Comparing initial antimicrobial treatments for bovine respiratory disease in feedlot cattle following tulathromycin metaphylaxis

Taylor B. McAtee,[1] MS; Calvin W. Booker,[2] DVM, MVetSc; Breck D. Hunsaker,[2] DVM, PhD; Christopher A. McMullen,[2] PhD; R. Kent Fenton,[2] DVM; Holly S. Raaphorst,[2] BSc; Lonty K. Bryant,[3] DVM, MS; Lucas M. Horton,[1] MS, PhD; *David G. Renter,[1] DVM, PhD

[1]Center for Outcomes Research and Epidemiology, Department of Diagnostic Medicine and Pathobiology, Kansas State University, College of Veterinary Medicine, Manhattan, KS 66506
[2]TELUS Agriculture & Consumer Goods, Okotoks, AB T1S 2A2
[3]Merck Animal Health, Lenexa, KS 67835
***Corresponding author:** Dr. David Renter, **drenter@vet.k-state.edu**

Abstract

Our objective was to compare bovine respiratory disease (BRD) first treatment protocols following metaphylaxis with tulathromycin in a two-phase study. The primary objective of Phase 1 was to compare effects of tulathromycin + ketoprofen versus florfenicol + flunixin meglumine (FLO+F) on primary health outcomes (retreatment and mortality) in ultra-high-risk feedlot cattle that received on-arrival metaphylaxis with tulathromycin. The Phase 2 objective was similar, but tildipirosin was added as a third treatment group. In Phase 1, steers and heifers (n = 521; 402 ± 57 lb [182 ± 26 kg]) were enrolled at a Texas feedlot, and in Phase 2, steers (n = 788; 640 ± 105 lb [290 ± 48 kg]) were enrolled at a Canadian feedlot. At first BRD diagnosis from natural exposure, cases were individually randomized to experimental treatments. Linear and generalized linear models were used for statistical analyses. Case (BRD) fatality for cattle enrolled in Phases 1 and 2 were 2.36% (12/508) and 11.04% (87/788), respectively. In Phase 1, there was no evidence of differences in health outcomes (all *P* values ≥ 0.60). In Phase 2, retreatment risk did not significantly differ (*P* = 0.93), but total and BRD-specific mortality were reduced and survival from enrollment to mortality was longer (*P* values < 0.05) for FLO+F compared to the other two treatments. Following tulathromycin metaphylaxis, antimicrobials used for first BRD treatment had similar effectiveness when subsequent health outcomes were infrequent (Phase 1), but FLO+F reduced mortalities when case fatality was higher (Phase 2).

Key words: florfenicol, flunixin meglumine, ketoprofen, macrolide, tildipirosin

Introduction

Bovine respiratory disease (BRD) is the leading reason for injectable antimicrobial drug use in North American feedlot cattle[1,2] and is estimated to affect approximately 16.2% of feedlot cattle.[3] It is well established as the primary cause of morbidity and mortality in feedlot systems and imposes a substantial economic burden on the beef industry.[4,5] To mitigate BRD risk, metaphylactic antimicrobial therapy upon arrival has been widely adopted and has been proven effective at reducing BRD occurrence and mortality in high-risk cattle populations.[6-9] However, despite the effectiveness of metaphylaxis, a subset of cattle still develop clinical BRD and require treatment. Responses to antimicrobial therapy vary across studies and cattle populations,[6,8] emphasizing the need for further evaluation of treatment strategies following metaphylactic administration.

The macrolide class of antimicrobials has been suggested to offer superior efficacy for BRD control compared to other antimicrobial classes.[6] The 2011 National Animal Health Monitoring System survey reported that 21.3% of feedlot cattle received antimicrobial metaphylaxis upon arrival,[10] with tulathromycin (TUL[a]) being one of the most commonly used metaphylactic drugs in North American feedlots.[10] Treatment options for the animals that still develop clinical BRD have been extensively reviewed in systematic reviews and meta-analyses, summarizing the comparative effectiveness of available antimicrobials.[11]

Despite the broad use of antimicrobial therapies for BRD, research needs still exist for the direct evaluation and comparison of new treatment protocols, particularly those following antimicrobial metaphylaxis.[12] Furthermore, few studies have directly compared the efficacy of different antimicrobial classes when used following metaphylactic TUL administration. Notably, a more recently approved combination product containing TUL (a macrolide) and ketoprofen (a non-steroidal anti-inflammatory drug, NSAID; TUL+K[b]) is available for use. However, its efficacy relative to other commonly used macrolide antimicrobials, such as tildipirosin (TIL[c]), remains largely unstudied. Additionally, no published research has directly compared the combination antimicrobial/NSAID formulations of TUL and florfenicol (FLO[d]), despite previous studies reporting differences in health and growth performance outcomes between TUL and FLO alone.[11,13-15] Given its recent approval in the United States, there is limited knowledge on the efficacy of TUL+K relative to other BRD treatment regimens, particularly in the context of cattle that have received on-arrival metaphylaxis with TUL.

Both TUL+K and florfenicol + flunixin meglumine (FLO+F[e]) contain anti-inflammatory agents as part of their active ingredients (ketoprofen and flunixin meglumine, respectively), whereas TIL does not. Additionally, while both TUL+K and TIL are macrolides, they differ in chemical structure, with TUL classified as a 16-membered ring macrolide[16] and TIL classified as a 15-membered ring macrolide.[17] In contrast, FLO+F contains FLO, a broad-spectrum antimicrobial from the phenicol class.[18] Ketoprofen, an NSAID belonging to the propionic acid derivative class, exhibits analgesic and antipyretic

properties,[19] whereas flunixin meglumine is an organoammonium salt NSAID with anti-inflammatory, anti-endotoxic, and antipyretic properties.[20] The inclusion of NSAIDs in BRD therapy has been shown to reduce pyrexia and inflammation and may improve clinical signs and welfare outcomes, though evidence for consistent improvements in treatment success or performance outcomes remains limited.[21]

Two randomized clinical trials – denoted as Phases 1 and 2 – were conducted to evaluate whether a FLO-based regimen or macrolide alternatives are optimal for first clinical BRD therapy following macrolide metaphylaxis, specifically in terms of treatment success, retreatment risk, mortality and chronicity. The primary objective of Phase 1 was to evaluate the relative effectiveness of administering either TUL+K or a FLO+F combination product for the treatment of initial clinical BRD on animal health outcomes in feedlot cattle at ultra-high-risk (UHR) of developing BRD that received on-arrival metaphylaxis with TUL. The primary objective of Phase 2 was to evaluate the relative effectiveness of administering either a TUL+K combination product, TIL, or a FLO+F combination product for the treatment of initial clinical BRD on animal health outcomes, specifically case fatality, in UHR feedlot steers that received on-arrival metaphylaxis with TUL.

Materials and methods

All procedures involving live animals were approved by the TELUS Agriculture Animal Care Committee, a holder of a Certificate of Good Animal Practice, and were conducted in accordance with the guidelines of the Canadian Council on Animal Care (2009), with informed consent obtained from animal owners.

Cattle populations

Phase 1 was conducted at a commercial feedlot in Texas between November 2021 and June 2022. A total of 521 mixed beef-breed steers and heifers classified as UHR upon arrival were enrolled from a source population of 1,941 cattle across 5 lots that all received metaphylaxis. Phase 2 was conducted at a commercial feedlot in Saskatchewan, Canada between October and November 2023. A total of 96 lots were processed and received metaphylaxis, providing a source population of 24,427 cattle, from which 813 UHR, auction-market-derived beef steers were enrolled. Ultra-high-risk status was defined based on expected lot-level BRD morbidity of 10 to 20%, BRD mortality (case fatality) of 10 to 15%, and overall mortality of 1.5 to 3% following metaphylaxis with TUL.

Cattle were enrolled at the time of first clinical BRD diagnosis and randomly allocated to treatment groups. In Phase 1, two treatment groups were evaluated: TUL+K and FLO+F. Phase 2 incorporated an additional treatment group – TIL – which was evaluated along with TUL+K and FLO+F. The primary health-related outcomes evaluated included BRD retreatment risk, first treatment failure, second and third BRD retreatment, chronicity, wastage, total mortality, BRD-specific mortality, other mortality, and days-on-feed (DOF) from enrollment to death (total and BRD-related).

Treatment structure and experimental design

Both Phase 1 and Phase 2 followed a one-way factorial treatment structure in a completely randomized design. In both phases, cattle were eligible for inclusion if they required a first-time treatment for clinical BRD following a 5-day post-metaphylaxis interval (PMI) and met the following criteria: 1) absence of abnormal clinical signs referable to organ systems other than the respiratory tract, 2) no prior treatment for BRD, 3) a rectal temperature ≥ 104.0 °F (≥ 40.0 °C), and 4) between 5 and 80 DOF. The experimental protocols were identical across both phases except for the number of treatment groups and differences in cattle populations. All animals were monitored under similar commercial feedlot management conditions between phases. Cattle were randomly assigned to treatment groups using a proprietary computer-generated allocation table. All antimicrobials were administered following manufacturer recommendations and Beef Quality Assurance (BQA) guidelines, using 16-gauge × 5/8-inch (15.88 mm) needles. Each animal was individually weighed at allocation to ensure accurate dosing. After treatment, cattle were returned to their original feedlot pens. Study animals were monitored for 100 days post-allocation in both phases.

In Phase 1, cattle were randomly assigned to one of the previously mentioned treatment groups at the time of first clinical BRD treatment: TUL+K or FLO+F. An a priori sample size calculation using $\alpha = 0.05$ and $\beta = 0.20$ (80% power) estimated that 250 animals per treatment group would be required to detect an absolute difference in case fatality of 8.5%, using a likelihood ratio test to compare 2 independent proportions and relevant historical baseline case fatality data. Cattle in the TUL+K group received a single subcutaneous (SC) injection of TUL+K at a dosage of 1.1 mL/100 lb body weight (BW; 2.5 mg TUL and 3 mg ketoprofen per kg BW). Cattle in the FLO+F group received a single SC injection of FLO+F at a dosage of 6 mL/100 lb BW (40 mg FLO and 2.2 mg flunixin meglumine per kg BW). The post-treatment interval for both groups was 3 days (Table 1).

In Phase 2, 3 treatment groups were evaluated: TUL+K, FLO+F, and TIL. An a priori sample size calculation using $\alpha = 0.05$ and $\beta = 0.20$ (80% power) estimated that 250 animals per treatment group would be required to detect an absolute difference in case fatality of 7.0%, using a likelihood ratio test to compare independent proportions and relevant historical baseline case fatality data. Cattle in the TUL+K group received SC TUL+K, and cattle in the FLO+F group received SC FLO+F at the previously described dosages (Table 1). Cattle in the TIL group received a single SC injection of TIL at a dosage of 1 mL/100 lb (4 mg/kg) BW. The post-treatment interval was 3 days for all groups (Table 1).

Cattle management and stewardship

Upon arrival, cattle in both Phase 1 and Phase 2 were processed following standard commercial feedlot protocols for health and production management. All animals were individually identified and administered SC TUL at a dosage of 1.13 mL/100 lb (2.5 mg/kg) BW in the lateral neck as metaphylaxis. In Phase 1, all steers and heifers received a multivalent clostridial vaccine[f], and two separate multivalent modified live viral vaccines[g,h]. Steers were additionally treated with an injectable parasiticide[i] and implanted with trenbolone acetate and estradiol benzoate[j]. Heifers in Phase 1 also received an oral dewormer[k] and a pour-on parasiticide[l]. In Phase 2, all cattle received a multivalent clostridial and *Histophilus somni* bacterin-toxoid[m], and a multivalent modified live viral vaccine with *Mannheimia haemolytica* toxoid[n]. Additionally, a pour-on parasiticide[o] was administered, and steers were implanted with trenbolone acetate and estradiol[p]. All health and production

Table 1: Characteristics of antimicrobial treatments, tulathromycin and ketoprofen (TUL+K), florfenicol and flunixin meglumine (FLO+F), and tildipirosin (TIL) used as first treatment for clinical bovine respiratory disease following tulathromycin metaphylaxis in beef cattle in a randomized clinical trial in Phases 1 and 2 conducted at commercial feedlots.

	Treatment		
Item	**TUL+K†**	**FLO+F‡**	**TIL§**
Dosage, mL/100 lb	1.1	6	1
Post-treatment-interval‖, days	3	3	3
Pre-harvest withdrawal¶, days	18[us]/49[c]	38[us]/60[c]	21[us]/42[c]

† Tulathromycin and ketoprofen (Draxxin KP®; Zoetis Animal Health, Parsippany, NJ) administered subcutaneously.

‡ Florfenicol and flunixin meglumine (Resflor®; Merck Animal Health, Madison, NJ) administered subcutaneously.

§ Tildipirosin (Zuprevo®; Merck Animal Health, Madison, NJ) administered subcutaneously in Phase 2 only.

‖ The interval between antimicrobial administration and the earliest point at which an animal could be re-treated if clinical signs of BRD persisted or reappeared.

¶ Time between when the antimicrobial was administered and when the animal could be harvested for consumption.

[us] Pre-harvest withdrawal period in days for cattle treated in the U.S. (Phase 1).

[c] Pre-harvest withdrawal period in days for cattle treated in Canada (Phase 2).

procedures were standardized across experimental groups, with the exception of experimental treatments administered at the time of initial BRD diagnosis.

Cattle in both phases were provided ad libitum access to water and a standardized, mixed complete feedlot diet formulated to meet or exceed the nutritional requirements for beef cattle (NASEM, 2016). Diets were mixed in truck-mounted mixer boxes equipped with electronic load cells and delivered up to twice daily. Animals were transitioned to a high-concentrate diet through multiple step-up rations, following feedlot protocols. Housing conditions were consistent between phases, with cattle housed in open-air pens with dirt floors, arranged side-by-side along central feed alleys. In Phase 2, additional 20% porosity wood-fence windbreaks were present. Each handling facility was equipped with an individual animal scale and a chute-side computer system integrated with data collection and management software[q]. Open-air containment pens were adjacent to each facility.

The primary health-related outcomes were assessed over a 100-day follow-up period and included BRD retreatment risk, first treatment failure, second and third retreatments, chronicity, wastage, total mortality, BRD-specific mortality, other mortality, and DOF from enrollment to death (total and BRD-related) as defined in Table 2. Bovine respiratory disease retreatment risk was defined as the percentage of enrolled animals that required a second BRD treatment at any time within the 100-day period. First treatment failure was assessed using 2 definitions: 1) the proportion of enrolled animals that required a second BRD treatment and/or died from any cause within 100 days, and 2) the proportion of enrolled animals that required a second BRD treatment and/or died specifically from BRD within 100 days.

Second and third retreatments were calculated as the proportion of enrolled animals requiring additional BRD treatments (i.e., a third or fourth treatment) at any point during the 100-day period. Chronicity was defined as the percentage of enrolled animals designated as chronic cases by the end of the study, while wastage referred to the proportion that were chronic animals and did not die. Mortality outcomes were categorized into total mortality (death from any cause), BRD-specific mortality and mortality due to other causes, including *Histophilus* (HS), metabolic disease, lameness and miscellaneous causes. Days-on-feed from enrollment to death was recorded separately for total mortality and BRD-related mortality. Cattle were monitored daily by trained animal caretakers, who assessed health outcomes and determined the need for BRD retreatment. Cattle were eligible for retreatment if clinical signs persisted, provided they were beyond the 3-day post-treatment interval. Retreatment decisions were based solely on clinical signs, with rectal temperature recorded but not used as a determining factor. Days-on-feed and BW were recorded at the time of retreatment.

Retreatment protocols varied slightly between phases. In Phase 1, first-time BRD retreatment (second overall treatment) consisted of SC enrofloxacin[r] at 5.5 mL/100 lb (12.5 mg/kg) BW. Second-time BRD retreatment (third overall treatment) involved an intramuscular injection of oxytetracycline[s] at 4.5 mL/100 lb (30 mg/kg) BW in the lateral neck. Third-time BRD retreatment (fourth overall treatment) was a SC injection of tilmicosin[t] at 1.5 mL/100 lb (10 mg/kg) BW. In Phase 2, first-time BRD retreatment (second overall treatment) involved a SC injection of danofloxacin mesylate[u] at 2 mL/100 lb (8 mg/kg) BW in the lateral neck. Second-time BRD retreatment (third overall treatment) consisted of SC FLO at 6 mL/100 lb (40 mg/kg) BW. Third-time BRD retreatment (fourth overall treatment) involved an intramuscular injection of oxytetracycline dihydrate[v] at 4.5 mL/100 lb (20 mg/kg) BW.

Cattle requiring a fourth retreatment (fifth overall BRD treatment) in either phase were classified as chronic and no further therapy for BRD occurred. Chronics that did not result in mortality during the study were defined as wastage. All non-BRD diseases were treated according to standard feedlot protocols established by the consulting veterinarian(s), utilizing a hierarchical evidence-based approach and economic modeling to determine the most cost-effective treatment strategy. Treatment protocols for all non-BRD diseases were standardized across experimental groups. Necropsies were conducted by trained feedlot personnel or a licensed veterinarian when possible. All health outcome assessments were performed by animal caretakers who were blinded to experimental treatments.

Table 2: Definitions and calculations of individual animal-level health outcome variables in Phases 1 and 2 which evaluated feedlot cattle that received on-arrival tulathromycin for the control of bovine respiratory disease (BRD) and were subsequently treated with either tulathromycin and ketoprofen (TUL+K), florfenicol and flunixin meglumine (FLO+F), or tildipirosin (TIL) upon first clinical signs of BRD.

Morbidity		
Retreatment risk (treated twice)	% of enrolled animals treated for BRD a second time	Number treated for BRD2/ number enrolled
First treatment failure, Retreatment and/or any death	% of enrolled animals treated for BRD a second time and/or died of any cause	Number treated for BRD2 and/or died of any causes/number enrolled
First treatment failure, Retreatment and/or BRD death	% of enrolled animals treated for BRD a second time and/or died of BRD	Number treated for BRD2 and/or died of BRD/number enrolled
Second retreatment	% of BRD2 animals treated for BRD a third time	Number treated for BRD3/ number treated for BRD2
Third retreatment	% of BRD3 animals treated for BRD a fourth time	Number treated for BRD4/ number treated for BRD3
Chronicity	% of enrolled animals that became chronic	Number of chronic animals/ number enrolled
Wastage	% of enrolled animals that became chronic that did not die	Number of wastage animals/ number enrolled
Mortality		
Total mortality	% of enrolled animals that died of all causes	Number of enrolled animals that died of all causes/number enrolled
BRD mortality	% of enrolled animals that died of BRD	Number of enrolled animals that died of BRD/number enrolled
Histophilus mortality	% of enrolled animals that died of HS	Number of enrolled animals that died of HS/number enrolled
Metabolic mortality	% of enrolled animals that died of metabolic disease	Number of enrolled animals that died of metabolic disease/number enrolled
Lameness mortality	% of enrolled animals that died of lameness	Number of enrolled animals that died of lameness/number enrolled
Other mortality	% of enrolled animals that died of miscellaneous causes	Number of enrolled animals that died of miscellaneous causes/number enrolled

Statistical analyses

The same statistical approach was applied to both Phase 1 and Phase 2 datasets. Linear or generalized linear models (LM or GLM, respectively) were used to assess the outcomes of interest, and were implemented using Proc GLIMMIX (SAS 9.4[w]). In all models, the individual steer or heifer was specified as both the experimental and observational unit, with treatment as a fixed effect. In Phase 1, sex was additionally included in all models as a fixed effect for the adjustment of treatment means, regardless of its significance ($\alpha = 0.05$). The interaction between treatment and sex was also tested but was not found to be significant for any outcome and was therefore not included in the final models.

For continuous outcomes, LMs were fitted using a Gaussian distribution with an identity link function. Model estimation was conducted using restricted maximum likelihood and utilized Newton-Raphson with ridging optimization procedures. A Kenward-Roger degrees of freedom adjustment was applied for estimation of standard errors. Model assumptions of homoscedasticity and normality were assessed through visual inspection of marginal studentized residual plots. For dichotomous outcomes, GLMs were fitted using a binary distribution with a logit link function, were estimated via maximum likelihood, and again included a Kenward-Roger degrees of freedom adjustment and Newton-Raphson with ridging optimization procedures. All GLM estimates were back-transformed to the original scale for interpretation. In all models, a statistical significance threshold of $\alpha = 0.05$ was set a priori for overall treatment effects, and a Tukey-Kramer adjustment was applied to adjust for multiple pairwise comparisons among treatment means with $\alpha = 0.10$.

Results

Phase 1

In Phase 1, cattle were enrolled at an average of 11 DOF (range: 5 to 70 DOF) between January 8, 2022, and June 18, 2022. Table 3 presents the summary statistics for the enrollment characteristics of steers and heifers included in the trial, where TUL+K and FLO+F had 252 and 256 animals enrolled, respectively. No significant differences were observed between treatment groups for enrollment body weight ($P = 0.68$), rectal temperature ($P = 0.45$), or DOF ($P = 0.45$), suggesting

Table 3: Model adjusted means and standard errors of the means (SEM) for enrollment data on feedlot cattle that received on-arrival tulathromycin for the control of bovine respiratory disease (BRD) and were then randomly assigned tulathromycin and ketoprofen (TUL+K) or florfenicol and flunixin meglumine (FLO+F) treatments upon first clinical signs of BRD in Phase 1.*

	Treatment			
Item	**TUL+K†**	**FLO+F‡**	**SEM**	***P*-value**
BRD cases enrolled§, *n*	252	256	–	–
Initial body weight, lb	400	403	3.6	0.52
Days-on-feed at enrollment, *n*	10.9	11.4	0.54	0.45
Rectal temperature at enrollment, °F	104.81	104.86	0.053	0.45

* Trial was conducted as a randomized clinical trial at a feedlot in Texas, and randomly assigned BRD cases to one of the 2 experimental treatments; steers and heifers received on arrival metaphylaxis with tulathromycin (Draxxin®; Zoetis Animal Health, Parsippany, NJ).

† Tulathromycin and ketoprofen (Draxxin KP®; Zoetis Animal Health, Parsippany, NJ) administered subcutaneously.

‡ Florfenicol and flunixin meglumine (Resflor Gold®; Merck Animal Health, Madison, NJ) administered subcutaneously.

that the randomization process effectively yielded balanced comparison groups. Across the two treatment groups, the mean initial BW ranged from 400 to 403 lbs (182 to 183 kg), mean rectal temperature ranged from 104.8 to 104.9 °F (40.4 to 40.5 °C), and the mean DOF at the time of the first clinical BRD treatment ranged from 10.9 to 11.4 days. A total of 13 animals were removed from the study prior to analysis: 5 animals received incorrect relapse products, 7 were shipped prior to reaching 100 days on trial, and 1 animal was treated off-protocol within the 3-day post-treatment interval window. As a result, the final number of animals analyzed for the primary outcomes was 252 in the TUL+K group and 256 in the FLO+F group, out of the 261 and 260 animals originally enrolled, respectively.

The treatment group means for BRD treatment failure and retreatment are in Table 4. The retreatment risks (treated twice) for TUL+K and FLO+F were 61.0% and 59.1%, respectively, which did not differ significantly ($P = 0.67$). There was no evidence for a difference between treatment groups for the probability of having a first treatment failure and/or any death ($P = 0.60$). There was no evidence for differences between treatment groups for probabilities of having a second BRD treatment ($P = 0.68$) or third BRD treatment ($P = 0.83$). The effects of treatment group on the probability of becoming chronic, wastage, or a mortality are also in Table 4. There was no evidence of a difference for BRD mortality (case fatality; $P = 0.98$) or total mortality ($P = 0.76$) between treatment groups. There were also no significant differences for chronics ($P = 0.85$) or wastage ($P = 0.78$). The timing of mortality events, based on DOF from enrollment to any mortality ($P = 0.88$) or BRD mortality (case fatality; $P = 0.87$), also did not differ significantly between treatment groups.

Phase 2

In Phase 2, cattle were enrolled at an average of 33 DOF (range: 5 to 79 DOF) between November 16, 2023, and December 24, 2023. Table 5 summarizes the enrollment characteristics of steers included in the trial, where 265, 260 and 263 animals were enrolled for TUL+K, FLO+F, and TIL, respectively. There were no significant differences among treatment groups in enrollment body weight ($P = 0.70$), rectal temperature ($P = 0.25$), or DOF ($P = 0.46$), again indicating that the randomization process resulted in balanced groups. Across the 3 treatment groups, the mean initial body weight ranged from 637 to 644 lbs (289 to 292 kg), the mean rectal temperature was approximately 105.3 °F (41.0 °C), and the mean DOF at the first clinical BRD treatment ranged from 32.0 to 33.6 days. A total of 25 animals were removed from the study prior to analysis due to protocol deviations: 1 animal was not enrolled at the time of initial BRD diagnosis, 1 received the incorrect allocation product, 1 was enrolled twice, 3 animals were not listed on the allocation sheet, and 19 animals received incorrect relapse products. Consequently, the number of animals analyzed for the primary outcomes was 265 in the TUL+K group, 263 in the TIL group, and 260 in the FLO+F group, compared to the originally enrolled 272, 272 and 269 animals, respectively.

The effects of experimental treatments on health outcomes are in Table 6. Retreatment risks (treated twice) for TUL+K, FLO+F, and TIL were 32.5%, 31.2% and 31.2%, respectively, which did not differ significantly ($P = 0.93$). There was no evidence for a difference among treatment groups for the probability of having a first treatment failure and/or any death ($P = 0.25$), or BRD death ($P = 0.31$). There was no evidence of a difference among treatment groups for the probability of having a second BRD retreatment ($P = 0.10$) or third BRD retreatment ($P = 0.58$). There were no significant differences for the probability of cattle classified as chronic ($P = 0.26$) or wastage ($P = 0.60$).

Total mortality was significantly impacted by the experimental treatment regimen used for first clinical BRD treatment ($P = 0.05$); it was reduced for the FLO+F group (12.31%) compared to the TUL+K (19.62%, $P = 0.06$) and TIL (19.01%, $P = 0.09$) groups (Table 6). Similarly, BRD-specific mortality was affected by treatment regimen ($P = 0.01$), as it was lower for the FLO+F group (6.15%) than for the TUL+K (13.58%, $P = 0.02$) and TIL (13.31%, $P = 0.02$) groups (Table 6). There was no evidence of differences across treatment groups for any other health outcome (Table 6). However, the mean DOF from enrollment to any death differed among the treatment groups ($P < 0.01$), as it was significantly longer for the FLO+F group (43.59 days) than for the TUL+K (26.13 days, $P = 0.004$) or TIL (25.80 days, $P = 0.003$) groups (Table 6). Similarly, the mean DOF from enrollment to BRD death was impacted by treatment group ($P < 0.01$); it was longer for the FLO+F group (49.13 days) than for the TUL+K (24.39 days, $P = 0.001$) and TIL (29.49 days, $P = 0.01$) groups (Table 6).

Table 4: Model adjusted means and standard errors of the means (SEM) for subsequent health outcomes of feedlot cattle that received on-arrival tulathromycin for the control of bovine respiratory disease (BRD) and were then randomly assigned either tulathromycin and ketoprofen (TUL+K) or florfenicol and flunixin meglumine (FLO+F) treatments upon first clinical signs of BRD in Phase 1.*

	Treatment						
	TUL+K[†]			FLO+F[‡]			
Items,	**Mean**	**SEM**	***n***	**Mean**	**SEM**	***n***	***P*-value**
Morbidity, %							
Retreatment risk (treated twice)[§]	61.03	3.18	157	59.11	3.18	155	0.67
First treatment failure, Retreatment and/or any death	62.28	3.16	160	59.94	3.16	157	0.60
Second retreatment[‖]	63.28	4.12	104	60.83	4.26	100	0.68
Third retreatment[¶]	46.28	5.84	55	48.07	6.17	56	0.83
Chronicity	17.12	2.78	55	16.39	2.79	56	0.85
Wastage	15.28	2.78	53	16.39	2.79	56	0.78
Mortality, %							
Total mortality	3.22	1.12	8	2.76	1.04	7	0.76
BRD mortality	2.42	0.97	6	2.38	0.96	6	0.98
Other mortality	0.81	0.57	2	0.003	0.40	1	0.97
Days-on-feed from enrollment to any death	18.25	4.78	8	17.13	5.16	7	0.88
Days-on-feed from enrollment to BRD death	14.17	5.52	6	15.50	5.52	6	0.87

* Trial was conducted as a randomized clinical trial at a feedlot in Texas, and randomly assigned BRD cases to one of the 2 experimental treatments; steers and heifers received on arrival metaphylaxis with tulathromycin (Draxxin®; Zoetis, Parsippany, NJ).

† Tulathromycin and ketoprofen (Draxxin KP®; Zoetis Animal Health, Parsippany, NJ) administered subcutaneously.

‡ Florfenicol and flunixin meglumine (Resflor Gold®; Merck Animal Health, Madison, NJ) administered subcutaneously.

§ Steers requiring a second treatment at any time for BRD were administered enrofloxacin (Quellaxin™ 100, Aspen Veterinary Resources, Ltd., Liberty, MO).

‖ Steers requiring a third treatment at any time for BRD were administered oxytetracycline (Noromycin 300 LA, Norbrook Inc., Lenexa, KS).

¶ Steers requiring a fourth treatment at any time for BRD were administered tilmicosin (Micotil™ 300 Injection, Elanco US, Inc., Greenfield, IN).

Table 5: Model adjusted means and standard errors of the means (SEM) for enrollment data on feedlot cattle that received on-arrival tulathromycin for the control of bovine respiratory disease (BRD) and were then randomly assigned tulathromycin and ketoprofen (TUL+K), florfenicol and flunixin meglumine (FLO+F), or tildipirosin (TIL) treatments upon first clinical signs of BRD in Phase 2.*

	Treatment				
Item	**TUL+K[†]**	**FLO+F[‡]**	**TIL[§]**	**SEM**	***P*-value**
Animals enrolled, *n*	265	260	263	–	–
Initial body weight, lb	644	637	638	6.54	0.70
Days-on-feed at enrollment, *n*	34	32	32	0.98	0.46
Rectal temperature at enrollment, °F	105.34	105.32	105.26	0.06	0.25

* Trial was conducted as a randomized clinical trial at a feedlot in Saskatchewan, Canada, and randomly assigned BRD cases to one of the 3 experimental treatments; steers received on arrival metaphylaxis with tulathromycin (Draxxin®; Zoetis, Parsippany, NJ).

† Tulathromycin and ketoprofen (Draxxin KP®; Zoetis Animal Health, Parsippany, NJ) administered subcutaneously.

‡ Florfenicol and flunixin meglumine (Resflor®; Merck Animal Health, Madison, NJ) administered subcutaneously.

§ Tildipirosin (Zuprevo®; Merck Animal Health, Madison, NJ) administered subcutaneously.

Table 6: Model adjusted means and standard errors of the means (SEM) for subsequent health outcomes of feedlot cattle that received on-arrival tulathromycin for the control of bovine respiratory disease (BRD) and were then randomly assigned either tulathromycin and ketoprofen (TUL+K), florfenicol and flunixin meglumine (FLO+F), or tildipirosin (TIL) treatments upon first clinical signs of BRD in Phase 2.*

	Treatment Group*									
	TUL+K†			FLO+F‡			TIL§			
Items,	**Mean**	**SEM**	***n***	**Mean**	**SEM**	***n***	**Mean**	**SEM**	***n***	***P*-value**
Morbidity, %										
Retreatment Risk (treated twice)‖	32.45	2.88	86	31.15	2.87	81	31.18	2.86	82	0.93
First treatment failure, Retreatment and/or any death	43.02	3.04	114	36.15	2.98	94	41.44	3.04	109	0.25
Retreatment and/or BRD death	38.87	2.99	103	32.69	2.91	85	37.26	2.98	98	0.31
Second Retreatment¶	45.35	5.37	39	35.80	5.33	29	29.27	5.03	24	0.10
Third Retreatment	28.21	7.21	11	17.24	7.01	5	25.00	8.84	6	0.58
Chronicity	4.15	1.23	11	1.92	0.85	5	2.28	0.09	6	0.26
Wastage	2.26	0.91	6	1.15	0.66	3	1.52	0.75	4	0.60
Mortality, %										
Total mortality	19.62[b]	2.44	52	12.31[a]	2.04	32	19.01[b]	2.42	50	0.05
BRD mortality	13.58[b]	2.11	36	6.15[a]	1.49	16	13.31[b]	2.09	35	0.01
HS mortality	3.40	1.11	9	3.46	1.13	9	3.80	1.18	10	0.96
Metabolic mortality	0.75	0.53	2	0.38	0.38	1	0.00	0.00	0	0.86
Lameness mortality	0.75	0.53	2	1.15	0.66	3	0.38	0.38	1	0.62
Other mortality	1.13	0.65	3	1.15	0.66	3	1.52	0.75	4	0.91
Days-on-feed from enrollment to any death	26.13[b]	4.63	52	43.59[a]	4.63	32	25.80[b]	4.63	50	< 0.01
Days-on-feed from enrollment to BRD death	24.39[b]	6.08	36	49.13[a]	6.08	16	29.49[b]	6.08	35	< 0.01

* Trial was conducted as a randomized clinical trial at a feedlot in Saskatchewan, Canada, and randomly assigned BRD cases to one of the 3 experimental treatments; all steers received on arrival metaphylaxis with tulathromycin (Draxxin®; Zoetis Animal Health, Parsippany, NJ).

[a,b] Means with different superscript letters, within rows, differ significantly ($P \leq 0.05$) after adjusting for multiple comparisons.

† Tulathromycin and ketoprofen (Draxxin KP®; Zoetis Animal Health, Parsippany, NJ) administered subcutaneously.

‡ Florfenicol and flunixin meglumine (Resflor®; Merck Animal Health, Madison, NJ) administered subcutaneously.

§ Tildipirosin (Zuprevo®; Merck Animal Health, Madison, NJ) administered subcutaneously.

‖ Steers requiring a second treatment at any time for BRD were administered danofloxacin (A180™, Zoetis Canada Inc., Kirkland, Québec, CA).

¶ Steers requiring a third treatment at any time for BRD were administered florfenicol (Fenicyl™, Vetoquinol N.-A. Inc., Lavaltrie, Québec, CA).

Discussion

This research was conducted in 2 phases to evaluate the effectiveness of first BRD treatments following metaphylactic TUL administration in 2 different study populations. In the initial study comparing TUL+K to FLO+F (Phase 1), the BRD risk profile in the enrolled population was lower than anticipated – evidenced by low overall mortality (case fatality) for both treatment groups. Overall BRD mortality (BRD case fatality) for cattle enrolled in Phase 1 was 2.36% (12/508), whereas for Phase 2, case fatality was 11.04% (87/788). The lack of observed differences among treatment groups in Phase 1 could be due to infrequent occurrences of subsequent negative clinical outcomes. Specifically, there were no significant effects on BRD treatment failure, retreatment risk, case fatality, total mortality, chronicity or wastage between TUL+K and FLO+F. Given these findings and the lower-than-expected BRD risk profile, Phase 2 provided a follow-up study with higher risk cattle to better evaluate treatments in a population more aligned with the initial targeted health burden. Phase 2 was designed to target UHR cattle and to expand treatment comparisons by including TIL as an additional macrolide for evaluation. The UHR population in Phase 2 consisted of auction-market-derived, beef-breed steers in a commercial feedlot in Saskatchewan, Canada; a population of cattle where lot-level BRD morbidity of 10 to 20%, BRD case fatality of 10 to 15%, and overall mortality of 1.5 to 3% are expected following TUL metaphylaxis.

Macrolides – particularly TUL – are often regarded as an antimicrobial class of choice, as they have been consistently ranked as top options for both treatment[11] and control[8,9] (i.e., metaphylaxis) of BRD from meta-analyses. Although TUL has been shown to yield improved health outcomes over FLO, there are studies where the inverse has been observed.[22,23] The bulk of published literature on comparative efficacy or effectiveness of the specific antimicrobials used herein has been without the addition of NSAIDs, therefore offering limited direct comparisons to the current study. Both NSAIDs incorporated in the treatment groups are meant to reduce fever and inflammation, but it is important to recognize that their pharmacodynamics may differ. Unlike the overall findings of the previously referenced meta-analyses of TUL and FLO,[8,9,11] TUL+K did not yield improved treatment outcomes compared to FLO+F in either Phases 1 or 2 of this study.

Previous research has demonstrated that antimicrobial choices for BRD treatment can significantly influence health outcomes, particularly in the context of prior metaphylactic treatment. For example, a multi-site study by Skogerboe et al. (2005)[24] comparing TUL, FLO and TIM (tilmicosin) for BRD treatment found that TUL had improved treatment success and lower mortality than FLO in certain locations. An important distinction, however, is that the cattle in that study did not receive an antimicrobial upon arrival at the feedlot. Unlike Skogerboe et al. (2005),[24] and also Hannon et al. (2009)[25] where FLO-treated cattle had a higher retreatment risk than those administered TUL, there were no significant differences in treatment failure or retreatment risk across treatment groups in Phases 1 and 2 in this study. However, total and BRD-specific mortality were significantly lower for cattle treated with FLO+F compared to those treated with TUL+K or TIL in Phase 2 of this study. These results suggest that while a FLO-based treatment may provide a survival advantage following macrolide metaphylaxis – potentially dependent on cattle populations (i.e., Phases 1 vs. 2) – differences in retreatment risks may depend on factors such as disease pressure, the antimicrobial class used for metaphylaxis, or NSAID inclusion.

The lower observed total- and BRD-specific mortality for cattle treated with FLO+F compared to those treated with TUL+K or TIL in Phase 2 could be due to one or more factors. It is unclear whether the observed advantage of FLO+F versus TUL+K was attributable to superiority of flunixin meglumine versus ketoprofen, superiority of florfenicol versus tulathromycin, the impact of prior metaphylactic treatment with a macrolide, or a combination of these factors. Some practitioners may argue against using the same antimicrobial, or even the same class of antimicrobial for both metaphylaxis and first treatment of clinical BRD, although there is minimal published literature on this topic. Coetzee et al. (2020)[25] reported that alternating between bacteriostatic and bactericidal antimicrobials for bovine respiratory disease treatment was associated with morbidity (but not mortality), performance and carcass quality outcomes in feedlot cattle. However, these observations were based on survey data, not prospective experimental studies. The antimicrobial treatments evaluated herein and used after TUL metaphylaxis are classified as bacteriostatic, and our study design does not enable a direct comparison with Coetzee et al. (2020)[25]. Further research would be needed to validate and explain our findings, testing effects of the antimicrobials with and without an NSAID(s), potentially in multiple cattle populations, including those that received one or more antimicrobial metaphylaxis options and those that do not.

In addition, the timing of first treatment relative to prior metaphylaxis (PMI) and the timing of retreatment (PTI) are important considerations for BRD treatment studies. This study applied a 5-day PMI, reflecting standard practices in the feedlots during Phases 1 and 2 and aligning their protocols. However, previous research with tulathromycin and other macrolides has demonstrated that longer PMIs, such as 7-, 10-, or 14-day intervals, can reduce BRD pulls and retreatments without adversely affecting mortality or performance,[26,27] suggesting that treatment timing may have influenced the observed outcomes. Similarly, with the 3 different treatments evaluated in this study (TUL+K, FLO+F, TIL), different PTIs could have been used. However, to achieve a similar time at-risk for subsequent health outcomes, a 3-day PTI was used for all treatment groups.

An additional consideration that was not evaluated in our study was the potential impact of antimicrobial resistance. It is possible that the sequential use of the same antimicrobial (TUL metaphylaxis followed by TUL+K) or the same antimicrobial class (macrolides TUL metaphylaxis followed by TIL) could lead towards increased and selective resistance pressure, which could alternatively be circumvented by use of a different antimicrobial class (e.g., FLO). However, this may not necessarily be the case, as it has been observed that rotating between bacteriostatic and bactericidal antimicrobials for treatment and re-treatment of BRD may yield increased resistant pathogen isolation compared to repeated use of antimicrobials with similar mechanisms.[26] This same observation could be true when comparing the antimicrobial classes, pharmacodynamics and their combinations in our trials; however, this is an area that would require future research and a study designed to specifically address that question.

When comparing the 2 macrolide treatment groups in Phase 2, TUL+K and TIL, no significant differences were observed. When these treatments were used as the first treatment regimen for clinical BRD, variable responses have been reported. Similar to our findings, some have reported comparable treatment effects between TUL and TIL,[29,30] while Dodd et al. (2018)[31] conversely found reduced mortality and improved first treatment success for heifers given TUL compared to TIL (again noting that TUL did not contain ketoprofen in these studies). Cattle populations (e.g., sex, risk), management (e.g., prior metaphylaxis), and environmental factors potentially impact the disparities between these studies. Fewer direct comparisons between FLO and TIL in the literature have been made, and their comparative clinical effectiveness in feedlot cattle is largely dependent on estimates from meta-analyses.[11] Research in pre-weaned dairy calves has suggested that both antimicrobials are similarly effective at treating clinical pneumonia symptoms and lowering the risk of relapse.[32,33] Unlike TUL+K and FLO+F, the TIL treatments did not include an NSAID; while this yields a relevant comparison between products available on the market, it also potentially yields a biased assessment of the antimicrobial agents themselves.

This is the first publication known by the authors to compare these specific antimicrobials in a randomized clinical trial when used for first treatment of clinical BRD after metaphylaxis with TUL. Van Donkersgoed et al. (2009)[34] reported that TUL was less effective for BRD treatment compared to a FLO+F combination product in cattle that had received metaphylactic TIM at arrival, again suggesting that prior macrolide metaphylaxis may have reduced the relative effectiveness of TUL for clinical treatment. Although TIM and TIL are distinct antimicrobial compounds, both are 16-membered ring macrolides and share a similar mechanism of action, inhibiting bacterial growth by binding to the 50S ribosomal subunit and disrupting protein synthesis.[35] The findings of Phase 1 further support the notion that in populations with lower disease pressure, the effectiveness of these treatment regimens may not be distinguishable. The lack of significant differences in morbidity and mortality in Phase 1 aligns with findings from previous studies where macrolide- and FLO-based treatments performed similarly when BRD risk was lower.[23] However, in the higher-risk population evaluated in Phase 2, FLO+F demonstrated a substantial mortality advantage over TUL+K and TIL, reinforcing the idea that disease burden plays a key role in influencing biologically significant treatment outcomes.

In addition to treatment impacts on mortality, the mean DOF from enrollment to any-cause death was longer for FLO+F than TUL+K or TIL. Van Donkersgoed et al. (2009)[34] reported differences in DOF before mortality between treatment groups, with the median DOF at mortality being 32 days for FLO+F treated cattle compared to 25 days for TUL treated cattle. Additionally, the median days between the first BRD treatment and death was 26 days for FLO+F and 14 days for TUL, indicating a longer survival period for FLO treated cattle.[36] Similarly, Hannon et al. (2009)[24] found that FLO+F treated cattle survived longer on average before mortality than those treated with TUL. These findings align with the results of the Phase 2, where mean DOF from enrollment to death was significantly longer for cattle treated with FLO+F compared to those treated with TUL+K or TIL.

Despite careful design, several limitations should be acknowledged when interpreting these results. First, Phase 1 may have been underpowered for mortality outcomes due to unexpectedly low BRD mortality (case fatality) risk, reducing the ability to detect meaningful differences in treatment effects. The 2 study phases were conducted in different regions (Texas vs. Saskatchewan) and at different times of year, making direct comparisons more complex. Differences in season, circulating pathogens, and environmental conditions between sites may have contributed to variation in BRD dynamics. Furthermore, diagnosis and retreatment decisions were based largely on clinical signs observed by caretakers, introducing an element of subjectivity that could vary with individual training and experience. Although rectal temperature was recorded, it was not the sole determinant for retreatment, which may affect consistency in identifying and managing relapses.

As typical for commercial feedlot production systems, neither study phase included detailed pathogen identification or antimicrobial resistance profiling, leaving open questions about the specific bacterial strains and resistance patterns that could have influenced treatment responses. The study also focused on short-term outcomes related to animal health over a 100-day period. There are other outcomes or stakeholder values that were not measured, such as animal performance, carcass characteristics, cost effectiveness and antimicrobial stewardship, which could result in alternative decisions depending on their prioritizations. Finally, each phase was carried out within a single commercial feedlot using specific vaccination and management protocols, which may limit the external validity of these findings for operations with different practices. Taken together, these factors underscore the need for caution in extrapolating these results broadly, and highlight opportunities for future research to address these limitations.

Conclusions

In Phase 1, the disease burden was lower than expected and there was no evidence for differences in clinical outcomes between calves given TUL+K versus FLO+F for first-time clinical BRD treatment following on-arrival metaphylaxis with TUL. In Phase 2, which experienced a higher disease burden as evidenced by the overall and BRD case fatality in all groups, first-time clinical BRD treatment with FLO+F resulted in significantly lower BRD-specific mortality (case fatality) and total mortality than treatments with either TUL+K or TIL. Steers treated with FLO+F also survived longer from first treatment to death, both for all-cause and BRD-specific mortality as compared to either TUL+K or TIL. However, no statistically significant differences were observed in morbidity-related outcomes, such as retreatment risk or chronicity. These findings underscore the possibility that, in populations under higher disease pressure, the phenicol-NSAID combination may confer a survival advantage relative to macrolide-based therapies following macrolide metaphylaxis.

Despite similar morbidity outcomes across treatments, the observed reduction in mortality highlights a potential clinical benefit for producers seeking to manage severe BRD in high-risk cattle. Future research could build on these results by exploring the economic implications of different antimicrobial choices. Additional investigations into how different antimicrobial classes might be rotated or used strategically also could contribute to broader antimicrobial stewardship goals,

given the industry-wide priority to maintain effective therapies for BRD. Ultimately, the optimal first-treatment antimicrobial for BRD following TUL metaphylaxis may depend on cattle population risk level, disease burden and management practices, calling for continued refinement of these strategies under diverse production conditions.

Endnotes

[a] TUL; Draxxin®, Zoetis Canada Inc., Kirkland, Quebec, CA; Zoetis Animal Health, Parsippany, NJ; or generic equivalent

[b] TUL+K; Draxxin KP®, Zoetis Animal Health, Parsippany, NJ

[c] TIL; Zuprevo®, Merck Animal Health, Madison, NJ

[d] FLO; Fenicyl™, Vetoquinol N.-A. Inc., Lavaltrie, Quebec, CA; or generic equivalent

[e] FLO+F; Resflor Gold®, Merck Animal Health, Madison, NJ

[f] Cavalry 9, Merck Animal Health, Intervet Inc., Madison, NJ

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

[h] Inforce 3, Zoetis Inc., Parsippany, NJ

[i] Dectomax Injectable, Zoetis Inc., Parsippany, NJ

[j] Synovex Choice, Zoetis Inc., Parsippany, NJ

[k] Safe-Guard Suspension 10%, Merck Animal Health, Intervet Inc., Madison, NJ

[l] Cydectin Pour-on, Elanco US Inc., Greenfield, IN

[m] Ultrabac 7 Somubac, Zoetis Inc., Parsippany, NJ

[n] Bovi-Shield Gold One Shot, Zoetis Inc., Parsippany, NJ

[o] Bimectin Pour-on, Bimeda Animal Health, Dublin, Ireland

[p] Revalor 100, Merck Animal Health, Madison, NJ

[q] iFHMS©; Feedlot Health, Okotoks, Alberta, or TELUS Agriculture & Consumer Goods, Okotoks, Alberta

[r] Quellaxin™ 100, Aspen Veterinary Resources, Ltd., Liberty, MO

[s] Noromycin 300 LA, Norbrook Inc., Lenexa, KS

[t] Micotil™ 300 Injection, Elanco US, Inc., Greenfield, IN; or generic equivalent

[u] A180™, Zoetis Canada Inc., Kirkland, Quebec, CA

[v] Oxyvet® 300 LA, Vetoquinol N.-A. Inc., Lavaltrie, Quebec, CA

[w] SAS Institute Inc., Cary, NC

Acknowledgements

We thank the management and staff of Hall Cattle Feeders (Shamrock, TX) and Buffalo Plains Cattle Company Ltd. (Bethune, SK) for their support in conducting Phases 1 and 2 of this study. Additionally, we thank Holly Raaphorst, BSc, of TELUS Agriculture & Consumer Goods for serving as the lead research project coordinator for both phases.

Funding

This project was supported by research grants from Merck Animal Health, Madison, N.J. Authors TM and DR were supported by Kansas State University's Center for Outcomes Research and Epidemiology and the College of Veterinary Medicine.

Conflicts of interest

One of the co-authors is employed by Merck Animal Health which provided funding for this study. Other co-authors have received grant funding and/or consulting revenue from both Merck and Zoetis.

Author contributions

CB, LB, BH, KF and CM were involved in the conception and design of the study. CB, BH, KF, HR and CM were involved in acquisition of study data. CB, BH, KF, CM, TM, LH and DR were involved in analysis and interpretation of study data. All authors were involved in the manuscript drafting and/or revising process. All authors have approved the final version of this manuscript for publication.

References

1. Brault SA, Hannon SJ, Gow SP, et al. Antimicrobial use on 36 beef feedlots in western Canada: 2008-2012. *Front Vet Sci.* 2019;6:329. **https://doi.org/10.3389/fvets.2019.00329**

2. White B, Larson B. Impact of bovine respiratory disease in U.S. beef cattle. *Anim Health Res Rev.* 2020;21:132-134. **https://doi.org/10.1017/S1466252320000079**

3. USDA Feedlot. *Part III: Trends in health and management practices on U.S. Feedlots, 1994-2011.* USDA-APHIS-VS-CEAH, *NAHMS*. Fort Collins, CO; 2011. Report #637-0413

4. Griffin D. Economic impact associated with respiratory disease in beef cattle. *Vet Clin North Am Food Anim Pract.* 1997;13:367-377. **https://doi.org/10.1016/S0749-0720(15)30302-9**

5. Engler M, Defoor P, King C, et al. The impact of bovine respiratory disease: the current feedlot experience. *Anim Health Res Rev.* 2014;15:126-129. **https://doi.org/10.1017/S1466252314000139**

6. Nickell JS, White BJ. Metaphylactic antimicrobial therapy for bovine respiratory disease in stocker and feedlot cattle. *Vet Clin North Am Food Anim Pract.* 2010;26(2):285-301. **https://doi.org/10.1016/j.cvfa.2010.04.006**

7. Ives SE, Richeson JT. Use of antimicrobial metaphylaxis for the control of bovine respiratory disease in high-risk cattle. *Vet Clin North Am Food Anim Pract.* 2015;31:341-350. **https://doi.org/10.1016/j.cvfa.2015.05.008**

8. Abell KM, Theurer ME, Larson RL, et al. A mixed treatment comparison meta-analysis of metaphylaxis treatments for bovine respiratory disease in beef cattle. *J Anim Sci.* 2017;95:626. **https://doi.org/10.2527/jas2016.1062**

9. O'Connor AM, Hu D, Totton SC, et al. A systematic review and network meta-analysis of injectable antibiotic options for the control of bovine respiratory disease in the first 45 days post arrival at the feedlot. *Anim Health Res Rev.* 2019;20:163-181. **https://doi.org/10.1017/S1466252320000031**

10. USDA-NAHMS. Part IV: Health and Health Management on U.S. Feedlots with a Capacity of 1,000 or More Head. Ft. Collins, CO; 2013.

11. O'Connor AM, Yuan C, Cullen JN, Coetzee JF, da Silva N, Wang C. A mixed treatment meta-analysis of antibiotic treatment options for bovine respiratory disease – an update. *Prev Vet Med.* 2016;132:130-139. **https://doi.org/10.1016/j.prevetmed.2016.07.003**

12. Coetzee JF, Magstadt DR, Sidhu PK, et al. Association between antimicrobial drug class for treatment and retreatment of bovine respiratory disease (BRD) and frequency of resistant BRD pathogen isolation from veterinary diagnostic laboratory samples. *PLoS ONE* 2019;14(12):e0219104. **https://doi.org/10.1371/journal.pone.0219104**

13. Nutsch RG, Skogerboe TL, Rooney KA, et al. Comparative efficacy of tulathromycin, tilmicosin, and florfenicol in the treatment of bovine respiratory disease in stocker cattle. V*et Ther.* 2005;6:167-179.

14. O'Connor AM, Coetzee JF, da Silva N, Wang C. A mixed treatment comparison meta-analysis of antibiotic treatments for bovine respiratory disease. *Prev Vet Med.* 2013;110:77-87. **https://doi.org/10.1016/j.prevetmed.2012.11.025**

15. Wellman NG and O'Connor AM. Meta-analysis of treatment of cattle with bovine respiratory disease with tulathromycin. *J Vet Pharmacol Ther.* 2007;30:231-241. **https://doi.org/10.1111/j.1365-2885.2007.00846.x**

16. National Center for Biotechnology Information. PubChem Compound Summary for CID 9832301, Tulathromycin. *PubChem*. Accessed Feb 14, 2025. Available at: **https://pubchem.ncbi.nlm.nih.gov/compound/9832301**

17. National Center for Biotechnology Information. PubChem Compound Summary for CID 24860548, Tildipirosin. *PubChem*. Accessed Feb 14, 2025. Available at: **https://pubchem.ncbi.nlm.nih.gov/compound/24860548**

18. National Center for Biotechnology Information. PubChem Compound Summary for CID 114811, Florfenicol. *PubChem*. Accessed Feb 14, 2025. Available at: **https://pubchem.ncbi.nlm.nih.gov/compound/114811**

19. National Center for Biotechnology Information. PubChem Compound Summary for CID 3825, Ketoprofen. *PubChem*. Accessed Feb 14, 2025. Available at: **https://pubchem.ncbi.nlm.nih.gov/compound/3825**

20. National Center for Biotechnology Information. PubChem Compound Summary for CID 39212, Flunixin meglumine. *PubChem*. Accessed Feb 14, 2025. Available at: **https://pubchem.ncbi.nlm.nih.gov/compound/39212**

21. Kamel MS, Davidson JL, and Verma MS. Strategies for bovine respiratory disease (BRD) diagnosis and prognosis: A comprehensive overview. *Animals.* 2024;14(4):627. **https://doi.org/10.3390/ani14040627**

22. Perrett T, Abutarbush SM, Wildman BK, et al. A comparison of florfenicol and tulathromycin for the treatment of undifferentiated fever in feedlot calves. *Vet Ther.* 2008;9(2):128-40.

23. Van Donkersgoed J, Berg J, Hendrick S. Comparison of florfenicol and tulathromycin for the treatment of undifferentiated fever in Alberta feedlot calves. *Vet Ther.* 2008;9(4):275-81.

24. Skogerboe TL, Rooney KA, Nutsch RG, et al. Comparative efficacy of tulathromycin versus florfenicol and tilmicosin against undifferentiated bovine respiratory disease in feedlot cattle. *Vet Ther.* 2005;6(2):180-96.

25. Coetzee JF, Cernicchiaro N, Sidhu PK, et al. Association between antimicrobial drug class selection for treatment and retreatment of bovine respiratory disease and health, performance, and carcass quality outcomes in feedlot cattle. *J Anim Sci*. 2020;98(4):1-7. **https://doi.org/10.1093/jas/skaa109**

26. Szasz JI, Bryant TC, Bryant LK, Streeter MN, Hutcheson JP, Renter DG. Health and performance outcomes from a randomized clinical trial of post-metaphylactic intervals following tildipirosin metaphylaxis for control of naturally occurring bovine respiratory disease in commingled lightweight yearling steers in a commercial feedlot. *Bov Pract*. 2022;56(2):38-46. **https://doi.org/10.21423/bovine-vol56no2p38-46**

27. Pfizer Animal Health. Efficacy of DRAXXIN (tulathromycin) followed by 7-, 10-, or 14-day post-treatment intervals against naturally occurring bovine respiratory disease. Pfizer Animal Health Technical Bulletin. August 2006. Accessed Sep 23, 2025. Available at: **https://www.valleyvet.com/Library/lib_768rx_-Tech.pdf**

28. Coetzee JF, Magstadt DR, Sidhu PK, et al. Association between antimicrobial drug class for treatment and retreatment of bovine respiratory disease (BRD) and frequency of resistant BRD pathogen isolation from veterinary diagnostic laboratory samples. *PLoS One.* 2019;14(12):e0219104. **https://doi.org/10.1371/journal.pone.0219104**

29. Theurer ME, Fox JT, Bryant LK, et al. Treatment efficacy of tildipirosin or tulathromycin for first treatment of naturally occurring bovine respiratory disease in a commercial feedlot. *Bov Pract.* 2018;52:154-159. **https://doi.org/10.21423/bovine-vol52no2p154-159**

30. Horton LM, Hardee I, Meyer NF, et al. A randomized trial comparing the effects of tulathromycin, tildipirosin and gamithromycin used as first treatment for clinical bovine respiratory disease in commercial feedlot steers. *Bov Pract.* 2024;58(2):43-50. **https://doi.org/10.21423/bpj20249022**

31. Dodd CC, Bechtol DT, Waite A, et al. Randomized trial to compare the efficacy of tildipirosin and tulathromycin for initial treatment of bovine respiratory disease in naturally exposed commercial feedlot heifers. *Bov Pract.* 2018;52:39-45. **https://doi.org/10.21423/bovine-vol52no1p39-45**

32. Bringhenti L, Pallu M, Silva J, et al. Effect of treatment of pneumonia and otitis media with tildipirosin or florfenicol + flunixin meglumine on health and upper respiratory tract microbiota of preweaned Holstein dairy heifers. *J Dairy Sci.* 2021;104:10291-10309. **https://doi.org/10.3168/jds.2020-19945**

33. Tomazi A, Tomazi T, Bringhenti L, et al. Treatment with 2 commercial antibiotics reduced clinical and systemic signs of pneumonia and the abundance of pathogenic bacteria in the upper respiratory tract of preweaning dairy calves. *J Dairy Sci.* 2023;106:2750-2771. **https://doi.org/10.3168/jds.2022-22451**

34. Van Donkersgoed J, Berg J, Hendrick S. A comparison of florfenicol-flunixin meglumine versus tulathromycin for the treatment of undifferentiated fever in fall-placed feedlot calves. *Vet Ther.* 2009;10(1-2):78-85.

35. Mercer MA. Macrolide use in animals. *Merck Veterinary Manual*. Published 2022. Accessed February 14, 2025. Available at: **https://www.merckvetmanual.com/pharmacology/antibacterial-agents/macrolide-use-in-animals**

36. Hannon SJ, Perrett T, Wildman BK, et al. Efficacy of a florfenicol-flunixin meglumine combination product versus tulathromycin or ceftiofur crystalline free acid for the treatment of undifferentiated fever in feedlot calves. *Vet Ther.* 2009;10(4):E1-18.

