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

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Abstract

This study's objectives were to assess health (primary) and performance (secondary) outcomes in yearling steers randomized to pens with 4-day, 7-day, 10-day, or 13-day post-metaphylaxis intervals (PMI) following arrival administration of tildipirosin (Zuprevo®). The primary objective was to assess linear or non-linear responses to different PMI. Crossbred beef steers (N = 8,160), 648 lb overall mean body weight, were allocated to 40 pens, in 10 blocks, over a 3-week period at a commercial feedlot. Study blocks were defined by arrival and processing date. Data were analyzed using mixed models for a randomized complete block design with pen as the experimental unit. Across all pens and blocks, the incidence of bovine respiratory disease (BRD) first pulls, morbidity (rectal temperature > 103.5°F), mortality, and removals were: 11.67%, 9.20%, 0.89% and 0.92%, respectively. During the first 45 days, there were linear relationships between PMI and BRD morbidity ($P = 0.006$) and BRD first pulls ($P = 0.003$) indicating that apparent incidence decreased linearly as PMI increased. Over the entire feeding period (mean = 217 days), apparent BRD morbidity also decreased linearly ($P = 0.01$) as PMI increased; however, there was a quadratic (non-linear) relationship between BRD first pulls and PMI (group means were 12.0%, 12.9%, 11.08% and 9.49%, respectively). There were no significant associations (P values > 0.10) between PMI and BRD relapses, first treatment success, case fatality, mortality or any live and carcass performance measures. In this study population, longer PMI (fewer days eligible for treatment) led to reduced BRD first treatments, with no evidence for negative impacts on mortality or performance.

Key words: metaphylaxis, moratorium, PMI, bovine respiratory disease, feedlot cattle

Introduction

Bovine respiratory disease (BRD) is the most common and costly disease in feedlot and stocker cattle. The leading cause of morbidity and mortality, BRD also has a significant negative impact on the industry through decreased live cattle performance and carcass value, and costs associated with prevention, control and treatment.[1,2,3] The BRD complex can be difficult to manage in feeder cattle production systems due to the interaction of multiple potential bacterial and viral pathogens, as well as host, environmental, nutritional and management factors, which can affect BRD risk and subsequent health and production outcomes.[3,4] In addition, the poor sensitivity and specificity of current BRD field diagnostic methods and feedlot labor limitations result in further challenges to effectively managing BRD, particularly in high-risk calves, in many production systems.[3]

The use of antimicrobial metaphylaxis when at-risk cattle arrive to the feedlot has been shown to be an effective tool for reducing BRD morbidity, mortality and other negative health and performance indices.[3,5] Metaphylaxis is the practice of administering an approved antimicrobial to an entire cohort (lot or pen) of cattle with the intent of controlling the incidence of BRD in cattle at significant risk for BRD.[3,5] When metaphylaxis is used, often a post-metaphylactic interval (PMI) is applied, which is a period of time following metaphylaxis when no cattle can be pulled for treatment of respiratory disease.[6] The PMI may last anywhere from 3 days to 14 days or more depending largely on the pharmacological properties of the antimicrobial used.[6,7] For example, with some of the newer macrolide antimicrobials that provide several days of therapy, an extended PMI may be justified.[3,7] However, there are no approved dosing intervals for treatment following metaphylaxis for any of the antimicrobials approved for metaphylaxis. The application of metaphylaxis and a corresponding PMI has several potential benefits for both the animals and the production system, particularly during the acclimation period of new animal arrivals. In addition to realizing the direct benefits of metaphylaxis for reducing morbidity and mortality, the PMI period eliminates the need for daily sorting, handling, restraint and potentially unnecessary further treatment for BRD diagnoses, which could add further stress, and potentially stress-induced immune dysfunction, in

animals already considered at-risk for BRD.[3,5] The PMI period also allows cattle care-givers to focus on important animal husbandry issues during the critical arrival and acclimation period rather than focusing on BRD detection.[3]

Despite the importance of metaphylaxis and a corresponding PMI for managing cattle at risk for BRD, there are limited published clinical trial data documenting the optimal PMI for antimicrobials and different feeder cattle populations, which may be diverse in their risk factors for BRD and subsequent response to metaphylaxis. Given the increased concern surrounding antimicrobial use in food animals, additional data to judiciously guide decisions on use of antimicrobials is warranted. While there are studies comparing different metaphylaxis antimicrobials, PMIs and/or subsequent antimicrobials treatments,[7,8] we have found only 2 publications comparing different PMI times for the same antimicrobial, and neither evaluated the macrolide tildipirosin.[9,10] In fact, previous authors have specifically mentioned that there are no published clinical trial data defining the optimal PMI for some antimicrobials, including for tildipirosin.[11]

The objectives for this study were to assess health (primary) and performance (secondary) outcomes from 4-day, 7-day, 10-day or 13-day PMI following arrival administration of tildipirosin for metaphylaxis in yearling steers randomized to pens and PMI treatments in a pen-level randomized complete block design in a commercial feedlot. The primary objective was to use orthogonal contrasts to determine whether changes in PMI resulted in linear or non-linear (quadratic) changes in outcomes. Including equally-spaced (3 day) time intervals around the feedlot's standard PMI of 7 days facilitated this approach. Two different BRD case definitions (described in detail below) and subsequent therapeutic protocols, reflected different industry practices and enabled the study objective to be addressed in 2 subsets of the same study population.

Materials and methods

Study design and cattle population

The study was a clinical effectiveness study using a balanced randomized complete block design with pen as the experimental unit. Although the a priori hypothesis was that there would be linear or quadratic responses to treatment (different PMI), there were no preliminary data to estimate these potential responses to treatment. Thus, number of pens (and animals within pens) was optimized to detect a 10% difference in first treatment BRD morbidity between the standard PMI group (7-day) and one other treatment group, assuming the observed morbidity in the standard PMI group would be 15% in this study population. The level of significance was set at a more liberal value of $P \leq 0.10$ due to limitations in preliminary data and the number of pens available, and power was set at 80%. This study population was to represent a cohort of 650 lb (295 kg) body weight (BW) auction market-derived steers that were assumed to be at-risk of developing BRD (estimated 15% morbidity, 1% death loss and 1% removals due to chronic BRD following metaphylaxis). Over a 21-day period in September 2019, crossbred beef steers originating from Texas, Georgia, Florida, Arkansas and Louisiana (Table 2) were enrolled at a commercial feedlot in the Texas panhandle. Study blocks (replicates) were defined by arrival and processing date.

Randomization and arrival processing

Upon arrival to the facility, steers were placed into pens, by source and time of arrival, for approximately 24 to 48 hours prior to processing. Prior to study enrollment and processing, steers were observed for any abnormalities when unloading from the truck and again prior to processing; only steers with no observable clinical disease were enrolled. Steers were randomized to 1 of 4 experimental treatments at the time of initial processing: 1) 4-day PMI following arrival tildipirosin, 2) 7-day PMI following arrival tildipirosin, 3) 10-day PMI following arrival tildipirosin, and 4) 13-day PMI following arrival tildipirosin. A chute-side computer with a randomization schedule in Microsoft Excel was used to randomize experimental treatment to animals. Randomized cattle were sorted into 1 of 4 pens as they exited the squeeze chute. A randomization function in Microsoft Excel also was used to allocate 4 sort pens to 4 home pens. Ten blocks of 4 pens were used, resulting in a total of 40 pens. At processing, steers (N = 8,160) received unique numbered tags in each ear and the following products (administered per label): tildipirosina (1.8 mg/lb (4 mg/kg)) administered subcutaneously (SC) in the right lateral neck, modified live bovine rhinotracheitis and bovine virus diarrhea virus vaccine[b] (2 mL) administered SC in the right lateral neck, multivalent clostridial bacterin[c] (2 mL) administered SC in the left lateral neck, ivermectin[d] (1%) injection (90.9 mcg/lb [200 mcg/kg] of body weight) administered SC in the left lateral neck, albendazole[e] (4.54 mg/lb (10 mg/kg)) drench administered per os, and an estradiol (40 mg) and trenbolone acetate (200 mg) implant[f] administered in the caudal aspect of the left ear. Injectable animal health products were administered according to Beef Quality Assurance guidelines using syringes fitted with 16-gauge × ⅝" needles. Upon completion of processing a block, sort pens were then moved to 1 of 4 adjacent home pens. Steers were weighed in groups on a platform scale following randomization and processing to get an initial pen weight.

Housing and feeding

Pens within an experimental block were provided similar square footage (132 to 162 ft^2 per head), bunk space (8.2 to 9" per head), water tank space (1 to 2.3" per head) and were oriented in the same direction and had the pen-floor slope in the same direction. Cattle were fed twice daily a milled ration consisting of steam-flaked corn, wheat and/or corn silage, corn-milling byproducts and supplemental ingredients. Cattle were fed a starter ration and were gradually adapted to a finish (top) ration using a single intermediate ration and a series of step-up feeding schedules. Monensin[g] and tylosin[h] were included in the top ration at a target dosage of 330 mg monensin/d and 90 mg tylosin/d, respectively. Steers were fed ractopamine[i] at a target level of 250 mg ractopamine/d for 34 days followed by a 4-d withdrawal immediately before harvest; tylosin was not included in the beta-agonist diet.

Animal health

The PMI was defined as the period of time between metaphylaxis and when calves were eligible for further treatment. Following the assigned PMI, cattle were observed daily by pen riders. Whenever possible, a single pen rider observed cattle in all pens within a block, and all pulls within a block were trailed to and treated at the same hospital facility. Pen riders were not on the crews administering metaphylaxis or implementing the allocation process at enrollment, and only rarely did they help the hospital crews responsible for administering

any subsequent clinical treatments (i.e., at the chute) when cattle were pulled. The study feedlot utilizes PMI as a standard practice so the presence of pens that can and cannot be pulled is common practice. Further, pen riders rode/pulled cattle in multiple pens that were enrolled in the study with a rolling enrollment (different days) over a 3-week period, which resulted in pens staggered in terms of their eligibility for treatment (PMI). Thus, while the pen riders were not completely blinded (since they needed to know which pens could be ridden/pulled on any given day), effectively they did not know the treatment group designation of any given pen.

Animals were pulled based on a standardized clinical attitude scoring system (CAS), as follows: 0 = normal (bright, alert and responsive), 1 = mild depression (signs of weakness usually not present), 2 = moderate to marked depression (reluctant to stand), and 3 = severe depression (unable to stand without assistance). The case definition of BRD was a CAS > 1. First pulls were treated with 18.2 mg/lb (40 mg/kg) body weight of florfenicol with 1 mg/lb (2.2 mg/kg) body weight of flunixin meglumine[j] if their rectal temperature was > 103.5°F, or with 9 mg/lb (19.8mg/kg) of oxytetracycline[k] if their rectal temperature was < 103.5°F. Second pulls were all treated with 3.64 mg/lb (8 mg/kg) of danofloxacin[l]. If pulled a third time for BRD, steers were removed from the study pens (removal). A post-treatment interval (PTI) of 4 days was observed for treatment drugs. Antimicrobials were administered using syringes fitted with 16-gauge x ⅝″ needles. All antimicrobials were administered SC according to Beef Quality Assurance guidelines. Standard feedlot protocols were used for treatment of diseases unrelated to BRD, and treatment protocols were identical across experimental treatments. Cattle convalesced in hospital pens for a minimum of 24 hours, but not more than 72 hours, before returning to their respective home pen; cattle that did not respond to treatment were retreated as per the treatment protocols. Cattle were removals if a disease or malady did not have a practical treatment option available or when cattle were pulled for the same non-BRD disease a fourth time. Mortalities were subjected to postmortem examination performed by trained personnel that were unaware of treatment group designations.

Measurements and calculations

The performance and clinical outcome variables of interest were average daily body weight gain (ADG), and BRD treatment morbidity, treatment success, mortality and case fatality. All analyses were conducted at the pen-level. The primary outcome variables were calculated (for each pen) using the following general formulas shown in Table 1.

Steers were shipped, by block, to a commercial packing plant in Cactus, Texas as they became market-ready in March, April and May 2019. Steers were weighed across a platform scale in multiple drafts at the time of shipping. Live weights were shrunk by 4% to adjust for digestive tract fill. Carcass data were delivered electronically from the plant. Performance values are expressed with the effect of dead and removed animals included.

Statistical analysis

Data were analyzed as a randomized complete block design with pen as the experimental unit. Continuous data (e.g., body weight) were analyzed using linear mixed models (Proc Mixed, SAS)[m] with experimental treatment as the fixed effect, and block (i.e., replicate) as a random intercept. Categorical data were analyzed using generalized linear mixed models (Proc Glimmix, SAS)[m] with the model effects described previously. For pen-level proportions, model estimation was performed using a logit scale to link events/trials responses to a binomial distribution. Orthogonal trend analysis was conducted using coefficients for each PMI group which were generated via Proc Iml (SAS)[m]. Orthogonal polynomials were used to determine whether changes in PMI resulted in linear or non-linear (quadratic) changes in outcomes. Estimates of treatment means and respective standard errors or 95% confidence intervals are reported on the data scale, using an inverse link method (Ilink option, SAS)[m] for generalized linear

Table 1: Formulas used in calculating primary outcome variables

BRD 1st pulls	=	# calves treated for BRD during trial period regardless of rectal temp. / # calves allocated to pen
BRD morbidity	=	# calves treated for BRD during trial period with rectal temp. ≥ 103.5 / # calves allocated to pen
Treatment success	=	# BRD treated calves that were not retreated, BRD dead or removal / # calves treated for BRD
BRD relapse	=	# calves treated twice for BRD during trial period / # calves treated for BRD
BRD mortality	=	# calves dead from BRD during trial period / # calves allocated to pen
Overall mortality	=	# calves dead regardless of cause / # calves allocated to pen
Case fatality	=	# calves treated for BRD that died of BRD / # calves treated for BRD
ADG (deads-in)	=	total cattle weight at end – initial total cattle weight / # head-days on trial

Table 2: Descriptive information on 8,160 crossbred beef steers allocated to compare post-metaphylactic intervals in a commercial feedlot and their subsequent bovine respiratory disease (BRD) cumulative incidence measures by study block.

Study block	# Head	Head per pen	In date	Mean body weight, lb (kg)	State of origin	Origin sources	% BRD pulls	% BRD morbidity > 103.5°F (39.7°C)	% BRD mortality	% BRD removal
1	880	220	9/6/18	611 (278)	TX	15	15.2	9.3	2.2	1.3
2	880	220	9/6/18	644 (293)	TX, GA, FL	11	8.0	5.2	0.2	0.1
3	880	220	9/12/18	652 (296)	TX	10	9.5	6.4	1.0	0.7
4	880	220	9/17/18	641 (291)	TX, GA	14	16.0	12.5	1.8	1.5
5	880	220	9/20/18	594 (270)	TX, AR	6	11.8	8.5	1.3	1.0
6	400	100	9/20/18	656 (298)	TX	5	10.5	5.5	0	0
7	880	220	9/20/18	594 (270)	TX, AR	4	9.0	5.5	0.3	1.3
8	880	220	9/26/18	624 (284)	TX	6	6.9	5.2	0.5	0.5
9	880	220	9/26/18	624 (284)	TX, LA	13	9.5	6.1	0.5	0.6
10	720	180	9/27/18	601 (273)	TX	7	8.2	3.9	0.7	1.7

models. Statistical differences were reported at $\alpha < 0.10$, and trends were described at α 0.10 to 0.15.

Results

A total of 8,160 crossbred beef steers were enrolled and allocated to 40 pens, in blocks of 4 pens, over a three-week period (Table 2). Pen-level mean body weight was 648 lb (294 kg) with a standard deviation of 22.9 lb (10.4 kg). The number of head per pen ranged from 100 to 220 but were identical within blocks. The number of cattle origins per block ranged from 15 to 4. The cumulative incidence of BRD first pulls, BRD morbidity (rectal temperature > 103.5°F), BRD mortality and BRD removals are given by block in Table 2. The overall crude percentages across all pens and blocks (with 95% confidence intervals) for these BRD outcomes were: 11.67% (10.98 to 12.38%), 9.20% (8.58 to 9.85%), 0.89% (0.70 to 1.12%) and 0.92% (0.72 to 1.15%), respectively.

In total, 123 (1.51%) animals died (all causes) and 132 (1.62%) were removed (all causes). In most study pens (35 of 40) there were no steers that died from BRD without ever being pulled and treated. However, in the 4-day PMI group, there was one pen with 2 steers and another pen with 1 steer that died from BRD without being pulled and treated. In the 7-day PMI group there were none, in the 10-day group there was one pen with one steer, and in the 13-day PMI group there were two pens that each had one steer that died from BRD but was never pulled and treated.

Analysis results for measures of BRD by PMI treatment group are provided in Table 4. During the first 45 days on feed, there were significant linear relationships between PMI group and BRD morbidity ($P = 0.006$) and BRD first pulls ($P = 0.003$) indicating that apparent incidence decreased linearly as PMI increased. Concurrently, days on feed (DOF) at first pull and DOF at apparent morbidity were both increased linearly as PMI increased (Table 2). There was no evidence that either animal body weight or rectal temperature for BRD morbidity or first pulls were significantly associated with PMI during the first 45 DOF (Table 3).

When considering the entire feeding period (mean = 217 DOF), BRD morbidity decreased linearly ($P = 0.01$) with corresponding linear increases in DOF ($P = 0.03$) and body weight ($P = 0.051$) as PMI increased (Table 3). Similarly, DOF ($P = 0.064$) and body weight ($P = 0.07$) of BRD first pulls tended to increase linearly as PMI increased (Table 3). However, there was evidence of a quadratic relationship between BRD first pulls and PMI (Table 3). Figures 1 and 2 display graphically the treatment group means and the significant quadratic and linear relationships between PMI and cattle first-treated for BRD regardless of rectal temperature (first pulls) or with a temperature ≥ 103.5°F (morbidity), respectively. The differences in PMI group means for the overall first pulls and for those with an elevated temperature given in Figures 1 and 2 (and also in Table 3) indicate that 79.25%, 75.08%, 77.26% and 77.77% of the cattle treated (in PMI groups 4, 7, 10 and 13 respectively) had rectal temperatures ≥ 103.5°F. In other words, the proportion of treated cattle in each of the two BRD first-treatment designations were similar across different PMI groups.

There was no evidence for significant associations between PMI group and BRD relapses or BRD first treatment success (Table 3). Similarly, there was no evidence for significant associations between PMI group and BRD case fatality or various measures of mortality or removal incidence or corresponding DOF at occurrence (Table 4). As demonstrated in Table 5, there was no evidence that PMI significantly affected final body weight, average daily gain, dry matter intake, feed conversion, hot carcass weight, dressing percentage or measure of quality and yield grade of the carcasses (Table 5).

Discussion

Despite the benefits of metaphylaxis and post-metaphylactic intervals for managing BRD in at-risk feeder cattle,[3,5,6] this is the first study demonstrating how different PMI times for tildipirosin affect cattle health and performance. In general, the PMI significantly affected the percentage of cattle pulled and treated for BRD, but there was no evidence that the PMI

Table 3: Effects of post-metaphylactic intervals on morbidity outcome means (standard errors)* for 8,160 crossbred beef steers that received on-arrival tildipirosin for control of bovine respiratory disease (BRD) in a commercial feedlot.

	Post-metaphylactic interval (PMI)				*P* - value†	
Item	**4-days**	**7-days**	**10-days**	**13-days**	**LIN**	**QUAD**
Pens (Head) enrolled	10 (2,040)	10 (2,040)	10 (2,040)	10 (2,040)		
BRD morbidity (with rectal temperature > 103.5°F)						
0 to 45 days on feed						
Percent of enrolled	5.91 (1.01)	5.72 (0.99)	4.68 (0.84)	4.18 (0.77)	0.006	0.669
Days on feed	20 (1.1)	22 (1.1)	24 (1.1)	25 (1.1)	0.001	0.824
Body weight	660 (16.0)	653 (16.0)	671 (16.0)	675 (16.0)	0.299	0.662
Rectal temperature	104.3 (0.07)	104.5 (0.07)	104.3 (0.07)	104.3 (0.07)	0.459	0.173
Entire feeding period						
Percent of enrolled	9.51 (1.153)	9.70 (1.117)	8.56 (1.065)	7.38 (0.951)	0.010	0.246
Days on feed	44 (4.30)	45 (4.30)	53 (4.30)	53 (4.30)	0.030	0.243
Body weight	747 (24.3)	743 (24.3)	786 (24.3)	784 (24.3)	0.051	0.361
Rectal temperature	104.5 (0.06)	104.5 (0.06)	104.5 (0.06)	104.5 (0.06)	0.713	0.347
BRD first pulls (all rectal temperatures included)						
0 to 45 days on feed						
Percent of enrolled	7.57 (1.186)	7.90 (1.228)	6.08 (0.992)	5.52 (0.918)	0.003	0.402
Days on feed	19.7 (0.91)	22.1 (0.91)	23.7 (0.91)	24.6 (0.91)	0.001	0.353
Body weight	658 (15.2)	657 (15.2)	671 (15.2)	675 (15.2)	0.189	0.807
Rectal temperature	104.0 (0.10)	104.0 (0.10)	104.0 (0.10)	103.9 (0.10)	0.460	0.642
Entire feeding period						
Percent of enrolled	12.00 (1.21)	12.92 (1.27)	11.08 (1.14)	9.49 (1.02)	0.005	0.076
Days on feed	44 (4.60)	44 (4.60)	54 (4.60)	51 (4.60)	0.064	0.679
Body weight	748 (24.5)	744 (24.5)	797 (24.5)	779 (24.5)	0.070	0.680
Rectal temperature	104.1 (0.09)	104.1 (0.09)	104.1 (0.09)	104.1 (0.09)	0.668	0.806
BRD relapses, % of first pull	20.0 (2.96)	18.4 (2.76)	16.4 (2.78)	14.8 (2.79)	0.131	0.967
BRD first treatment success, % of first pull‡	69.2 (3.27)	70.0 (3.15)	72.2(3.27)	75.4 (3.37)	0.138	0.666

* from general and generalized linear mixed model analyses.

† for orthogonal polynomial contrasts of PMI means: LIN = Linear, QUAD = Quadratic.

‡ percent of BRD treated cattle that were not re-treated or died due to BRD.

affected other health metrics or measures of live and carcass performance in this study population. Overall, the results indicate that longer PMI, or fewer eligible days for treatments following metaphylaxis, results in less cattle pulled and treated for BRD without negatively impacting mortality or performance. Importantly, the cattle population in this study was limited to crossbred, relatively lightweight yearling, auction market-derived beef steers, with relatively moderate estimated BRD morbidity (15%), mortality (1%) and BRD removals (1%) following metaphylaxis. The observed incidence of BRD first pulls (11.67%) and apparent BRD morbidity (rectal temperature > 103.5°F; 9.20%) in this study population were somewhat lower than expected, with a relatively wide range among study blocks (16% to 6.9%, and 12.5% to 3.9%,), but these data are from a large population of 8,160 feeder steers procured from many sources (Table 2).

Given that there are very limited published clinical trial data defining the optimal PMI for antimicrobials, and none for the macrolide tildipirosin,[11] our results are unique and cannot be directly compared to results from previous field studies. There is one published paper evaluating 2 different PMI groups (3 and 7 day) for ceftiofur crystalline free acid (Excede®)[n] in feedlot calves, where the authors concluded that a PMI of more than 3 days was not beneficial; however, that study used much higher risk calves and a different class of antimicrobial.[9] In another publication there were 2 small 60-day

studies in high risk calves that evaluated PMI for the macrolide tilmicosin (Micotil®)[o].[10] The first study demonstrated no evidence for differences among 3-day, 5-day and 7-day PMI groups, while the other demonstrated that apparent BRD morbidity with a 10-day PMI (39.3%) was significantly lower than in 3-day (55.7%), 5-day (56.4%) and 7-day (52.l%) PMI groups.[10] One recent clinical trial of post-treatment intervals (PTI), not PMI, for a different macrolide (gamithromycin), demonstrated that for treatment success a 9-day PTI was significantly better than a 3-day PTI and was numerically but not statistically superior to 6- and 12-day PTI.[12]

Our study used Zuprevo®, a macrolide antimicrobial, that contains 180 mg tildipirosin, and is labeled for control of respiratory disease (metaphylaxis) in cattle at risk of developing BRD associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*.[a] The label further states that a single dose of Zuprevo® concentrates in the lungs for 28 days and in bronchial fluid for 21 days.[a] However, like other antimicrobials approved for metaphylaxis, there are no clinical data indicating appropriate dosing interval(s), or PMI, following metaphylaxis. Pharmacokinetic studies of tildipirosin have shown that the drug is rapidly and extensively distributed to, and slowly eliminated from the bovine respiratory tract.[13]

In our study, the number of days that cattle were eligible to be pulled and treated (i.e., days at-risk for being pulled and treated) was inherently different with PMI groups of 4, 7, 10 and 13 days. The mean number of DOF, and in some instances average body weight, when cattle were pulled and treated tended to be greater as PMI increased (Table 3). While an extended PMI should inherently increase the mean DOF at treatment, the corresponding increase in mean body weight indicates that, on average, cattle treated for BRD in the extended PMI groups continued to consume feed and grow while ineligible for treatment. During the first 45 days on feed, there were significant linear decreases in apparent BRD morbidity and BRD first pulls as PMI increased (Table 3). Similar results were found with the data on these BRD incidence measures over the entire feeding period (closeout). However, there was evidence of a quadratic (non-linear) relationship PMI and BRD first pulls from the entire feeding period as shown graphically in Figure 1. The changes in BRD treatments associated with changes in PMI could be due to the inherently different days at-risk (eligibility) for further treatment, or declines in true clinical BRD incidence over time related to the effectiveness of metaphylaxis or a reduction in BRD burden as DOF increase. Given that correctly diagnosing BRD in the field is known to be challenging and that spontaneous recovery in some untreated animals is expected, particularly in lower-risk yearlings,[14] it is reasonable to assume that some animals treated in the shorter PMI groups did not need treatment. Regardless, the results from this study indicate that the longer PMI led to reduced BRD treatments without significantly impacting mortality (Table 4) or performance (Table 5) measures.

Several studies have demonstrated that cumulative BRD morbidity in feedlot cattle is associated with increased mortality and decreased live and carcass performance.[3,5] Here we found no evidence that PMI affected mortality or performance measures, despite significant differences in BRD pulls and apparent morbidity associated PMI. However, it is plausible that these observed differences in BRD treatments following metaphylaxis are not reflective of the true BRD burden, but simply differences in apparent BRD due to differences in days eligible for treatment. The overall BRD burden, and BRD mortality and BRD removals in particular (0.89% and

Table 4: Effects of post-metaphylactic intervals on mortality and removal outcome means (standard errors)* for 8,160 crossbred beef steers that received on-arrival tildipirosin for control of bovine respiratory disease (BRD) in a commercial feedlot.

	Post-metaphylactic interval (PMI)				*P*-value†	
Item	**4-days**	**7-days**	**10-days**	**13-days**	**LIN**	**QUAD**
BRD case fatality, %‡	5.44 (1.655)	5.55 (1.633)	6.76 (1.950)	5.69 (1.832)	0.770	0.696
Mortality, % of enrolled						
BRD	0.76 (0.250)	0.72 (0.240)	0.80 (0.260)	0.64 (0.220)	0.703	0.720
Digestive§	0.23 (0.110)	0.42 (0.154)	0.37 (0.144)	0.28 (0.122)	0.821	0.269
Other	0.19 (0.101)	0.34 (0.137)	0.34 (0.137)	0.19 (0.101)	1.000	0.217
Total	1.27 (0.298)	1.54 (0.341)	1.59 (0.348)	1.18 (0.291)	0.821	0.184
Days on feed at death	58 (17.3)	73 (17.3)	64 (17.3)	50 (17.3)	0.656	0.354
Removals, % of enrolled						
BRD	0.985 (0.256)	0.985 (0.256)	0.938 (0.248)	0.610 (0.190)	0.187	0.367
Total	1.80 (0.327)	1.65 (0.311)	1.74 (0.322)	1.21 (0.261)	0.177	0.431
Days on feed at removal	88 (16.1)	84 (16.1)	100 (16.1)	113 (16.1)	0.219	0.597
Mortality + removal, % of enrolled	3.06 (0.495)	3.20 (0.511)	3.34 (0.527)	2.40 (0.425)	0.246	0.142

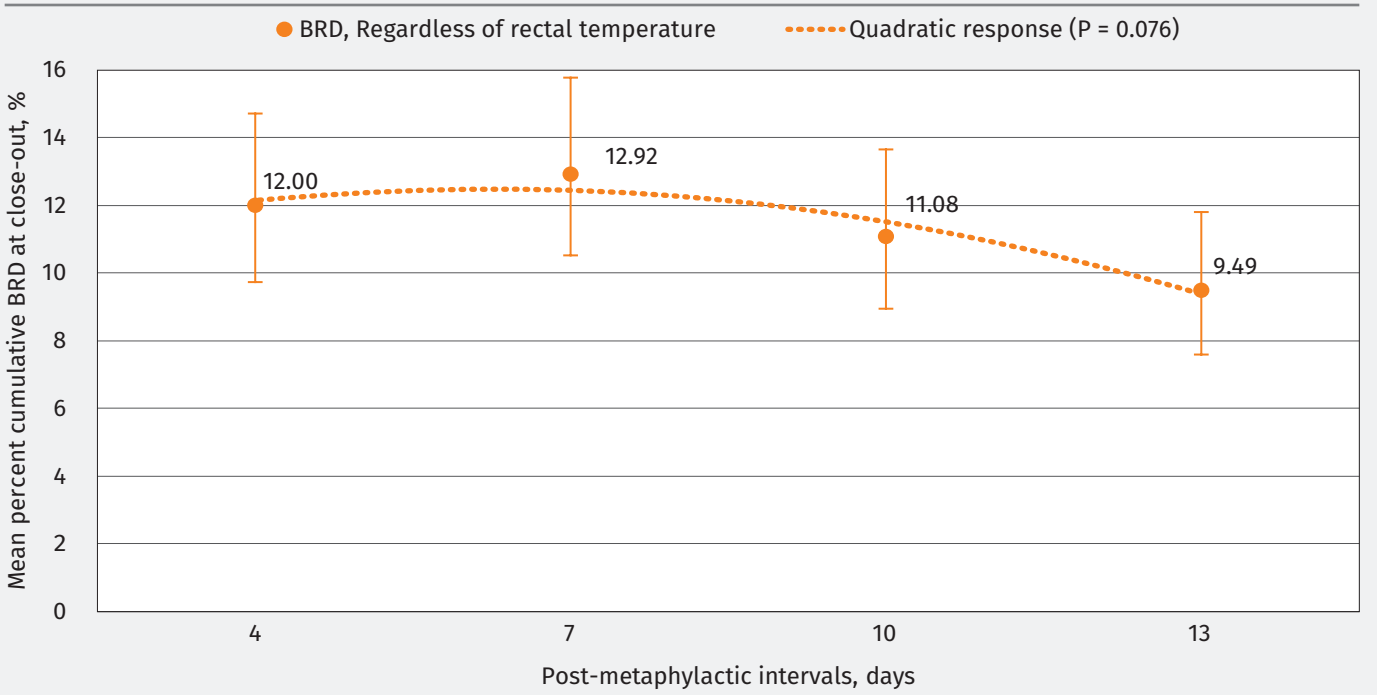
* from general and generalized linear mixed model analyses.

† for orthogonal polynomial contrasts of PMI means: LIN = Linear, QUAD = Quadratic.

‡ percent of cattle pulled and treated for BRD that subsequently died of BRD.

§ includes causes of death attributed to ruminal tympany (bloat), acidosis, diarrhea/enteritis, liver abscess(es), peritonitis.

Figure 1: Model-adjusted mean percentages (95% confidence intervals) of cattle treated for bovine respiratory disease (BRD), regardless of rectal temperature, by post-metaphylactic interval (PMI) group, and the corresponding quadratic response curve for a study of 8,160 crossbred beef steers that received on-arrival tildipirosin for control of BRD in a commercial feedlot.



0.92%, respectively) were relatively low in this study population. Thus, there may not have been sufficient enough disease burden in this study population to significantly exacerbate performance, mortality or removal effects. In addition, the steers were fed for a relatively long period of time (217 days in total) following metaphylaxis and past the time period where most of the BRD morbidity occurred (mean average DOF for observed morbidity by PMI groups ranged from 44 to 53; Table 3). However, collectively these data indicate that a shorter PMI increases the apparent morbidity, and that additional clinical treatments soon after the initial metaphylaxis may not be necessary for preventing subsequent mortality or negative impacts on performance.

Although this study's objective was to assess impacts of different PMI, there were limitations to the number of different PMI treatment groups. It is not appropriate to extrapolate results beyond a 13-day PMI, and similarly, there was no PMI shorter than 4 days. In addition, there was a large but fairly narrowly defined study population, and it is very plausible that the PMI effects observed in this study do not reflect what would be seen in different cattle populations, such as higher risk, lighter weight feeder calves. Given the potential importance of an optimal PMI to appropriate implementation of metaphylaxis programs in the field, there is a need for additional data on PMI effects in different cattle populations and/or using different antimicrobials.

In this study population of yearling beef steers with relatively moderate BRD risk, we can conclude that the PMI following arrival administration of tildipirosin (Zuprevo®) significantly affected the percentage of cattle that were pulled and treated for BRD, without significantly impacting other health metrics or measures of live and carcass performance. In particular, a longer PMI, or less days in which cattle were eligible to be treated, led to reductions in apparent BRD morbidity and first pulls. Long PMI may lead to concerns that some cattle may not receive needed treatment, or may not receive it soon enough; yet, in this study there was no evidence for a longer PMI resulting in negative impacts on mortality, weight gain and other health and performance variables. One could assume that this study population included cattle that did not need any additional antimicrobial therapy following metaphylaxis, and on average those cattle in the longer PMI groups didn't receive as many unnecessary doses. These results may be useful for practitioners considering tildipirosin metaphylaxis for similar feeder steer populations.

Endnotes

[a]Zuprevo®, Merck Animal Health, Summit, NJ.

[b]Bovi-Shield Gold IBR-BVD®, Zoetis, Kalamazoo, MI.

[c]Ultrachoice 8®, Zoetis, Kalamazoo, MI.

[d]Noromectin®, Norbrook, Lenexa, KS.

[e]Valbazen®, Zoetis, Kalamazoo, MI.

[f]Revalor XS®, Merck Animal Health, Summit, NJ.

[g]Monensin®, Elanco Animal Health, Greenfield, IN.

[h]Tylosin®, Elanco Animal Health, Greenfield, IN.

[i]Optaflexx®, Elanco Animal Health Greenfield, IN.

[j]Resflor Gold®, Merck Animal Health, Summit, NJ.

[k]Noromycin 300®, Norbrook, Lenexa, KS.

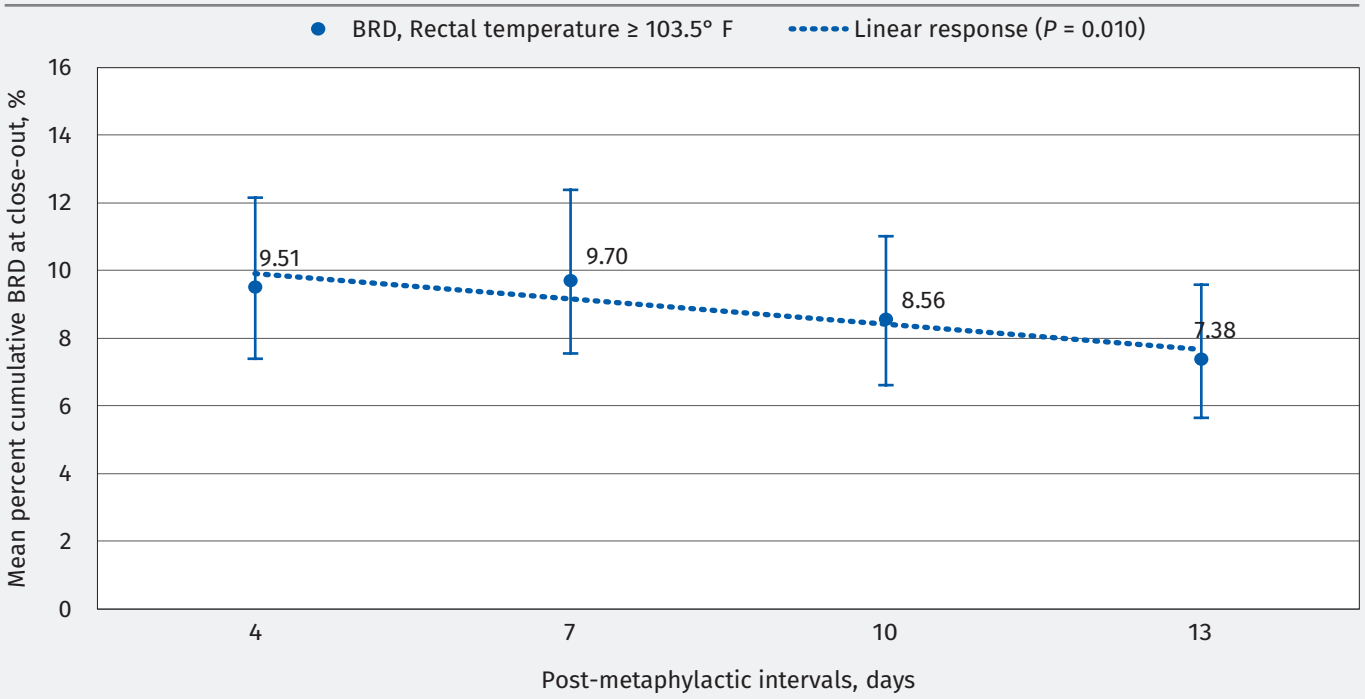
[l]Advocin®, Zoetis, Kalamazoo, MI.

Table 5: Effects of post-metaphylactic intervals on live and carcass performance means (standard errors)* for 8,160 crossbred beef steers that received on-arrival tildipirosin for control of bovine respiratory disease (BRD) in a commercial feedlot.

	Post-metaphylactic interval (PMI)				*P*-value†	
Item	**4-days**	**7-days**	**10-days**	**13-days**	**LIN**	**QUAD**
Live body weight						
Initial, lb	648 (7.5)	648 (7.5)	647 (7.5)	647 (7.5)	0.531	0.822
Final, lb‡	1,309 (11.1)	1,311 (11.1)	1,305 (11.1)	1,312 (11.1)	0.964	0.586
Days on feed	217	217	217	217	-	-
Dry matter intake, lb	18.6 (0.224)	18.7 (0.22)	18.6 (0.22)	18.6 (0.22)	0.884	0.671
Average daily gain§, lb	3.01 (0.05)	3.01 (0.05)	2.97 (0.05)	3.02 (0.05)	0.958	0.308
Dry feed conversion	6.20 (0.08)	6.22 (0.08)	6.27 (0.08)	6.17 (0.08)	0.930	0.201
Hot carcass weight, lb	857 (0.75)	858 (0.75)	856 (0.75)	858 (0.75)	0.920	0.945
Dressing percentage	64.9 (0.18)	64.9 (0.18)	65.1 (0.18)	65.1 (0.18)	0.084	0.952
USDA choice and prime,%	60.3 (2.65)	58.5 (2.68)	58.9 (2.68)	60.5 (2.64)	0.847	0.133
USDA select,%	36.4 (2.31)	37.8 (2.35)	38.1 (2.35)	36.5 (2.32)	0.896	0.178
USDA sub-select,%	2.6 (0.58)	2.2 (0.52)	2.2 (0.53)	1.9 (0.46)	0.184	0.966
USDA yield grade 1 and 2,%	50.9 (2.55)	53.4 (2.54)	53.6 (2.54)	49.8 (2.55)	0.405	0.007
USDA yield grade 3,%	44.4 (2.18)	41.4 (2.15)	40.5 (2.13)	45.7 (2.19)	0.577	0.001
USDA yield grade 4 and 5,%	3.8 (0.90)	4.1 (0.98)	4.7 (1.1)	3.9 (0.93)	0.630	0.170

* from general and generalized linear mixed model analyses.
† for orthogonal polynomial contrasts of PMI means: LIN = Linear, QUAD = Quadratic.
‡ four percent (4%) "pencil shrink" applied.
§ on a deads-in basis

Figure 2: Model-adjusted mean percentages (95% confidence intervals) of cattle treated for bovine respiratory disease (BRD), with a rectal temperature ≥ 103.5°F, by post-metaphylactic interval (PMI) group, and the corresponding linear response for a study of 8,160 crossbred beef steers that received on-arrival tildipirosin for control of BRD in a commercial feedlot.



[m]SAS Institute Inc., Cary, NC.

[n]Excede®, Zoetis, Kalamazoo, MI.

[o]Micotil®, Elanco Animal Health Greenfield, IN.

Declaration of conflicting interests

Authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Drs. L. Bryant, Streeter and Hutcheson are employees of Merck Animal Health. Drs. Szasz, T. Bryant and Renter have had previous research or consulting paid by Merck Animal Health.

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