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# A Comparison of 3-, 5-, 7- and 10-day Post-metaphylaxis Evaluation Periods on Health and Performance Following On-arrival Treatment with Tilmicosin in Feeder Cattle – A Summary of Two Studies

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**Abstract**

Two 60-day studies were conducted comparing various post-metaphylaxis evaluation periods (PMEPs) following administration of tilmicosin to beef feeder cattle at arrival-processing. Calves in Study I were randomly assigned to a control group (no metaphylaxis) or administered tilmicosin at label dose (4.55 mg/lb; 10 mg/kg BW) and assigned to a 3-, 5- or 7-day PMEP (n=160 calves per treatment). Morbidity due to bovine respiratory disease (BRD) was reduced ($P<0.01$) in calves treated metaphylactically with tilmicosin compared to controls (9.6 vs 33.8%, respectively). Average daily gain (ADG) was improved ($P<0.05$) in all three PMEP groups compared to gain of calves in the control group.

Calves in Study II were randomly assigned to a control group (no metaphylaxis) or administered tilmicosin at label dose and assigned to one of four PMEP (3-, 5-, 7- or 10-days) groups (n=140 per treatment). Morbidity caused by BRD was reduced ($P<0.05$) in all tilmicosin metaphylaxis groups compared to controls (55.7, 56.4, 52.1, 39.3 and 69.3% for the 3-, 5-, 7- and 10-day PMEP groups and controls, respectively). The morbidity rate due to BRD was lower ($P<0.01$) in the 10-day PMEP group compared to other PMEP groups, however, mortality in this group was numerically higher than the other PMEP groups. There was no difference in ADG among treatments.

Calves diagnosed with clinical BRD following the PMEP and control calves showing signs of BRD were treated with tulathromycin (1.14 mg/lb; 2.5 mg/kg BW) in both studies. Treatment success was similar across all treatments in each study, but was numerically higher in Study I (88.0%) compared to Study II (66.8%).

**Keywords:** bovine, feedlot, BRD, metaphylaxis, tilmicosin

**Résumé**

Deux études de 60 jours ont été menées afin de comparer différentes périodes d'évaluation suite à l'administration métaphylactique de tilmicosine à des bovins de boucherie à leur arrivée au parc d'engraissement. Dans l'étude I, les veaux ont été assignés aléatoirement soit à un groupe témoin (sans métaphylaxie) ou soit à un groupe traité à la dose recommandée de tilmicosine (4.55 mg/lb; 10 mg/kg de masse corporelle) avec une période d'évaluation de 3, 5 ou 7 jours (n=160 veaux par traitement). La morbidité causée par les maladies respiratoires bovines était moins élevée ($p<0.01$) chez les veaux traités métaphylactiquement avec la tilmicosine que chez les veaux du groupe témoin (9.6 versus 33.8%, respectivement). Le gain moyen quotidien était plus élevé ($p<0.05$) chez les veaux des trois groupes d'évaluation post-métaphylactique que chez les veaux du groupe témoin.

Les veaux dans l'étude II ont été alloués aléatoirement soit à un groupe témoin (sans métaphylaxie) ou soit à un groupe traité à la dose recommandé de tilmicosine avec une période d'évaluation de 3, 5, 7 ou 10 jours (n=140 par traitement). La morbidité causée par les maladies respiratoires bovines était moins élevée ($p<0.05$) chez les veaux de tous les groupes recevant la tilmicosine que chez les veaux du groupe témoin (55.7, 56.4, 52.1, 39.3 et 69.3% pour les groupes avec évaluation à 3, 5, 7 et 10 jours et pour le groupe témoin, respectivement). Le taux de morbidité associé aux maladies respiratoires bovines était moins élevé ($p<0.01$) dans le groupe d'évaluation à 10 jours que dans les autres groupes d'évaluation. Toutefois, la mortalité dans ce groupe était numériquement plus élevée que dans les autres groupes. Il n'y avait pas de différence entre les groupes en ce qui concerne le gain moyen quotidien.

Les veaux diagnostiqués avec une maladie respiratoire bovine chronique suite à la période d'évaluation et les veaux du groupe témoin montrant des signes de maladies respiratoires bovines ont été traités avec de la tulathromycine (1.14 mg/lb; 2.5 mg/kg de masse corporelle) dans les deux études. Le taux de succès du traitement était similaire dans tous les traitements de chacune des études mais était numériquement plus élevé dans l'étude I que dans l'étude II (88 versus 66.8%, respectivement).

## Introduction

Tilmicosin,[a] a macrolide antibiotic, was approved in the United States (US) in 1992 for treatment of bovine respiratory disease (BRD) caused by *Mannheimia haemolytica*. In 1996, tilmicosin was approved for control of BRD in cattle at high risk of developing BRD. At that time, the term metaphylaxis was first used in the United States, and is defined as treatment given to animals experiencing any level of viral or bacterial disease before clinical signs of disease appear.[15]

Pharmacokinetic studies[16,17] have demonstrated significant lung concentrations of tilmicosin above the $MIC_{90}$ for *M. haemolytica* for 72 to 96 hours following treatment with a single 4.55 mg/lb (10 mg/kg) dose administered subcutaneously (SC). Other studies showed intracellular accumulation of tilmicosin in alveolar macrophages[6,14,17] and circulating neutrophils[7] for up to 10 days post-injection. Intracellular accumulation of tilmicosin has been shown to enhance the bactericidal capabilities of inflammatory cells,[2] and provide a mechanism for transport and accumulation of tilmicosin at the site of inflammation.[6,7]

Numerous studies have demonstrated the efficacy of tilmicosin for controlling BRD in cattle at risk of contracting respiratory disease.[1,4,5,8,9,10,11,12,13,18] The majority of these studies utilized a two-to-three day post-metaphylaxis evaluation period (PMEP). After the two-or-three day PMEP, calves showing signs of BRD and meeting minimal body temperature criteria were considered failures of the antibiotic metaphylaxis program. These calves were subsequently treated with first-line antibiotic therapy for clinical BRD. In a more recent study that evaluated 3-, 5- or 7-day post-treatment intervals following therapeutic use of tilmicosin for clinical BRD, Carter *et al*[3] demonstrated that extending the post-treatment interval to seven days improved treatment success rate without increasing mortality or chronic rates. The authors concluded a three day post-treatment interval may lead to over-estimation of treatment failures, thus leading to unnecessary treatments and costs.

The objective of these studies was to evaluate various PMEPs beyond the three-day moratorium traditionally observed following administration of tilmicosin to high risk calves to control BRD.

## Materials and Methods

*Scope of the Studies*

In two separate studies, feedlot calves at high risk of developing BRD were utilized to evaluate various PMEPs beyond the three-day period typically observed following metaphylactic use of tilmicosin at arrival processing. Calves were housed and fed in a research feedlot with management similar to that in commercial feedlots, except smaller pens were utilized. Calves in each treatment group were fed in the same pen, and pen was the experimental unit.

Calves were followed for 60 days following arrival into the feedlot, at which time the study was terminated. Outcome variables measured included health and performance differences between controls (no metaphylaxis at arrival processing) and calves treated with tilmicosin at processing with PMEPs ranging from three to 10 days. Economic differences were not calculated, and because calves were not followed until harvest, no carcass data were available.

Statistical analyses were conducted to determine if observed differences in health and performance variables between treatments were statistically significant.

*Research Facility*

Both studies were conducted in a research facility in the Texas panhandle. The design of the facility is similar to commercial feedlots on the high plains in the US. Calves were housed in outdoor pens with dirt floors, and feed was delivered into permanent concrete feedbunks along the front side of the pens. Feeding pens were 52x36 feet (15.8x10.9 meters), which allowed 93.6 sq ft (8.6 sq m) of pen space and 21.6 linear inches (54.9 cm) of bunk space for each calf. A hospital facility similar to those found in commercial feeding facilities was used to evaluate and treat sick cattle. The hydraulic chute was equipped with a scale to individually weigh animals, and health information was entered into the hospital computer system. Treated calves were not housed in hospital pens.

*Study Calves*

Study I was conducted in the spring of 2006, while Study II was done in the winter of 2006-2007. A total of 640 English crossbred steers were purchased from Texas and Oklahoma livestock markets for use in Study I, and transported by truck to the research feedlot. Mean arrival body weight was 517 lb (235 kg), with a range of 401-686 lb (182-312 kg). For Study II, English crossbred steer (N=158) and bull calves (N=542) were

purchased from livestock markets in Texas, Oklahoma, Arkansas, Georgia and Alabama. Mean arrival weight was 567 lb (258 kg) (range 421-757 lb; 191-344 kg). Any calf that arrived at the research feedlot with signs of pre-existing BRD was excluded from the studies.

Within 24 hours of arrival at the feedlot, calves in both studies were processed as follows:

- Serially-numbered lot tag was placed in the ear.
- Individual rectal temperature was taken and recorded.
- Individual body weight was recorded.
- Modified-live infectious bovine rhinotracheitis (IBR) virus, bovine viral diarrhea (BVD) virus, parainfluenza-3 (PI-3) virus and bovine respiratory syncytial (BRS) virus vaccine[b,c] was administered according to label instructions.
- 8-way clostridial bacterin-toxoid[d] was given according to label instructions.
- Calves were treated for internal parasites[e,f] according to label instructions.
- A growth promoting implant[g] was administered according to label instructions.
- Tilmicosin[a] (4.55 mg/lb; 10 mg/kg BW) was administered SC to calves allotted to a metaphylaxis treatment group. Dosage was based on individual body weight. Calves in the control groups did not receive tilmicosin.
- In Study II, bulls were castrated using a high-tension elastic band.[h] There were no bulls in Study I.
- A skin sample (ear notch) was taken from each calf, and placed in formalin.

Skin samples were submitted to the Texas Veterinary Diagnostic Laboratory (Amarillo) to identify calves persistently infected with BVDV. Immunohistochemical testing was utilized.

*Experimental Design*

In both studies, calves were randomly assigned to treatment during arrival processing utilizing a computer-based random-number generator. Calves from each truckload were equally assigned to each treatment. Body weight was not used to determine treatment assignment.

Calves in Study I were assigned to either the control group, or treated metaphylactically with tilmicosin and allocated to either a 3-, 5- or 7-day PMEP. There were eight replicates (pens), four pens per replicate with 20 calves per pen, for a total of 160 calves per treatment.

In Study II, calves were randomly allocated to one of five experimental treatments; control or treated metaphylactically with tilmicosin and assigned to either a 3-, 5-, 7- or 10-day PMEP. Calves arriving as bulls and banded were equally distributed among treatments. There were seven replicates (pens), five pens per replicate with 20 calves per pen, for a total of 140 calves per treatment.

*Feeding Management*

Upon arrival, calves were fed long-stem grass hay top-dressed over a basal starter ration. For the remainder of both studies, calves were fed a basal starter ration formulated to deliver 150 mg monensin[i] and 90 mg tylosin[j] per head per day. All cattle were fed the same ration. Feed offered to each pen was measured and recorded daily. Daily feed intake was measured on a pen basis, and calculated on an individual animal basis by dividing the amount of feed consumed by the number of calves in the pen. Intake was adjusted to a dry matter basis. Water was provided *ad libitum* via an automatic watering system.

*Animal Health Management*

Calves in both studies were observed daily by trained pen checkers; responsible animal health personnel were masked (blinded) to treatment. During the assigned PMEP, calves in the respiratory metaphylaxis groups were not removed from their pen and were not eligible to be treated for BRD unless they exhibited severe clinical signs of BRD defined as a clinical illness score (CIS) ≥ 4 on a 1-5 scale (Table 1). Control calves were eligible for treatment for BRD the day following processing (day 1).

**Table 1.** Clinical illness score (CIS).

| Clinical illness score (CIS) | Description | Clinical Appearance |
|---|---|---|
| 1 | Normal and healthy | No abnormal clinical signs. |
| 2 | Slightly ill | Mild abnormal character of respiration. Slight depression, gauntness and nasal and/or ocular discharge. |
| 3 | Moderately ill | Moderate abnormal character of respiration. Noticeable dyspnea, gauntness, depression, nasal and/or ocular discharge. |
| 4 | Severely ill | Severe abnormal character of respiration. Pronounced dyspnea, depression and gauntness. Nasal and/or ocular discharge. |
| 5 | Moribund | Down, near death. Open mouth breathing. |

Calves in the control groups and those eligible in PMEP treatment groups were removed from their home pen and taken to the hospital for further evaluation if they exhibited signs of BRD and had a CIS of ≥ 2. Calves with a CIS ≥2 and a rectal temperature ≥104°F (40°C) were treated for BRD. Those with a CIS ≥2 and a rectal temperature <104°F were not treated. All calves were returned to their designated home pen after evaluation and/or treatment.

Calves in either study diagnosed with BRD the first time were treated with tulathromycin[k] (1.14 mg/lb; 2.5 mg/kg) administered SC. Calves were not eligible for re-treatment for three days following the first or second treatment for BRD. Treatment outcome categories are outlined in Table 2.

If a calf experienced treatment failure or relapsed, it was treated with florfenicol[l] (18.2 mg/lb; 40 mg/kg) SC. Those relapsing a second time were treated with oxytetracycline[m] (4.5 mg/lb; 10 mg/kg) SC. Tripelennamine hydrochloride[n] was administered to all treated calves at label dose as adjunct therapy. The study veterinarian classified treated calves as "successful responder" or "chronic" based on visual evaluation at the end of the studies.

*Data Collection*

Individual body weights were collected at arrival processing and study completion (day 60). Primary treatment outcome measures for all groups included BRD morbidity, mortality and chronic rates; mean days to BRD onset; and mean rectal temperature at BRD onset. Performance measures included body weight gain, average daily gain (ADG) and feed efficiency. Outcome measures for first-line treatment of BRD with tulathromycin included treatment outcome (treatment success, relapse, failure) and case fatality rate. Treatment outcome variables for subsequent BRD therapies are not reported in this paper due to the relatively small number of cases.

*Statistical Analysis*

Pen was used as the experimental unit for all analyses in both studies. In Study I, the PROC FREQ procedure of SAS (SAS Institute, Cary, NC) was used to calculate BRD morbidity for all treatment groups. Differences in BRD morbidity for metaphylaxis treatments versus (vs) control were separated using Fisher's Exact Test (one-sided; $P<0.05$). Similarly, comparisons among PMEP treatments were made using a 2-sided Fisher's Exact Test ($P<0.05$). The PROC MIXED procedure of SAS was used to evaluate the effect of treatment on all performance parameters and days to first incidence of BRD. The model included treatment as a fixed effect and block as a random effect. Pair-wise comparisons of treatment least squares means were tested ($P<0.05$) using the 2-sided Student's t-test.

In Study II the PROC MIXED procedure of SAS was also used to evaluate the effect of treatment on all outcomes variables. A slight modification was made in the statistical model for Study II vs Study I. As in Study I, the model in Study II included treatment as the only fixed effect, but where a statistically significant treatment effect was observed ($P<0.05$), treatment groups were compared in a pair-wise fashion. Additionally, a contrast was constructed to compare the pooled effect of metaphylaxis vs the control.

In a separate PROC MIXED analysis, percent morbidity, mortality and chronics were evaluated by categorizing the cattle based on temperature at arrival, within pen. This analysis thus included treatment, temperature and the treatment-by-temperature interaction as fixed effects. If the treatment-by-temperature interaction was statistically significant ($P<0.05$), within-temperature treatment effects were evaluated.

**Table 2.** Bovine respiratory disease (BRD) therapy outcome categories.

| BRD therapy response variable | Description |
|---|---|
| Treatment success | A calf recovered at day 3. Clinical illness score (CIS) =1 or CIS < initial CIS and temperature <104.0°F following antibiotic therapy, and shows no additional signs of BRD or requires no additional therapy for BRD within 21 days of the previous BRD therapy. |
| Treatment failure | A calf that at three days post-treatment for BRD has a CIS greater than the initial CIS or CIS is >1 and rectal temperature is ≥104.0°F. |
| Relapse | A calf with an improved CIS at three days post-treatment, but observed with signs of BRD (CIS ≥ 1) and has a rectal temperature ≥104°F within 21 days of the previous BRD therapy. |
| New episode | A calf diagnosed with BRD (CIS ≥1) and a rectal temperature ≥104°F >21 days following the previous BRD episode. |
| Chronic | A calf judged by the masked, attending veterinarian to have a debilitating health condition that prevents it from continuing with other calves on the study. |

Otherwise, the main effects of treatment and temperature were evaluated.

Similarly, the effect of gender (bulls versus steers), treatment and the interaction between gender and treatment on BRD morbidity, mortality, chronic rate, days on study at mortality, and fatal disease onset were evaluated as described above for temperature on arrival vs treatment.

## Results

*Study I*

Mean arrival rectal temperature for all calves in Study I was 102.9°F (39.4°C), and 10.2% of calves had a rectal temperature ≥104.0°F. Percentage of calves with arrival body temperature ≥104.0°F was 8.8, 6.3, 11.9 and 13.8 for control, 3-, 5- and 7-day PMEP groups, respectively. Metaphylaxis using tilmicosin reduced (P<0.01) BRD morbidity compared to controls; 33.8, 11.3, 8.8 and 8.8% for control, 3-, 5- and 7-day PMEP groups, respectively. There was no difference in the BRD morbidity rates among the three PMEP groups (Table 3).

Mean days to onset of BRD during the 60-day study period were 12.3, 12.1, 18.9 and 17.3 days for control, 3-, 5- and 7-day PMEP groups, respectively (P>0.05; Table 3). Mean rectal temperature of calves when first diagnosed with BRD was 105.6, 105.9, 105.7 and 105.6°F (40.9, 41.1, 40.9 and 40.9°C) for control, 3-, 5- and 7-day PMEP groups, respectively (P>0.05; Table 4).

Six calves in the 5-day PMEP group and eight in the 7-day group had signs of BRD (CIS≥2) prior to the completion of their respective PMEP. Rectal temperature was not determined in these calves, therefore it is unknown if the case definition (CIS≥2 and rectal temperature ≥104.0°F) for BRD was met. Of the six calves with BRD signs in the 5-day PMEP group, three were later clinically diagnosed with BRD. Three of the eight calves in the 7-day PMEP group were later diagnosed with BRD during the study period.

The success rate in calves treated for BRD with tulathromycin was 88.0% overall, and not different

**Table 3.** Study I. Health outcomes of control calves or calves treated metaphylactically with tilmicosin with various post-metaphylaxis evaluation periods (PMEPs).[c] Study duration was 60 days.

| Item | Control | 3-day PMEP | 5-day PMEP | 7-day PMEP |
|---|---|---|---|---|
| No. calves (pens) | 160 (8) | 160 (8) | 160 (8) | 160 (8) |
| Mean rectal temperature at processing, °F | 102.8 | 102.9 | 102.9 | 102.9 |
| Rectal temp ≥104.0°F at processing, % | 8.8 | 6.3 | 11.9 | 13.8 |
| BRD morbidity, n (%) | 54 (33.8)[a] | 18 (11.3)[b] | 14 (8.8)[b] | 14 (8.8)[b] |
| Mean days to BRD onset | 12.3 | 12.1 | 18.9 | 17.3 |
| Chronic (all causes),[d] n (%) | 2 (1.3) | 1 (0.6) | 0 | 1 (0.6) |
| BRD mortality, n | 0 | 0 | 0 | 0 |
| Total mortality, n (%) | 1 (0.6) | 0 | 0 | 0 |

[ab]Different superscripts in same row differ (P<0.01).
[c]Data presented as an arithmetic means and analyzed on a pen means basis.
[d]Chronic as identified on examination by the study veterinarian at completion of study.

**Table 4.** Study I. Treatment response of calves treated for clinical bovine respiratory disease (BRD) with tulathromycin. At processing, calves were assigned to a control group (no metaphylaxis) or received tilmicosin metaphylaxis with a 3-, 5- or 7-day post-metaphylaxis evaluation period (PMEP).[a]

| Item | Control | 3-day PMEP | 5-day PMEP | 7-day PMEP |
|---|---|---|---|---|
| No. calves treated | 54 | 18 | 14 | 14 |
| Mean rectal temperature when treated, °F | 105.6 | 105.9 | 105.7 | 105.6 |
| Treatment success, n (%) | 48 (88.8) | 14 (77.8) | 14 (100.0) | 12 (85.7) |
| Treatment relapse, n (%) | 5 (9.4) | 3 (16.7) | 0 | 1 (7.1) |
| Treatment failure, n (%) | 1 (1.9) | 1 (5.6) | 0 | 1 (7.1) |
| New episode, n | 1 | 0 | 0 | 0 |

[a]Data presented as an arithmetic means and analyzed on a pen means basis.

(P>0.05) between experimental groups; 88.8, 77.8, 100.0 and 85.7 for the control, 3-, 5- and 7-day PMEP groups, respectively (Table 4). Response rates for cattle treated with florfenicol or oxytetracycline were not analyzed due to the small number of cases. There were no deaths due to BRD during the study. One calf in the control group died of encephalitis.

Performance outcomes (Table 5) in Study I are presented on a "deads-out" basis because there was only one mortality. Total weight gain and ADG were improved (P<0.05) in all metaphylaxis groups compared to controls. During the study, calves in the 3-, 5- and 7-day PMEP groups gained 15, 20 and 21 lb (6.8, 9.1 and 9.5 kg), respectively, more than controls. There was no difference (P>0.05) in gain among calves in the three metaphylaxis treatment groups. Dry matter intake (DMI) of calves in the metaphylaxis groups was higher (P<0.05) than those in the control group; there was no difference (P>0.05) in DMI among the three metaphylaxis treatments. There were no differences (P>0.05) in feed conversion (feed:gain) among the four treatment groups.

Immunohistochemistry staining revealed that two calves were persistently infected (PI) with BVDV, one

**Table 5.** Study I. Growth performance of control calves or calves treated metaphylactically with tilmicosin with various post-metaphylaxis evaluation periods (PMEPs).[c] Study duration was 60 days. Dead animals were not included in calculations.

| | Control | 3-day PMEP | 5-day PMEP | 7-day PMEP |
|---|---|---|---|---|
| No. calves | 159 | 160 | 160 | 160 |
| Starting weight, lb | 516 | 515 | 520 | 519 |
| Total weight gain, lb | 224[a] | 239[b] | 244[b] | 245[b] |
| Body weight gain difference at 60 days, lb | -- | 15 | 20 | 21 |
| ADG,[d] lb | 3.74[a] | 3.99[b] | 4.06[b] | 4.08[b] |
| DMI,[e] lb/day | 17.2[a] | 18.4[b] | 18.3[b] | 18.4[b] |
| Feed:gain | 4.64 | 4.63 | 4.51 | 4.51 |

[ab]Different superscripts in same row differ (P<0.05).
[c]Data presented as an arithmetic means and analyzed on a pen means basis.
[d]ADG = average daily gain.
[e]DMI = dry matter intake.

**Table 6.** Study II. Health outcomes of control calves or calves treated metaphylactically with tilmicosin with various post-metaphylaxis evaluation periods (PMEPs).[d] Study duration was 60 days.

| Item | Control | 3-day PMEP | 5-day PMEP | 7-day PMEP | 10-day PMEP | P-value[e] |
|---|---|---|---|---|---|---|
| No. calves (pens) | 140 (7) | 140 (7) | 140 (7) | 140 (7) | 140 (7) | - |
| Mean rectal temperature at processing, °F | 103.9 | 103.9 | 103.8 | 103.9 | 103.9 | - |
| Rectal temp ≥ 104.0°F at processing, % | 35.7 | 43.6 | 35.0 | 40.7 | 42.9 | 0.82 |
| BRD morbidity, n (%) | 97 (69.3)[a] | 78 (55.7)[b] | 79 (56.4)[b] | 73 (52.1)[b] | 55 (39.3)[c] | <0.01 |
| Mean days to BRD onset | 6.3[a] | 8.2[a] | 11.0[b] | 15.1[b] | 15.0[b] | <0.01 |
| BRD mortality, n (%) | 13 (9.3) | 8 (5.7) | 9 (6.4) | 9 (6.4) | 13 (9.3) | 0.64 |
| Chronics,[f] n (%) | 12 (8.6) | 8 (5.7) | 11 (7.9) | 15 (10.7) | 10 (7.1) | 0.45 |
| BRD mortality + chronics,[f] n (%) | 25 (17.9) | 16 (11.4) | 20 (14.3) | 24 (17.1) | 23 (16.4) | 0.64 |

[abc]Where the main effect of treatment was statistically significant (P < 0.05), all possible pairs of outcomes were evaluated. Means with different superscripts within a row are significantly different (P<0.01).
[d]Data presented as arithmetic means and statistically analyzed on a pen means basis.
[e]Main effect of treatment.
[f]Chronic as identified on examination by the study veterinarian at the completion of the study.

in the 3-day PMEP group and one in the 7-day PMEP group. One of these calves was treated for BRD; both survived through the duration of the study. Only one other clinical BRD case occurred in the pens housing a PI calf, and there were no deaths. Average daily gain at study completion was 4.12 and 3.93 lb (1.87 and 1.79 kg)/day for calves in the 3-day PMEP and 7-day PMEP pens housing a PI calf, respectively, which is similar to the ADG for other calves in these treatments (Table 5).

*Study II*

Calves in the control group had a higher (P<0.05) BRD morbidity rate than calves treated metaphylactically, 69.3% vs an average of 50.9% in the four metaphylaxis groups (Table 6). The BRD morbidity rate was higher (P<0.05) in controls than any of the metaphylaxis groups (69.3, 55.7, 56.4, 52.1 and 39.3% for control, 3-, 5-, 7- and 10-day PMEP groups, respectively). The lowest (P<0.05) BRD morbidity rate was in the 10-day PMEP group. Mean days to first onset of BRD was 6.3, 8.2, 11.0, 15.1 and 15.0 days for control, 3-, 5-, 7- and 10-day PMEP groups, respectively. Mean days to first onset of BRD was longer (P<0.05) for the 5-, 7- and 10-day PMEP groups than the control and the 3-day PMEP group.

Mean arrival body temperature was identical (103.9°F; 39.9°C) in all treatment groups (Table 6). The percentage of calves with an arrival rectal temperature ≥104.0°F was 35.7, 43.6, 35.0, 40.7 and 42.9% for control, 3-, 5-, 7- and 10-day PMEP groups, respectively (P>0.05). The respiratory morbidity rate (61.9% vs 49.8%), respiratory mortality rate (11.9% vs 4.5%) and the prevalence of chronic cases (11.2% vs 5.9%) were higher (P<0.05) in calves with an arrival rectal temperature ≥104.0°F compared to calves with an arrival rectal temperature <104.0°F, regardless of treatment (data not shown).

The morbidity rate due to BRD was higher (57.4 vs 44.9%; P=0.01) in bull calves banded at arrival-processing compared to those arriving as steers (data not shown). The death rate due to BRD (8.3 vs 4.4%), and the chronic rate at the completion of the study (8.5 vs 6.3%), were numerically higher in bull calves banded at arrival, but the differences were not statistically significant (P>0.05). Likewise, the day of fatal disease onset and days-on-feed when calves died were not different (P>0.05) between steer calves and calves that arrived as bulls and banded at processing.

Twenty-nine calves (5.2%) had severe signs of BRD (CIS ≥4) prior to completion of their respective PMEP (Table 7). All calves in this category were pulled and treated. Tulathromycin was administered at label dose to one calf in the 3-day PMEP group, four calves in the 5-day group, nine calves in the 7-day group and 15 calves in the 10-day PMEP group. Relapses, treatment failures and case fatality rates were very high.

A total of 232 calves were observed with signs of BRD (CIS≥2 but <4) prior to completion of their PMEP, but 88 of these (38%) did not show signs of BRD after the PMEP (Table 8). The proportion of calves observed with BRD signs during the PMEP, but never treated for BRD after the evaluation period, was 9.1, 22.6, 39.7 and 53.6% in the 3-, 5-, 7- and 10-day PMEP groups, respectively. The proportion of calves not treated for BRD following the PMEP period increased numerically as the length of the assigned PMEP increased. The rectal temperature was not collected on calves observed with signs of BRD prior to the end of the PMEP unless the CIS was ≥4, therefore the number that actu-

**Table 7.** Study II. Response to treatment of bovine respiratory disease (BRD) with tulathromycin in calves diagnosed with BRD prior to completion of a 3-, 5-, 7- or 10-day post-metaphylaxis evaluation period (PMEP) due to severe clinical signs (CIS≥4) of BRD. Data not analyzed for statistical significance.

| Item | 3-day PMEP | 5-day PMEP | 7-day PMEP | 10-day PMEP |
|---|---|---|---|---|
| No. calves | 1 | 4 | 9 | 15 |
| Mean rectal temperature, °F | 105.2 | 106.6 | 106.4 | 106.4 |
| Treatment successes, n (%) | 0 (0) | 1 (25.0) | 4 (44.4) | 5 (33.3) |
| Treatment relapses, n (%) | 0 (0) | 1 (25.0) | 1 (11.1) | 5 (33.3) |
| Treatment failures, n (%) | 1 (100.0) | 2 (50.0) | 4 (44.4) | 5 (33.3) |
| BRD mortality, n[a] | 1 | 1 | 4 | 7 |
| Case fatality rate, % | 100.0 | 25.0 | 44.4 | 47.7 |
| Chronics, n[b] | 0 | 2 | 3 | 1 |
| Pen deads not treated, n[c] | 0 | 0 | 1 | 3 |

[a]Mortality occurred at some time during the study and not necessarily during PMEP.
[b]Chronic as identified on examination by the study veterinarian at the completion of the study.
[c]Found dead in the pen during the PMEP and not treated.

ally met the case definition for BRD (rectal temperature ≥104.0°F) is unknown. Additional information is presented in Table 8.

Mean rectal temperature of calves when first diagnosed with BRD was 105.8, 105.6, 105.5, 105.1 and 105.5°F (41.0, 40.9, 40.8, 40.6 and 40.8°C) for the control, 3-, 5-, 7- and 10-day PMEP groups, respectively, and were not different (P>0.05; Table 9). Overall treatment success for calves treated with tulathromycin for clinical BRD was 66.8%, and was similar in all treatment groups. The treatment success rate for calves treated with tulathromycin was 65.6, 73.1, 68.4, 69.4 and 52.9% for control, 3-, 5-, 7- and 10-day PMEP groups, respectively (P>0.05). Similarly, there was no difference in treatment relapse or treatment failure rates in calves treated with tulathromycin.

Fifty-two (7.4%) calves died of BRD during the study. Mortality rates due to BRD were 9.3, 5.7, 6.4, 6.4 and 9.3% in the control, 3-, 5-, 7- and 10-day PMEP groups, respectively (Table 6). The chronic rate at the end of the study was 8.6, 5.7, 7.9, 10.7 and 7.1% for the control, 3-, 5-, 7- and 10-day PMEP groups, respectively. Mortality and chronic rates were similar (P>0.05) among treatments.

Dry matter intake, total weight gain, ADG and feed efficiency were calculated on both a "deads in–



**Table 8.** Study II. Time bovine respiratory disease (BRD) observations were made prior to completion of a 3-, 5-, 7- or 10-day post-metaphylaxis evaluation period (PMEP). Data not analyzed for statistical significance.

| Item | 3-day PMEP | 5-day PMEP | 7-day PMEP | 10-day PMEP |
|---|---|---|---|---|
| **All Calves[a]** | | | | |
| No. calves | 22 | 53 | 73 | 84 |
| Mean days with BRD observations prior to completion of PMEP | 1.1 | 1.6 | 1.8 | 2.5 |
| Range of days with BRD observations prior to completion of PMEP | 1-2 | 1-4 | 1-4 | 1-6 |
| **Calves Never Diagnosed with BRD following the PMEP[b]** | | | | |
| No. calves | 2 | 12 | 29 | 45 |
| Mean days of BRD observations prior to completion of PMEP | 1.0 | 1.4 | 1.6 | 1.8 |
| Range of days with BRD observations prior to completion of PMEP | 1 | 1-3 | 1-4 | 1-5 |

[a]All calves = calves observed with signs of BRD during their respective PMEP.
[b]Calves never diagnosed with BRD during the study = calves observed with signs of BRD during their respective PMEP, but were not diagnosed (treated) for BRD during the remainder of the study.

**Table 9.** Study II. Treatment response of calves treated for clinical bovine respiratory disease (BRD) with tulathromycin. At processing, calves were assigned to a control group (no metaphylaxis) or received tilmicosin metaphylaxis with a 3-, 5-, 7- or 10-day post-metaphylaxis evaluation period (PMEP).[a]

| Item | Control | 3-day PMEP | 5-day PMEP | 7-day PMEP | 10-day PMEP | P-value[b] |
|---|---|---|---|---|---|---|
| No. calves | 96 | 78 | 79 | 72 | 51 | - |
| Mean rectal temperature when pulled for BRD, °F | 105.8 | 105.6 | 105.5 | 105.1 | 105.5 | - |
| Treatment successes, n (%) | 63 (65.6) | 57 (73.1) | 54 (68.4) | 50 (69.4) | 27 (52.9) | 0.46 |
| Treatment relapses, n (%) | 22 (22.9) | 15 (19.2) | 13 (16.5) | 15 (20.8) | 16 (31.4) | 0.78 |
| Treatment failures, n (%) | 11 (11.5) | 6 (7.7) | 12 (15.2) | 7 (9.7) | 8 (15.7) | 0.57 |
| New episodes, n (%) | 4 (4.2) | 2 (2.6) | 2 (2.5) | 6 (8.3) | 2 (3.9) | 0.42 |
| Case fatality rate, % | 12.5 | 10.3 | 11.4 | 11.1 | 17.6 | 0.78 |

[a] Data presented as arithmetic means and statistically analyzed on a pen means basis.
[b] Main effect of treatment.

chronics in" and a "deads out–chronics out" basis. No differences were observed among treatment groups for any growth performance parameters measured (P>0.05; Tables 10 and 11).

Based on testing of ear notch samples, none of the calves in Study II were PI with BVDV.

## Discussion

These two studies demonstrated the value of metaphylaxis using tilmicosin to control BRD in high-risk calves, which is in agreement with earlier reports.[1,4,5,8,9,10,11,12,13,18] The overall incidence of BRD was reduced by 72.0% (33.8% in control vs 9.6% in metaphylaxis groups) in Study I (P<0.01), and 26.6% (69.3% in control vs 50.9% in metaphylaxis groups) in Study II (P<0.05). Although the BRD morbidity rate in metaphylaxis groups in Study II was significantly lower than controls, the magnitude of metaphylaxis effect on morbidity was less pronounced than in Study I.

Cattle treated metaphylactically with tilmicosin in Study I had a significant improvement in feeding performance compared to controls. Improvement in weight gain and feed conversion has been demonstrated in other studies,[1,9,12,13,18] and is likely attributed to the reduction in BRD, 72% in Study I. However, a similar improvement in feeding performance was not observed in Study II. The lack of performance improvement in Study II compared to Study I and other tilmicosin metaphylaxis studies[1,9,12,13,18] could have been

**Table 10.** Study II. Growth performance of control calves or calves treated metaphylactically with tilmicosin with various post-metaphylaxis evaluation periods (PMEP). Study duration was 60 days. Data from chronic and dead calves are not included in calculations.[a]

| Item | Control | 3-day PMEP | 5-day PMEP | 7-day PMEP | 10-day PMEP | P-value[b] |
|---|---|---|---|---|---|---|
| No. calves | 115 | 124 | 120 | 116 | 117 | - |
| No. pens | 7 | 7 | 7 | 7 | 7 | - |
| Starting weight, lb | 574.0 | 566.3 | 568.3 | 564.5 | 566.5 | 0.99 |
| Final weight, lb | 749.7 | 742.5 | 746.7 | 732.1 | 737.1 | 0.94 |
| Total weight gain, lb | 175.7 | 176.1 | 178.4 | 167.5 | 170.6 | 0.78 |
| ADG,[c] lb | 2.94 | 2.95 | 2.98 | 2.80 | 2.85 | 0.80 |
| DMI,[d] lb | 14.8 | 15.7 | 14.7 | 14.4 | 14.4 | 0.26 |
| Feed:gain | 5.03 | 5.31 | 4.94 | 5.16 | 5.09 | 0.68 |

[a]Data presented as arithmetic means and statistically analyzed on a pen means basis.
[b]Main effect of treatment.
[c]ADG = average daily gain.
[d]DMI = dry matter intake.

**Table 11.** Study II. Growth performance of control calves or calves treated metaphylactically with tilmicosin with various post-metaphylaxis evaluation periods (PMEP). Study duration was 60 days. Data from chronic and dead calves are included in calculations.[a]

| Item | Control | 3-day PMEP | 5-day PMEP | 7-day PMEP | 10-day PMEP | P-value[b] |
|---|---|---|---|---|---|---|
| No. calves | 140 | 140 | 140 | 140 | 140 | - |
| No. pens | 7 | 7 | 7 | 7 | 7 | - |
| Starting weight, lb | 574.2 | 566.9 | 567.1 | 562.5 | 565.9 | 0.99 |
| Final weight, lb | 668.5 | 691.2 | 686.5 | 671.6 | 659.6 | 0.88 |
| Total weight gain, lb | 94.3 | 124.3 | 119.4 | 109.0 | 93.7 | 0.66 |
| ADG,[c] lb | 1.67 | 2.16 | 2.06 | 1.89 | 1.64 | 0.67 |
| DMI,[d] lb | 14.7 | 15.6 | 14.7 | 14.4 | 14.3 | 0.27 |
| Feed:gain | 8.80 | 7.21 | 7.12 | 7.60 | 8.73 | 0.59 |

[a]Data presented as arithmetic means and statistically analyzed on a pen means basis.
[b]Main effect of treatment.
[c]ADG = average daily gain.
[d]DMI = dry matter intake.

related to a number of factors including source, high morbidity rates, the large number of bulls that had to be castrated at arrival, and adverse weather.

Bull calves received in Study II had a significant effect on the outcome of parameters measured. This was further magnified by the larger proportion of bulls in the study in relation to steers, 542 vs 142 head, respectively. The higher BRD morbidity rate (57.4 vs 44.9%), death rate (8.3 vs 4.4%) and chronic rate (8.5 vs 6.3%) in bull calves banded at arrival strongly supports discounting the purchase price of bulls in the marketplace. The health and performance liabilities of bull calves was reported nearly 30 years ago,[19] and yet bulls are commonly purchased by stocker and feeder operations. Data in this study supports aggressive health management of bull calves by veterinarians and producers.

In Study II, the incidence of BRD was less ($P<0.05$) in the 10-day PMEP group relative to other treatments. However, it appears a number of calves in the 10-day group should have been treated earlier based on the death rate due to BRD (Table 6) and the poor performance calculated on a deads-in and chronics-in basis (Table 11), compared to the other metaphylaxis treatment groups with shorter PMEPs. Likewise, the number of chronic calves in the 7-day PMEP group was numerically higher than other groups at the end of the study.

These two studies demonstrate that evaluation periods longer than two to three days can be utilized following metaphylaxis with tilmicosin in calves at high risk for BRD. Data from Study I suggest a 7-day PMEP may be appropriate; the BRD morbidity and mortality rates were not increased with the extended PMEP, and growth performance was similar to the shorter PMEP groups. Even with very high-risk calves, as in Study II, an extended evaluation period is logical, however, results of this study suggest seven days and 10 days may be too long given the high chronic rate in the 7-day group and the high mortality rate in the 10-day PMEP group.

Differences in health performance between the two studies are noteworthy. Although location, ration, processing procedures, antibiotic programs and overall management were identical in both studies, a number of BRD risk factors were different. Obvious differences between calves in the two studies that increased risk for calves in Study II were source (more southeastern calves), season (winter vs spring) and a higher proportion of bulls in the population.

The response to metaphylactic treatment with tilmicosin and first-line BRD therapy with tulathromycin was higher in Study I than in Study II. While it is often tempting to attribute a poor response to metaphylaxis to antibiotic failure, other significant variables such as environmental conditions and management factors that impair the immune response to infectious processes are at least equally important.

The ultimate goal of an extended post-metaphylaxis evaluation period is to reduce unnecessary BRD treatments without an increase in BRD mortality and chronic cases. In Study II, 232 calves (Table 8) showed clinical signs of BRD (CIS≥2 but <4) during their respective PMEP, which represents 41% of the calves that were treated metaphylactically with tilmicosin at processing. Eighty-eight (38%) of these calves did not show clinical signs of BRD after the respective PMEP passed. In these calves, it is possible that there was spontaneous remission of disease, but more likely these clinical signs were related to stress, fatigue or poor body condition that caused pen checkers to score the calves as reported. As a result of protocol compliance, these 88 calves were never treated, and did not show clinical signs after the PMEP.

Twenty-nine calves (5.2%) in metaphylaxis treatment groups in Study II had CIS ≥4 during their respective PMEP and were treated with tulathromycin. Treatment successes in these calves ranged from 0 to 44%, and case fatality rates ranged from 25 to 100%, supporting our suspicion that many of these calves were diseased at arrival. Under these conditions, health and performance outcomes are frequently compromised.

## Conclusions

These studies help define reasonable PMEPs in calves with different risk levels that received respiratory metaphylaxis with tilmicosin at processing. Two potential errors can occur when making a BRD treatment decision. First is evaluating and treating calves too early in the PMEP, which may result in unnecessary hospital treatments and associated medicine costs. The second error is failure to intervene early enough in calves at higher risk for BRD that are truly ill, thus potentially increasing the BRD mortality case fatality rate and incidence of chronic cases. In Study I, a 7-day PMEP was appropriate given the level of risk in these calves, whereas a 7- or 10-day PMEP was likely excessive in Study II.

## Endnotes

[a]Micotil® 300 Injection, Elanco Animal Health, Greenfield, IN 46140

[b]Jencine® 4, Schering-Plough Animal Health, Union, NJ 07083 (Study I)

[c]Vista™ SQ 5, Intervet Inc, Millsboro, DE 19966 (Study II)

[d]Covexin® 8, Schering-Plough Animal Health, Union, NJ 07083

[e]Ivomec Plus Injection for Cattle, Merial, Duluth, GA 30096 (Study I)
[f]Safe-Guard® Dewormer for Beef & Dairy Cattle and Goats, Intervet Inc, Millsboro, DE 19966 (Study II)
[g]Ralgro® Implants, Schering-Plough Animal Health, Union, NJ 07083
[h]Callicrate Smart Bander®, No-Bull Enterprises LLC, St. Francis, KS 67756
[i]Rumensin®, Elanco Animal Health, Greenfield, IN 46140
[j]Tylan®, Elanco Animal Health, Greenfield, IN 46140
[k]Draxxin™, Pfizer Animal Health, New York, NY 10017
[l]Nuflor®, Schering-Plough Animal Health, Union, NJ 07083
[m]Biomycin 200®, Boehringer Ingelheim, VETMEDICA, St. Joseph, MO 64506
[n]Tripelennamine hydrochloride, VetTek™, Blue Springs, MO 64014

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