were recorded and included in analyses as descriptive characteristics of steers at the time of retreatment. First-time BRD retreatments (second overall treatment) were administered florfenicol[k] at 6 mL/100 lbs (40 mg/kg) subcutaneously, and second time BRD retreatments (third overall treatment) were administered danofloxacin[l] at 2 mL/100 lb (8 mg/kg) subcutaneously per manufacturer labels and BQA guidelines. After the initial BRD treatment (at trial enrollment) and any subsequent retreatments, cattle convalesced in a hospital pen for one to 3 days before returning to their respective home pens. Steers that were retreated a third time (fourth overall BRD treatment) were considered chronic and removed from the trial. Animals also could be removed from the trial at any time and for any health reason (BRD or otherwise) when no practical treatment options existed for the disease or malady in question (severe cases). Necropsies were performed on deceased cattle by trained feedlot personnel or a licensed veterinarian when the reason for death was not obviously apparent. Animal caretakers assessing all health outcomes were blinded to experimental treatments. Steers completing the trial (not removed or deceased) were harvested at a commercial abattoir with their pen-mates once reaching a standard body composition.

Statistical analyses

Linear and generalized linear mixed models (LMM and GLMM, respectively) were fit to evaluate outcomes of interest using commercially available software (Proc GLIMMIX, SAS 9.4[d]). For all models, individual steer served as the experimental and observational unit, the fixed effect was treatment, and random intercepts for feedlot and block within feedlot were used to account for clustering. For continuous outcomes (LMM), a Gaussian distribution with identity link function was implemented using restricted maximum likelihood estimation, Newton-Raphson with ridging optimization procedures, and a Kenward-Roger degrees of freedom adjustment for standard errors. Visual assessments of conditional and marginal studentized residuals were plotted to evaluate model assumptions of homoscedasticity and normality. In order to satisfy these assumptions, DOF was either natural log or square-root transformed in models evaluating the outcome, and model estimates were back-transformed to their original scale for interpretation. For dichotomous outcomes (GLMM), a binary distribution with a logit link function was first fit using a Laplace approximation for assessment of overdispersion of residuals. In the absence of overdispersion (Pearson-Chi^2/df < 2), models were re-fit using residual pseudo-likelihood estimation and included Kenward-Rodger's degrees of freedom adjustment (Newton-Raphson with ridging optimization procedures were also employed in both steps). Estimates from GLMM were back transformed into probabilities for interpretation. A statistical significance threshold of $\alpha = 0.05$ was determined a priori, and if significant, a Tukey-Kramer adjustment for multiple comparisons was used for evaluation of differences between all pairwise combinations of treatment means.

Results

Summary statistics of the enrollment characteristics of steers used in the trial are in Table 2. There was no evidence for differences between treatments for enrollment BW ($P = 0.98$), rectal temperature ($P = 0.58$), or DOF ($P = 0.28$), indicating that balanced comparison groups were achieved through the randomization process. Across the 3 treatments, mean initial BW was 652 to 653 lbs (296 kg), mean rectal temperature was 104.8 to 104.9 °F (40.5 °C), and mean DOF at the time of first clinical BRD treatment was 8.2 to 8.6 days. The number of animals per treatment (326) is consistent with the number of experimental units analyzed for the primary outcomes of interest.

The probability of BRD treatment success and retreatment are in Table 3. The probability of treatment success for TUL, TILD and GAM was 64.8, 62.7 and 64.1%, respectively, which did not

Table 2: Model adjusted means and standard errors of the means (SEM) of enrollment statistics of beef feedlot steers administered 3 different macrolide antibiotics upon first clinical signs of bovine respiratory disease (BRD) at the time of allocation to experimental treatments.*

	Treatment				
Item	**TUL**[†]	**TILD**[‡]	**GAM**[§]	**SEM**	***P*-value**
Animals, n	326	326	326	–	–
Body weight, lb	653	653	652	13.2	0.98
Rectal temperature, °F	104.9	104.8	104.9	0.11	0.58
Days-on-feed	8.6	8.2	8.2	1.18	0.28

* Trial was conducted as a randomized complete block design at 2 feedlots in the U.S. High Plains, where a block consisted of 3 steers pulled for treatment of clinical BRD on the same day, and randomly assigned to one of the 3 experimental treatments (macrolide antibiotics); steers had no prior treatment history for any disorder (including antimicrobial metaphylaxis) and had no signs of concurrent disease at the time of enrollment.

† Tulathromycin (Draxxin®; Zoetis Animal Health, Parsippany, NJ) administered subcutaneously to deliver 1.1 mL/100 lb (45.4 kg) body weight.

‡ Tildipirosin (Zuprevo®; Merck Animal Health, De Soto, KS) administered subcutaneously to deliver 1.0 mL/100 lb (45.4 kg) body weight.

§ Gamithromycin (Zactran®; Boehringer Ingelheim, Duluth, GA) administered subcutaneously to deliver 1.8 mL/100 lb (45.4 kg) body weight.

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differ significantly ($P = 0.87$). There was no evidence for a difference between treatments for the probability of having a first-time BRD retreatment ($P = 0.81$). For the steers that had a first-time BRD retreatment, there were no significant differences between treatments for BW ($P = 0.47$), rectal temperature ($P = 0.82$), or elapsed DOF ($P = 0.70$; the number of DOF since trial enrollment) at the time of retreatment. Additionally, there was no evidence for a difference between groups for the probability of having a second BRD retreatment ($P = 0.75$), nor were there any significant differences for BW ($P = 0.21$), rectal temperature ($P = 0.15$), or elapsed DOF ($P = 0.53$) at second retreatment. For secondary outcomes (animal characteristics at the time of retreatment), the number of experimental units analyzed is consistent with the number of animals that had a first or second BRD retreatment; therefore, the effective sample size is reduced in comparison to primary outcomes.

Table 4 shows the effects of treatments on the probability of removal from the trial or mortality. There was no evidence of a difference for BRD case fatality ($P = 0.98$) or total mortality ($P = 0.96$) between treatments. There also were no significant treatment differences for the probability of being removed from the trial for BRD ($P = 0.37$) or all reasons ($P = 0.30$). As a whole, there was no evidence of a difference between treatment groups on the probability of trial fallout ($P = 0.68$; removal or death), or on the elapsed ($P = 0.57$) DOF at the time of fallout.

Discussion

No significant differences for any health outcome were observed between the 3 macrolide antibiotics used as first treatment regimens for clinical BRD. This could in part be due to the smaller than planned sample size. Steers meeting the enrollment criteria were more limited than expected, and after approximately 1 year, it was agreed by both the clinical investigator and trial sponsor to cease further enrollment. This was decided primarily due to time, resources, and the observed absence of meaningful treatment differences, which has been described as futility stopping.[18,19] Because

Table 3: Model adjusted means and standard errors of the means (SEM) for the effects of 3 different macrolide antibiotics administered upon first clinical signs of bovine respiratory disease (BRD) in beef feedlot steers on the probability of initial treatment success and retreatment for BRD.*

	Treatment				
Item	**TUL†**	**TILD‡**	**GAM§**	**SEM**	***P*-value**
BRD cases enrolled, n	326	326	326	–	–
Treatment success‖, % (SEM)	64.8 (13.62)	62.7 (13.95)	64.1 (13.74)	–	0.87
First retreatment¶, n	108	115	109	–	–
First retreatment, % (SEM)	33.9 (13.40)	36.3 (13.81)	34.3 (13.46)	–	0.81
Body weight, lb	734	756	759	47.3	0.47
Rectal temperature, °F	103.4	103.4	103.5	0.21	0.82
Elapsed DOF**	19.8	21.8	21.3	1.28	0.70
Second retreatment††, n	59	64	57	–	–
Second retreatment, % (SEM)	17.7 (9.14)	19.3 (9.76)	17.0 (8.88)	–	0.75
Body weight, lb	735	727	775	43.7	0.21
Rectal temperature, °F	103.6	103.4	103.1	0.26	0.15
Elapsed DOF**	32.4	30.4	35.3	1.25	0.53

* Trial was conducted as a randomized complete block design at 2 feedlots in the U.S. High Plains, where a block consisted of 3 steers pulled for treatment of clinical BRD on the same day, and randomly assigned to one of the 3 experimental treatments (macrolide antibiotics; n = 326 per treatment); steers had no prior treatment history for any disorder (including antimicrobial metaphylaxis) and had no signs of concurrent disease at the time of enrollment.

† Tulathromycin (Draxxin®; Zoetis Animal Health, Parsippany, NJ) administered subcutaneously to deliver 1.1 mL/100 lb (45.4 kg) body weight.

‡ Tildipirosin (Zuprevo®; Merck Animal Health, De Soto, KS) administered subcutaneously to deliver 1.0 mL/100 lb (45.4 kg) body weight.

§ Gamithromycin (Zactran®; Boehringer Ingelheim, Duluth, GA) administered subcutaneously to deliver 1.8 mL/100 lb (45.4 kg) body weight.

‖ Treatment success defined by steers that were never retreated for BRD, removed due to BRD, and/or were a BRD case fatality.

¶ Steers requiring a second treatment at any time for BRD were administered florfenicol (Nuflor® [Merck Animal Health] or Loncor® 300 [Elanco Animal Health, Greenfield, IN]).

** Elapsed days-on-feed (DOF) are days since trial enrollment.

†† Steers requiring a third treatment at any time for BRD were administered danofloxacin (AdvocinTM; Zoetis Animal Health).

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Table 4: Model adjusted means and standard errors of the means (SEM) for the effects of 3 different macrolide antibiotics administered upon first clinical signs of bovine respiratory disease (BRD) in beef feedlot steers on the probability of mortality and trial removal.*

	Treatment			
Item	**TUL†**	**TILD‡**	**GAM§**	***P*-value**
BRD cases enrolled, n	326	326	326	–
BRD case fatality, n	14	13	14	–
BRD case fatality, % (SEM)	4.3 (1.51)	4.0 (1.44)	4.3 (1.51)	0.98
Total mortality, n	24	26	25	–
Total mortality, % (SEM)	7.4 (1.88)	8.0 (1.98)	7.7 (1.93)	0.96
BRD removals, n	16	9	13	–
BRD removals, % (SEM)	4.9 (1.20)	2.8 (0.91)	4.0 (1.08)	0.37
Total removals, n	24	16	16	–
Total removals, % (SEM)	7.4 (1.45)	4.9 (1.20)	4.9 (1.20)	0.30
Total fallouts‖, n	48	42	41	–
Total fallouts, % (SEM)	14.8 (4.87)	12.9 (4.39)	12.6 (4.31)	0.68
Elapsed DOF¶	55.5 (0.22)	45.2 (0.25)	52.3 (0.27)	0.57

* Trial was conducted as a randomized complete block design at 2 feedlots in the U.S. High Plains, where a block consisted of 3 steers pulled for treatment of clinical BRD on the same day, and randomly assigned to one of the 3 experimental treatments (macrolide antibiotics; n = 326 per treatment); steers had no prior treatment history for any disorder (including antimicrobial metaphylaxis) and had no signs of concurrent disease at the time of enrollment.

† Tulathromycin (Draxxin®; Zoetis Animal Health, Parsippany, NJ) administered subcutaneously to deliver 1.1 mL/100 lb (45.4 kg) body weight.

‡ Tildipirosin (Zuprevo®; Merck Animal Health, De Soto, KS) administered subcutaneously to deliver 1.0 mL/100 lb (45.4 kg) body weight.

§ Gamithromycin (Zactran®; Boehringer Ingelheim, Duluth, GA) administered subcutaneously to deliver 1.8 mL/100 lb (45.4 kg) body weight.

‖ Fallouts are the total number of mortalities and animals removed from the trial combined.

¶ Elapsed days-on-feed (DOF) are days since trial enrollment at the time of animal fallout (death or removal).

premature stopping was not anticipated, no a priori stopping rules were established. While experimental design and analysis approaches were not performed for the assessment of equivalence, the numerical differences for primary outcomes of interest were of minimal magnitude, coinciding with a lack of evidence for treatment differences among the 3 macrolides used as first treatment regimens for clinical BRD in this study.

This is the first peer-reviewed publication known by the authors to concurrently compare the 3 macrolide antibiotics in question in a randomized controlled trial when used for first treatment of clinical BRD. A recent systematic review and meta-analysis suggested that macrolides are the most effective antimicrobial class for the control of BRD incidence in the first 45 days when administered metaphylactically.[9] In that review, TUL, GAM and TILD were the top 3 ranked antibiotics for reducing BRD incidence. Other reviews and meta-analyses on BRD treatment[13] and metaphylaxis[11] have made similar observations with TUL consistently ranked as the top antimicrobial, but with more variability in regard to GAM and TILD. Some disparities are relative to specific outcomes being evaluated (e.g., cumulative incidence of BRD morbidity vs mortality),[11] and in the case of TILD, there were very few comparisons from the body of searched literature that could be included in these papers at the time of publication.[9,11,13] The authors also note that 95% confidence intervals for odds or risk ratios from these reviews and meta-analyses generally overlap between TUL, TILD and GAM.

The majority of comparisons between these macrolides found in the literature pertain to metaphylactic use as opposed to treatment of clinical BRD;[20–24] also, it is important to note that they utilized a different study population than was used here. From the literature above, expected effectiveness of these macrolides for metaphylactic control of BRD may vary depending on cattle type (e.g., sex, breed), as well as risk classifications stemming from, e.g., cattle weight, origin and history. A primary motivation for this research was the lack of peer-reviewed publications evaluating the macrolides used herein as first treatment options for BRD. We also speculate that this is a research area with a fair amount of gray literature, where similar clinical trials have been conducted but were not peer-reviewed or published or are not easily accessible. There also may be cases where research has been conducted but not reported in any form, potentially due to insignificant findings.

When evaluating TUL and TILD for first treatment of clinical BRD in feedlot heifers, Dodd et al. (2018) observed greater first treatment success and reduced mortality (BRD and total) for heifers administered TUL compared to those administered

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TILD.[25] In contrast (and similar to our results), Theurer et al. (2018) observed no significant differences between TUL vs TILD when administered as a first treatment option for clinical BRD in a population of commercial feedlot calves described as medium- to low-risk for developing BRD.[26] As mentioned by Theurer et al., differences between these trials (including ours) may be due to disparities in cattle populations, namely risk classifications and sex. In a trial comparing TUL and GAM as first treatment regimens for clinical BRD, feedlot calves administered TUL (n = 526) had a lower BRD retreatment incidence compared to those administered GAM (n = 523),[27] which contrasted our results. Similar to our results, however, Torres et al. (2013b) also found no significant differences for any other health outcomes, for which the treatments were within equivalence limits.[27] We observed approximately 34% retreatments for both TUL and GAM, whereas Torres et al. (2013b) reported 9.0% vs 17.7% retreatments for TUL and GAM, respectively. Additionally, we observed 4.3% BRD case fatality for both TUL and GAM, while Torres et al. (2013b) reported 3.7% and 2.4% case fatality (not differing significantly) for TUL and GAM, respectively.[27] As an additional consideration, antimicrobial cross-resistance does occur, particularly for antimicrobials of the same class.[28–30] It could be hypothesized that cross-resistance potentially played a role in our findings; however, this is only speculation because sampling and antimicrobial susceptibility testing were not performed.

Source populations of cattle used in clinical trials likely have a substantial impact on antimicrobial effectiveness, as is evidenced by some of the differences in reviewed literature evaluating the macrolides in question for both metaphylactic and first clinical BRD treatment use cases. Populations were not always sufficiently described in the literature; e.g., there are cases where sex could not be distinguished, as "calves" was given as the only descriptor. This complicates comparability to a degree, as sex is a well-established risk-factor for BRD,[31] and it may have been beneficial for researchers to stratify or analytically control for sex, if in fact multiple sexes were used. Estimates for the outcomes provided herein are reflective of crossbred beef steers weighing between 400 and 850 lb with variable genetics, originating from lots that could be classified as low-to medium-risk for BRD (given that steers administered antimicrobial metaphylaxis were ineligible for the trial), at 2 commercial feedlots in Kansas and Oklahoma, which were enrolled over a 1-year period. In this population, there was no evidence of differing effects of these macrolide treatments, and numerical differences between primary outcomes were slight.

The primary limitation of this research is the small sample size relative to the observed outcome data, and thereby statistical power, as the number of cases enrolled was smaller than originally planned. While we observed no evidence of treatment effects, this is not conclusive evidence of effect absence. Post-hoc power calculations using observed data are not appropriate for estimating the power of a completed study or for determining what an alternative sample size should have been.[32–34] However, if researchers were to use our observed means for retreatment (Table 3) or case fatality (Table 4) to design a future study, the calculated sample sizes would likely be too large for practical implementation. It also could be argued that an equivalence or non-inferiority trial design could have been used instead; however, this was not the original research question or objective of the study. Due to experimental design and feedlot logistics, it was not possible to collect animal performance outcomes (e.g., daily gain, feed intake, carcass weight), which could have valuable implications for industry stakeholders. Additionally, inferences are specific to the cattle population used, meaning effects of these macrolides may differ if evaluating heifers, other weights, risk classifications, post-metaphylaxis use, and in different regions or management systems. Misclassification of BRD cases, such as acute interstitial pneumonia or ruminal acidosis, for both trial inclusion and diagnosis of steers requiring retreatment, was possible; however, any misclassification was likely non-differential between treatments. Given these limitations, external validity of the findings is still believed to be strong, considering that the research was conducted at multiple commercial feedlots under real-world conditions, over a timeframe incorporating a full seasonal cattle cycle.

Conclusions

In this population of feedlot steers fed in the U.S. High Plains, similar effects of TUL, TILD and GAM were observed with no evidence of differing health outcomes when administered as a first treatment regimen for clinical BRD. In similar cattle types, producers may be able to expect similar effectiveness between these 3 macrolide antibiotics, whereby availability and cost might be the ultimate deciding factors for use. Future research comparing macrolides for first time BRD treatment is still warranted, particularly for alternative cattle populations, and to evaluate research reproducibility.

Conflicts of interest

The authors declare the following potential conflicts of interest with respect to the research, authorship and or publication of this article: N.M. is employed by Boehringer Ingelheim but was not involved in data collection or statistical analyses; I.H. and D.R. have had previous research or consulting paid by Boehringer Ingelheim.

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Author contributions

Conception and design, I.H. and N.M.; data acquisition, I.H.; data analysis, L.H. and D.R.; interpretation, all authors; primary manuscript drafting, L.H.; critical review and revision of the manuscript, all authors; approval of the final published version, all authors.

Endnotes

[a] Draxxin®, Zoetis Animal Health, Parsippany, NJ

[b] Zuprevo®, Merck Animal Health, Lenexa, KS

[c] Zactran®, Boehringer Ingelheim Animal Health, Duluth, GA

[d] SAS Institute Inc., Cary, NC

[e] National Cattlemen's Beef Association, Centennial, CO

[f] Bovi-Shield® Gold IBR-BVD, Zoetis Animal Health, Parsippany, NJ

[g] UltraChoice® 7, Zoetis Animal Health, Parsippany, NJ

[h] Bimectin, Bimeda Animal Health, Dublin, Ireland; or Noromectin, Norbrook Inc., Lenexa, KS

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[i] Safeguard, Merck Animal Health, Lenexa, KS; or Synanthic, Boehringer Ingelheim Animal Health, Duluth, GA

[j] Revalor®-XH, Merck Animal Health, Lenexa, KS; or Component® TE-IS w/Tylan, Elanco Animal Health, Greenfield, IN; or Synovex® One Feedlot, Zoetis Animal Health, Parsippany, NJ

[k] Nuflor®, Merck Animal Health, Lenexa, KS; or Loncor® 300, Elanco Animal Health, Greenfield, IN

[l] Advocin™, Zoetis Animal Health, Parsippany, NJ

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