Comparison of Short-Term Health and Performance Effects Related to Prophylactic Administration of Tulathromycin versus Tilmicosin in Long-Hauled, Highly Stressed Beef Stocker Calves*

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CLINICAL RELEVANCE

Health and feed performance parameters of 293 beef stocker calves at risk for bovine respiratory disease were compared after metaphylactic administration of one of two antimicrobials (tulathromycin or tilmicosin) with different durations of activity; the antimicrobial was administered 1 day after arrival. Calves that received metaphylactic tulathromycin displayed significant improvement in morbidity, mortality, and first-treatment success rates ($P < .05$) compared with tilmicosin-treated calves. Tulathromycin-treated calves also showed a significantly improved average daily gain and feed:gain ratio ($P < .05$) compared with tilmicosin-treated calves. Under conditions of this study, calves receiving tulathromycin were healthier through a 43-day growing phase compared with calves receiving tilmicosin. This health difference likely accounted for the differences in feed performance between the treatment groups.

■ INTRODUCTION

Bovine respiratory disease (BRD) is the most prevalent health condition in both the stocker and feedlot stages of beef production.[1] This syndrome causes economic loss in the form of treatment costs, loss of feed performance, decreased quality grade, and higher mortality risk.[2] The BRD process is multifactorial and requires sound management techniques intended to maximize cattle health and reduce negative consequences attributed to BRD.[2]

Antimicrobials are commonly used not only in the treatment of calves stricken with BRD but also for administration to calves at high-risk of developing BRD. The practice of providing prophylactic or metaphylactic antimicrobial therapy to calves when they arrive at a feedlot facility has been intensely studied and repeatedly shown to be a cost-effective practice in many production settings.[3–10] To date, many commercial antibiotics are approved for use in calves to treat and control clinical signs of BRD or in calves at high-risk of developing BRD. Two of these drugs, tilmicosin (Micotil, Elanco Animal Health) and tulathromycin

timeframe in which to return a profit on the calves they purchase; therefore, maintaining a high level of health and growth performance is imperative. Most research evaluating metaphylaxis uses feedlot production systems, and data investigating the role of metaphylaxis in the shorter feeding phases associated with stocker cattle are scarce. To our knowledge, research comparing the effects of tulathromycin and tilmicosin during the stocker phase does not exist. The objective of this study was to determine whether health and performance differences were present when comparing a longer-acting (tulathromycin) antimicrobial with a shorter-

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(Draxxin, Pfizer Animal Health), are members of the macrolide class of antibiotics. Tilmicosin, which provides therapeutic drug concentration in the lung for 72 hours, was the first long-acting parenteral antimicrobial approved for use in the control and treatment of BRD.[11] Metaphylactic administration of tilmicosin has been shown to decrease morbidity associated with BRD and improve feeding performance in feedlot cattle.[4,5,8,9] Likewise, tulathromycin administered on arrival has been shown to improve the health status of feedlot calves.[3,7,12] Tulathromycin provides 14 days of therapeutic lung concentration.[13]

The stocker segment of the beef industry has traditionally been a grower phase for young, lightweight calves before their entry into a feedlot. These calves are typically fed in confinement lots or supplemented with concentrates while grazing. However, stocker calves are on feed for a much briefer time than calves in the finishing period in feedlots. The challenge for stocker operators relative to feedlot owners is the shorter

acting (tilmicosin) agent in beef stocker calves at arrival. The null hypothesis was that tulathromycin and tilmicosin were identical in their control of BRD in stocker calves.

■ MATERIALS AND METHODS
Pen and Treatment Allocation

All animals were handled in accordance with a protocol approved by the Kansas State University Animal Care and Use Committee. Two hundred ninety-three mixed-breed beef bulls and steers of weaning age were procured in the southeastern United States and shipped from Tennessee to Kansas. The calves were housed at the Kansas State Beef Stocker Unit outside Manhattan, Kansas. Ninety-eight head arrived on August 30, 2007. Two additional loads comprising 96 and 99 head, respectively, were delivered on September 1, 2007. On arrival, the calves were unloaded and allowed to rest for 1 hour. They were then individually weighed, number-tagged, and determined to be a bull or a steer. Cattle were blocked by load

of arrival. Each load of calves was assigned to one string of eight pens housing 12 to 13 calves/pen. Randomization of pen and treatment allocation was performed using a random number generator (Microsoft Excel 2003), and the first pen was assigned to treatment A or B by a coin flip. Each successive pen then received an alternate treatment. This process was repeated for each load. Therefore, four pens in each load were allocated to each treatment group, resulting in 12 pens in the tilmicosin group and 12 pens in the tulathromycin group.

Health and Nutrition Program

Twenty-four hours after arrival, each calf received 2 ml of a commercial modified-live, four-way viral respiratory vaccine containing infectious bovine rhinotracheitis virus, parinfluenzavirus-3, bovine viral diarrhea virus, and bovine respiratory syncytial virus (Jencine 4, Schering-Plough Animal Health), 2 ml of a multivalent clostridial vaccine (Calvary 9, Schering-Plough Animal Health), and in-

lathromycin/ml). The volume of each drug was based on the average weight of the respective load. To rule out the presence of individuals persistently infected with bovine viral diarrhea virus, a standard ear notch biopsy was collected from each calf at arrival using a commercial ear notch device (Large Ear Notcher; Stone Manufacturing, Kansas City, MO). The ear biopsies were analyzed by antigen capture ELISA at the Kansas State Veterinary Diagnostic Laboratory (KSVDL).

After processing and assignment to pens, steers from each load were offered (as-fed basis) approximately 3.0 kg/steer of a total mixed ration consisting of prairie hay, alfalfa, wet gluten feed, and cracked corn; the ration is calculated to contain 16% crude protein and 1.14 Mcal/kg net energy for gain (NE_g). On day 15 after arrival, steers were converted to a ration that contained the same ingredients but in different proportions, with a resulting calculated nutrient density of 15% crude protein and 1.19 Mcal/kg NE_g. A final diet change oc-

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jectable ivermectin (1 ml/50 kg [110 lb], Ivomec, Merial), and the bulls were surgically castrated. All products were administered according to label directions. Calves were revaccinated with both vaccines on day 10 (Loads 1 and 2) or 11 (Load 3) after arrival. Metaphylactic treatment was administered 24 hours after arrival. Calves allocated to treatment A received tilmicosin (1 ml/30 kg SC [1.5 ml/100 lb]; 300 mg tilmicosin/ml) and calves allocated to treatment B received tulathromycin (1 ml/40 kg SC [1.1 ml/100 lb]; 100 mg tu-

curred on day 25, again using the same ingredients in different proportions, with a calculated nutrient density of 15% crude protein and 1.24 Mcal/kg NE_g. Feed bunks were observed daily, and the amount of feed distributed to each pen was allocated based on the bunk score from that day reflecting consumption in the period since the last feeding. Total amount (as fed) of daily feed delivery to each pen was recorded. Each pen was equipped with an individual automatic waterer, and water was available ad libitum throughout the trial. The

amount fed/head/day was calculated using the current head count for each pen (total head entered minus head removed for death loss or chronic status) and the pounds of feed fed to each pen daily.

The Kansas State Beef Stocker Unit caretakers, who were responsible for daily evaluation of the cattle, were blinded to metaphylactic treatment assignment throughout the study. A 72-hour postmetaphylactic treatment moratorium was observed for both antimicrobials. Each pen was observed twice daily to identify calves with clinical signs of BRD. Once identified, affected calves were removed from the pen and walked to the processing unit. Rectal temperatures were recorded for each sick calf.

calves with chronic respiratory disease. Calves designated as having chronic respiratory disease were removed from the final performance analysis. All calves that died during the study period were necropsied at the KSVDL.

At the conclusion of the feeding phase, all loads exited the facility on the same day. Cattle were weighed individually on the day of departure. The ratio of pounds of feed to pounds of gain (F:G ratio) was calculated for each pen by dividing the total pounds fed to each pen (as fed) by the total weight gain for each pen (dead cattle not included in the analysis). The average daily gain (ADG) for each pen was calculated based on the average arrival weight of the pen and the average weight of the pen at exit

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Morbidity risk attributed to BRD was 32.8% for calves receiving tulathromycin and 68.1% for calves receiving tilmicosin.

Calves registering rectal temperatures ≥40°C (≥104°F) were classified as experiencing BRD and were treated according to a predesigned treatment protocol. Cattle meeting the treatment criteria were treated initially with enrofloxacin (7.5–12.5 mg/kg SC; Baytril, Bayer Animal Health). If cattle met the treatment criteria a second time, a minimum of 72 hours after initial treatment, they received florfenicol (40 mg/kg SC; Nuflor, Schering-Plough Animal Health). Cattle meeting treatment criteria a third time, a minimum of 72 hours after the second treatment, received oxytetracycline (20 mg/kg SC; Biomycin 200, Boehringer Ingelheim). After any treatment, cattle were immediately returned to their pen of origin. If a calf exhibited clinical signs of BRD and had been treated three times, it was removed from the original pen and assigned to a holding pen for

(dead cattle not included at exit).

Morbidity was calculated on a pen level by dividing the number of cattle receiving the first treatment by the initial number of cattle in each pen. Mortality confirmed to be attributed to BRD by the KSVDL was calculated by dividing the number of cattle that died during the feeding phase by the initial head count of the pen. Case fatality risk (CFR) was determined by the number of cattle that died divided by the number of cattle receiving the initial treatment in each pen. First-treatment success was calculated as the percentage of calves that were treated for BRD one time that did not require further treatment.

Statistical Analysis

Pen was the unit of analysis for all statistical models. Pounds fed/head/day were analyzed

using a general linear model that accounted for the lack of independence among pens with an unstructured random lot variable and included fixed effects of days on feed and metaphylaxis treatment (JMP 7.0, SAS Institute, Cary, NC). Days on feed at first treatment for BRD were analyzed using a general linear model that accounted for lack of independence among pens and lots with unstructured random variables and included fixed effects of animal gonadal status and metaphylaxis treatment. Proportions (pen-level morbidity, mortality, first-treatment success, and CFR) were evaluated with logistic regression models using PROC GENMOD in SAS (version 9.1, SAS). In the logistic models, lot and treatment were fixed effects. Kaplan–Meier survival analysis (JMP 7.0) was performed on raw data to illustrate the time elapsed between arrival and initial treatment for BRD for each of the two metaphylactic agents.

■ RESULTS

The three loads of stocker calves encompassed 180 bulls and 113 steers. Arrival information by treatment group can be found in Table 1. The cattle were at the growing facility for 43 (Load 1) or 41 days (Loads 2 and 3). All antigen-capture ELISA tests on ear biopsy specimens were negative for bovine viral diarrhea virus. There was no statistical difference ($P > .05$) between the average incoming weight of calves receiving tilmicosin and those receiving tulathromycin.

Health performance variables displayed statistical differences between treatment groups (Table 2). One hundred forty-nine calves were diagnosed and treated for BRD. Of those 149 calves, 71 were treated twice and 23 were treat-

TABLE 1. Percent of Bulls vs. Steers, Average Weight at Arrival, and Number of Head of the Three Arrival Loads of Study Cattle

	Tulathromycin	Tilmicosin
% Bulls	63.0%	61.9%
Average weight (lb) ± SE	483.0 ± 4.8	481.6 ± 4.8
No. of head	146	147

TABLE 2. Treatment Group Mean (±SE) for Performance and Health Parameters*

Parameter	Tulathromycin	Tilmicosin
Performance		
Average daily gain	2.5 ± 0.17^a	2.0 ± 0.17^b
Feed:gain ratio	5.9 ± 0.29^a	7.1 ± 0.29^b
Pounds fed/day	14.9 ± 0.51^a	13.2 ± 0.51^b
Health		
Morbidity (%)	32.8 ± 0.04^a	68.0 ± 0.04^b
Mortality (%)	3.6 ± 0.02^a	13.5 ± 0.03^b
First treatment success (%)	71.9 ± 0.07^a	49.5 ± 0.05^b
Case fatality	10.4 ± 0.04^a	20.4 ± 0.04^a
Chronic BRD (%)	1.4 ± 0.01^a	7.5 ± 0.01^b

*Based on least squares means and SEs from mixed models accounting for arrival lot and metaphylactic treatment as fixed effects. Only the results of the effect of interest (metaphylactic agent) are reported.
[a,b]Means in columns with different superscripts are significantly different ($P < .05$).

ed three times for BRD. Morbidity risk attributed to BRD was 32.8% for calves receiving tulathromycin and 68.1% for calves receiving tilmicosin ($P < .05$). One calf (in the tilmicosin group) was treated for a scrotal infection and was removed from the morbidity analysis. Calves administered metaphylactic tulathromycin displayed a lower BRD mortality risk of 3.9% compared with 13.6% in the tilmicosin treatment group ($P < .05$). One calf (in the tilmicosin group) died from a condition unrelated to BRD and was removed from the mortality analysis. Calves receiving tu-
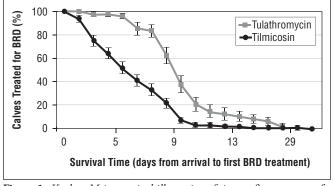
Figure 1. *Kaplan–Meier survival illustration of time to first treatment for bovine respiratory disease based on raw data of actual dates treated only, including treated animals from either tilmicosin or tulathromycin treatment groups. (Survival curves and SEs are based only on calves identified and treated for BRD during the feeding phase; nontreated calves were excluded from the illustration. Statistical differences in least squares mean days to first treatment were determined using general linear models described in the text.)*

lathromycin displayed a first-treatment success rate of 71.9% while calves in the tilmicosin group had a first-treatment success rate of 49.5% ($P < .05$). The tulathromycin group had fewer calves with chronic BRD (1.4%) compared with the tilmicosin group (7.5%) ($P < .05$). CFR was not significantly different ($P = .1$) between treatments; however, the CFR for tilmicosin-treated calves was twice that of calves receiving tulathromycin (20.4% versus 10.4%, respectively).

Comparisons of feeding and performance variables between calves receiving either tilmicosin or tulathromycin on arrival are summarized in Table 2. A significant difference was found between treatment groups for the measured performance parameters. Calves receiving tulathromycin had a significantly higher ($P < .05$) ADG (2.52 lb/head/day) compared with the tilmicosin group (2.0 lb/head/day). The F:G ratio of calves in the tulathromycin group was significantly ($P < .05$) lower (5.9 lb of feed/lb of gain) than in the tilmicosin group (7.1 lb of feed/lb of gain). Calves in the tu-

lathromycin group were fed more pounds/head/day when compared with the calves in the tilmicosin group ($P < .05$) (14.9 lb/head/day versus 13.2 lb/head/day, respectively). The days on feed for each pen was a significant factor in the model evaluating pounds fed/day, but there was no significant interaction between days on feed and metaphylactic treatment ($P > .05$).

In the model evaluating the number of days on feed at initial treatment for BRD, both metaphylactic treatment agent and animal gonadal status (steer or bull) were significant ($P < .05$). Calves treated with tilmicosin had a significantly lower ($P < .01$) least squares mean days on feed at first pull (6.4 days) compared with tulathromycin-treated calves (10.6 days). For illustrative purposes, a Kaplan–Meier survival analysis was performed on the raw data comparing the two treatments (Figure 1).

■ DISCUSSION

In this trial, tulathromycin was more effective than tilmicosin in improving health and feed performance in stocker calves when both agents were used in accordance with the labeled dose. Calves that received tulathromycin on arrival were healthier throughout the stocker phase compared with calves that received tilmicosin. Morbidity risk attributed to BRD in calves receiving tilmicosin was more than twice that of calves administered tulathromycin (68% versus 38.2%, respectively). Likewise, the overall mortality risk was greater in the tilmicosin group compared with the tulathromycin group (13.5% versus 3.6%, respectively). Other research evaluating tu-

lathromycin illustrated an improvement in morbidity risk, mortality risk, and treatment response proportions for calves entering a feedlot when compared with other metaphylactic agents and negative controls.[3,6,7,10] However, this is the first report of tulathromycin efficacy in a stocker calf production setting.

Beyond a reduction in morbidity risk, there were also differences related to the outcome after initial treatment for BRD (Table 2). Calves in the tulathromycin group displayed a first-treatment success rate of 71.9% compared with 49.5% in the tilmicosin group. Rooney and associates[7] showed that treatment success was significantly increased in feedlot cattle that received metaphylactic tulathromycin opposed to calves that received either tilmicosin or florfenicol.[7] Our research also illustrated that the tulathromycin group had significantly fewer animals classified as chronic by the end of the stocker phase. This finding is similar to that of other authors evaluating tulathromycin who reported significant reductions in mortality risk and cases of chronic BRD compared with calves given metaphylactic tilmicosin or florfenicol.[7] Our findings are unique because the mortality and chronicity reductions can be identified by the end of a relatively short (43 days) stocker phase.

As a class, the macrolides are considered to be time-dependent bacteriostatic antibiotics. Therefore, prolonged lung concentrations are necessary for the prevention or treatment of BRD.[13] The discrepancy in risk of BRD treatment between cattle treated metaphylactically with tulathromycin or tilmicosin could be attributed to the difference in duration of activity between the two drugs. Tulathromycin has been shown to sustain therapeutic lung concentrations for up to 14 days,[13] whereas tilmicosin possesses a 3-day period of antimicrobial action.[11] Based on those data, calves receiving metaphylactic tulathromycin are presumably protected from the development of bacterial pneumonia for a longer period. This is supported by the higher mean days on feed at first pull for tulathromycin (10.6 days) compared with tilmicosin (6.4 days) found in this study. The Kaplan–Meier survival analysis (Figure 1) illustrates that not only was the number of cattle treated for BRD different between metaphylactic agents, so was the time between arrival and first treatment.

In this trial, tulathromycin was more effective than tilmicosin in improving health and feed performance in stocker calves.

Although a 72-hour postmetaphylactic treatment moratorium was observed for both antimicrobials, calves treated with tilmicosin were treated sooner in the feeding phase, with the least squares mean time for treatment being 4 days earlier than in calves receiving tulathromycin. In a feedyard production system, 4 days is a small fraction of the feeding period. However, in this stocker system, a 4-day difference represents approximately 9% of days on feed. Therefore, the metaphylactic administration of tulathromycin may allow calves to maintain a higher degree of health for a longer duration of the feeding period relative to calves that received tilmicosin on arrival.

The increase in overall health of tulathromycin calves relative to those who received tilmicosin is an important element in

the differences in feed performance that we witnessed in this trial. Compared with the tilmicosin treatment group, calves receiving tulathromycin had higher ADG and feed delivery (consumption) resulting in a lower F:G ratio. This suggests that stocker calves receiving tulathromycin metaphylactically gain more weight and convert feed more efficiently than stocker calves administered tilmicosin. This illustrates the importance of maximizing the health of stocker calves to ensure efficient feed performance.

In comparison with feedlot data, our results agree with existing literature comparing tulathromycin with other metaphylactic antimicrobials. Booker and colleagues[3] reported that calves receiving tulathromycin on arrival at the feedlot had significantly lower initial BRD treatments and relapse risk, lower overall chronicity, lower overall mortality risk, higher ADG, and improved quality grades. However, the authors discovered that calves in the tulathromycin group displayed a significantly worse F:G ratio than calves that received tilmicosin; they speculated that this could be a consequence of an increase in the survival of calves possessing poor ability to convert feed.[3] This outcome in F:G ratio for tulathromycin calves contradicts our results, as we identified an improvement in F:G for calves that were administered tulathromycin at arrival.

Our findings could be attributed to the fewer days stocker cattle are on feed relative to feedlot calves. Although we also showed greater likelihood for survival in the tulathromycin group, the stocker calves were on feed for fewer days between treatment and marketing than calves in a feedlot scenario. Thus, the impact of chronic respiratory disease on performance would be smaller in the stocker phase relative to calves in the feedlot finishing phase.

One aspect of improving overall feed performance is maintaining the overall health of the cattle. As described above, the morbidity risk for tulathromycin-treated calves was significantly less than for tilmicosin-treated calves. In addition, the Kaplan–Meier survival analysis shows that calves receiving tulathromycin had an increase in the number of healthy days before getting sick in comparison with calves administered tilmicosin. One would expect that the longer calves stayed healthy, the longer they would be efficiently converting feed into pounds of gain. Therefore, feed performance could be driven not only by cumulative risk of morbidity but also by keeping calves healthier for a longer period before treatment for BRD. This may be especially true in a stocker system as there is a shorter timeframe, relative to feedlot systems, to add weight to the cattle and less time for calves to recover and reach their maximum feeding potential once they have been treated for BRD.

Cattle are very adept at concealing the early signs of BRD, even to experienced and astute personnel. Therefore, it is likely that a large number of true BRD cases go undiagnosed in both the stocker and feedlot sectors. Previous literature indicates that the presence of subclinical BRD may also influence growth and feed efficiency performance. Wittum et al[14] followed 469 steers to slaughter and reported that 68% of steers not treated for BRD displayed lung lesions and that the presence of lung lesions was associated with a decrease in ADG during the feeding period.[14] Likewise, Gardner and associates[15] found lesions in 33% of lungs at slaughter from treated and untreated feedlot steers and noted that steers with lung lesions, regardless of treatment history, had a lower (P < .05) ADG, poorer marbling scores, and lighter hot carcass weights than steers without lung lesions.[15] The literature supports the hypothesis that subclinical disease affects performance in cattle. Our research found per-

formance differences between the two treatment groups that may be the result of not only clinical disease risk (morbidity and mortality) but also underlying subclinical disease.

Thompson et al[16] evaluated clinical (treated) and subclinical (nontreated with lung lesions) calves and reported that subclinical cases occurring before day 35 on feed decreased ($P <$ .001) ADG by 91 g (0.20 lb). In addition, after day 35, calves that had been treated for BRD tended to grow faster than those with subclinical BRD.[16] This explains that not only does antimicrobial treatment decrease the economic loss associated with BRD but that cattle can recover and make the most of their remaining time on feed. This is advantageous for cattle in a feedlot setting as they have more time for this recovery. However, stocker cattle rarely have a long recovery period and, therefore, early cases of BRD may decrease a calf's ability to recover sufficiently and effectively begin to convert feed before the stocker phase has ended. Based on the referenced data, we believe that the greater growth and feed efficiency performance in tulathromycin-treated calves compared with tilmicosin-treated calves in our study may have been affected by a decrease in the number of subclinical, as well as clinical, cases of BRD in calves receiving tulathromycin. It also appears that increasing the number of healthy days before treatment for BRD is imperative in stocker cattle, more so than in feedlot cattle.

■ CONCLUSION

Under the conditions of this study, stocker calves administered tulathromycin on arrival are healthier throughout the stocker phase (display less death loss, respond more effectively to BRD treatment, and have more healthy days on feed) compared with calves that receive metaphylactic tilmicosin. The stocker segment of the beef industry poses different challenges relative to the feedlot sector. Because of a short feeding period, increasing the number of healthy days on feed before initiating BRD treatment is necessary to maximize feed performance. Administering tulathromycin on arrival as a metaphylactic agent appears to be an effective tool to optimize both health and performance in beef stocker calves at high risk for respiratory disease.

■ ACKNOWLEDGMENTS

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