

# Effects of two different doses of tilmicosin on pathogen load reduction and clinical outcome in feedlot cattle with naturally occurring bovine respiratory disease

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## Abstract

The objective of this study was to determine the effect of 2 different doses of tilmicosin on pathogen load reduction and clinical outcome in feedlot cattle experiencing acute bovine respiratory disease (BRD). Cattle diagnosed with BRD were randomly assigned to 1 of 3 treatments: tilmicosin at 4.55 mg/lb (10 mg/kg) (TIL10); tilmicosin at 9.1 mg/lb (20 mg/kg) (TIL20); or untreated positive controls (POSCON). Cohorts were completed with an apparently healthy asymptomatic negative control (ASYMP). A total of 143 animals were enrolled in the study. Treating cattle with tilmicosin at 9.1 mg/lb (20 mg/kg) resulted in greater pathogen load reduction and equivalent or improved clinical response compared to a dose of 4.55 mg/lb (10 mg/kg). Cattle in the TIL10 and TIL20 treatments had reduced pathogen loads and increased survival rates compared to POSCON ( $P < 0.05$ ). The *Mannheimia haemolytica* numbers in the lungs were significantly reduced in the TIL20 treatment group on day 9 compared to TIL10 ( $P < 0.05$ ). Survival of calves in the TIL10 and TIL20 groups did not differ ( $P > 0.05$ ) from ASYMP, but was decreased ( $P < 0.05$ ) in POSCON calves compared to other treatments.

**Key words:** bovine respiratory disease, BRD, feedlot, treatment, tilmicosin

## Résumé

L'objectif de cette étude était de déterminer l'effet de deux doses différentes de tilmicosine sur la réduction de la charge en agents pathogènes et les résultats cliniques chez des bovins en parc d'élevage affectés par le complexe respiratoire bovin. Les bovins diagnostiqués avec le complexe respiratoire bovin ont été assignés aléatoirement dans trois traitements : 1) tilmicosine à la concentration de 4.55 mg/lb (10 mg/kg) (TIL10), 2) tilmicosine à la concentration de 9.1 mg/lb (20 mg/kg) (TIL20), ou 3) témoin positif sans traitement (POSCON). On a aussi rajouté un groupe témoin négatif

comportant des animaux asymptomatiques apparemment sains (ASYMP). L'étude comportait 143 animaux au total. Il y a eu une plus grande réduction de la charge en agents pathogènes dans le traitement TIL20 que dans le traitement TIL10. Le résultat clinique dans le traitement TIL20 était similaire ou meilleur que celui dans le traitement TIL10. Les bovins dans les traitements TIL10 et TIL20 avaient une charge en agents pathogènes moindre et un taux de survie plus élevé que les bovins dans le traitement POSCON ( $P < 0.05$ ). Le nombre de *Mannheimia haemolytica* dans les poumons était significativement moins élevé dans le traitement TIL20 au jour 9 que dans le traitement TIL10 ( $P < 0.05$ ). Le taux de survie des veaux dans le traitement TIL10 et dans le traitement TIL20 n'était pas différent ( $P > 0.05$ ) de celui dans le traitement ASYMP mais était moindre ( $P < 0.05$ ) chez les veaux du traitement POSCON que chez les veaux des autres traitements.

## Introduction

Tilmicosin<sup>a</sup> is a macrolide antimicrobial drug labeled in North America for treatment and reduction of morbidity in feedlot cattle associated with bovine respiratory disease (BRD).<sup>5</sup> The deleterious effects of BRD on health and well-being of beef cattle and the economic prospects of cattle owners are well documented in peer-reviewed literature.<sup>9</sup>

When first approved for use in the United States, tilmicosin was labeled for administration at a dose of 4.55 mg/lb (10 mg/kg) bodyweight (BW).<sup>5</sup> Earlier research conducted in partial fulfillment of North American approval requirements demonstrated cattle treated for clinical BRD at doses of 2.28, 4.55, and 9.1 mg/lb (5, 10, and 20 mg/kg) BW tilmicosin had a significant reduction in case fatality rate and body temperature while also gaining more weight than placebo-treated cattle.<sup>6</sup> The only significant difference observed in treated cattle was a reduction in mean body temperature for the first 10 days following treatment in cattle receiving 9.1 mg/lb (20 mg/kg) BW tilmicosin compared to those administered 2.28 mg/lb (5 mg/kg) BW.<sup>6</sup>

In 2009, a label claim extension for tilmicosin was granted in the United States allowing for a flexible dose range of 4.55 mg/lb (10 mg/kg) BW to 9.1 mg/lb (20 mg/kg) BW for treatment and control of BRD.<sup>5</sup> The same year, 2 studies reported the effects of dose on the clinical efficacy of tilmicosin administered metaphylactically at initial processing.<sup>4</sup> Doses of 4.55 mg/lb (10 mg/kg) BW and 9.1 mg/lb (20 mg/kg) BW (calculated using individual animal BW) were compared to untreated negative controls. In the first study, cattle receiving tilmicosin at initial processing experienced significantly less BRD morbidity and mortality compared to negative controls. Morbidity attributable to BRD was significantly reduced in cattle receiving 9.1 mg/lb (20 mg/kg) BW tilmicosin (16.8%) compared to those administered 4.55 mg/lb (10 mg/kg) BW tilmicosin (24.3%) and negative controls (34.0%). In the second study, BRD morbidity was significantly reduced in treated cattle compared to negative controls (68.5%), but no differences were seen between groups treated with the 2 dosages of tilmicosin, 49.9% and 44.0% for 4.55 mg/lb and 9.1 mg/lb (10 mg/kg and 20 mg/kg) treatments, respectively.<sup>4</sup>

More recently, researchers evaluated the effects of tilmicosin administered at 6.75 mg/lb (14.85 mg/kg) BW on *Mannheimia haemolytica* and *Histophilus somni* concentrations in bronchial lavage (BL) fluid recovered from feedlot cattle with naturally occurring BRD.<sup>1</sup> *M. haemolytica* concentrations in treated animals, as determined by serial dilution and quantification, were significantly reduced at 72, 144, and 216 hours post-treatment compared to untreated controls. Additionally, treated cattle had significantly lower mean rectal temperatures and clinical respiratory and depression scores compared to controls at all post-treatment time points.<sup>1</sup>

The objective of the present study was to determine the effects of 2 different tilmicosin doses on bacterial pathogen load in the lungs and clinical outcome in newly received feedlot cattle with naturally occurring BRD.

## Materials and Methods

### Study Animals

The Johnson Research, LLC, Institutional Animal Care and Use Committee approved the protocol for this study. In May and June of 2013, a total of 5 shipments of uniform beef calves and lightweight yearlings at high risk of developing BRD (mixed origin, no known history of vaccination or antimicrobial therapy) were purchased in small groups from public auction markets in central California. The cattle and procurement methods were typical for cattle purchased for backgrounding at feedyards in the Pacific Northwest during late spring and early summer. Following purchase and assembly of truckload lots, study animals were held at the auction market for an additional 24 to 48 hours before being transported by truck to the research feedlot in Parma, Idaho. After arrival, cattle were provided access to

automatic waterers and allowed to rest for 12 to 30 hours prior to processing.

Processing procedures varied slightly among loads; however, all cattle received uniquely numbered visual ear tags, an injectable anthelmintic<sup>b</sup>, and a pentavalent modified-live virus vaccine<sup>c</sup> containing bovine herpesvirus-1, bovine viral diarrhea virus types 1 and 2, bovine parainfluenza virus type-3, and bovine respiratory syncytial virus antigens. Loads 1 and 2 also received an 8-way<sup>d</sup> or 9-way<sup>e</sup> clostridial bacterin-toxoid, respectively, and steers received a growth-promoting implant<sup>f</sup> subcutaneously in the dorsal aspect of the right ear. Cattle were not given bacterin-toxoids for *M. haemolytica*, *Pasteurella multocida*, or *Histophilus somni*, nor did they receive an antimicrobial for the control of BRD (metaphylaxis) at initial processing.

Following processing, cattle were housed in open-air, dirt-floor pens with dimensions of 25 by 70 feet (7.6 by 21.3 m) at an initial density of 20 ± 3 animals/pen, providing approximately 15 inches (38 cm) of linear bunk space and 87.5 ft<sup>2</sup> (8.1 m<sup>2</sup>) of pen space/animal. A balanced feedlot starter ration containing monensin sodium<sup>g</sup> and tylosin phosphate<sup>h</sup> was provided once daily. Water was provided *ad libitum* via automatic waterers, which were shared between adjacent pens.

Animal health observations were conducted each morning to monitor for development of clinical signs of BRD. A clinical impression score (CIS) adapted from pivotal studies involving tilmicosin was assigned on a 4-point scale (0 to 3) for respiration and signs of general depression (Table 1).<sup>5</sup> Animals assigned a score of 1 for both respiration and depression or ≥ 2 in either category were removed from the pen and brought to the feedlot hospital, where the rectal temperature was obtained using a digital thermometer<sup>i</sup>. Case definition was met with a CIS ≥ 2 and rectal temperature ≥ 104°F (40.0°C). Forms for recording daily observations and CIS scores were designed such that the animal health evaluator (HMT) could not readily ascertain scores assigned on previous days.

### Experimental Design

Cattle meeting the case definition were enrolled in the study and randomly assigned to 1 of 3 treatments within a cohort. Treatments were pre-randomized using a spreadsheet software program<sup>j</sup> and assigned to animals in the order in which they presented to the chute. Treatments for BRD cases were: tilmicosin at a dose of 4.55 mg/lb (10 mg/kg) BW (TIL10); tilmicosin at a dose of 9.1 mg/lb (20 mg/kg) BW (TIL20); or untreated positive controls (POSCON). Four-animal cohorts were completed with the enrollment of a clinically normal asymptomatic negative control (ASYMP). Each cohort remained open for enrollment for up to 36 hours after enrollment of the first case or until 2 additional cases were added to complete the cohort. If after 36 hours a cohort could not be completed, it was closed for enrollment and the original case(s) and ASYMP animal remained as a partial cohort.

### Asymptomatic Negative Controls

On the same day that a cohort was opened for enrollment, an ASYMP animal was also enrolled. These cattle were clinically normal (CIS = 0) with a rectal temperature < 103°F (39.5°C). ASYMP animals were housed in a separate pen in order to limit direct contact with animals enrolled as cases and candidate animals not yet enrolled in the study. When labor availability allowed, an additional ASYMP animal was added to a cohort during the 36-hour enrollment window such that all cohorts included a minimum of 1 and up to 2 ASYMP animals. This measure was intended to account for the potential loss of ASYMP cattle due to the development of BRD during the observation period.

### Day 0 Sampling Procedure

Following enrollment, approximately half of the animals (cohorts 1 to 12, 14, 16, 18, 20, 22, 24, and 26) enrolled in the study were subjected to a deep nasal swab (DNS) as part of a parallel study. Following the DNS, a bronchial lavage (BL) was performed using a previously described technique.<sup>1</sup> Following BL, whole blood was collected via jugular venipuncture from all cattle and saved for later analysis as part of a second parallel study.

### Day 3 Sampling Procedure

Following health observations in the pen on day 3, previously enrolled cattle were brought to the chute for additional observations and sampling. Body weight and rectal temperature were recorded, DNS and BL were repeated, and blood samples were again collected.

### Day 6 and Day 9 Sampling Procedure

On days 6 and 9, cattle enrolled in the study were observed in the pen and assigned a CIS. Study animals were then moved to the chute, where BW and rectal temperature were recorded and DNS and BL procedures were repeated. Following final study observations and sampling on day 9, any POSCON animal still demonstrating clinical signs consistent with BRD was treated and released from the chute.

### Test Article and Treatment Administration

After collection of microbiological and blood samples

on day 0, tilimicosin was administered subcutaneously per label instructions to animals assigned to the TIL10 and TIL20 treatment groups. Animals assigned to the POSCON and ASYMP treatments were released without antimicrobial therapy. For the remainder of the 9-day observation period, TIL10, TIL20, and POSCON treatments were commingled in specially designated hospital pens. The animal health evaluator was not blinded to treatment assignment; however, no visual indicator was used to distinguish between treatment assignments so as to limit the potential for assessment bias during daily health observations. Furthermore, the health evaluator was not blinded as to the treatment assignment of ASYMP animals due to the need for maintaining them in a separate pen to avoid commingling with clinically ill cattle.

Following treatment assignment and day 0 procedures, TIL10, TIL20, and POSCON cattle were not eligible for additional therapy until after final observations and sample collection on day 9. Animals that became moribund (depression score = 3), unable to reach feed and/or water, or that were otherwise deemed unlikely to recover were euthanized by penetrating captive bolt per guidelines developed by the American Association of Bovine Practitioners Animal Welfare Committee.<sup>2</sup> Death was confirmed by absence of a corneal reflex and cessation of visible respiration.

### Mortality Procedures

A necropsy was performed on all animals that were euthanized or succumbed during the 9-day observation period. Additionally, a final BL sample was collected by removing the larynx, trachea, heart, and lungs, placing them in normal anatomic orientation, and lavaging the lungs using a procedure similar to that described for live animals. Recovered lavage samples were transported to the laboratory for subsequent dilution, culture, speciation, and quantification.

### Microbiological Procedures

Recovered BL samples were transported on ice to an on-site microbiology laboratory where stock samples were diluted logarithmically in phosphate-buffered saline and plated on a previously described selective growth medium.<sup>8</sup> Sterile borosilicate glass beads<sup>k</sup> were utilized to ensure an even distribution of diluted BL fluid on the surface of the selective media.

**Table 1.** Clinical impression score (CIS) definitions.\*

| Score      | Clinical signs  |   |
|------------|---|---|
|            | Depression  | Respiratory   |
| 0-none     | Clinically normal animal  | Clinically normal animal  |
| 1-mild     | Stands or lies isolated from other cattle with head drooped. Responds to visual stimulation, moves away from observer | Serous nasal or ocular discharge, dry cough and/or elevated respiratory rate, subtle excessive salivation, dehydration                                |
| 2-moderate | Drooped head, slower to respond to the observer. Difficulty standing, lack of stretching and may knuckle when walking | Purulent or muco-purulent nasal and/or ocular discharge, productive cough and forced respiratory effort, excessive salivation, pronounced dehydration |
| 3-severe   | Moribund  | Open-mouth breathing, dyspnea, excessive salivation   |

\*From Corbin MJ, Gould JA, Carter BL, McClary DG, Portillo TA. Effects and economic implications of metaphylactic treatment of feeder cattle with two different dosages of tilimicosin on the incidence of bovine respiratory disease (BRD) - a summary of two studies. *Bov Pract* 2009; 43:140-152. Used with permission.

Plates were incubated overnight at 95.7°F (35.4°C) and evaluated at 18 and 42 hours post-inoculation for growth of *M. haemolytica* and *P. multocida*. *M. haemolytica* and *P. multocida* suspects were subjected to benchtop biochemical tests, which included oxidase, catalase, and indole spot tests. A preliminary count of suspected *M. haemolytica* and *P. multocida* colonies was recorded, and up to 3 representative colonies of each species were subcultured onto Columbia blood agar. Subcultures were allowed to incubate overnight, and benchtop biochemical tests were repeated the following day. At that time, the corresponding colony counts were recorded as either confirmed or unconfirmed. Suspect colonies with discordant results were referred to a diagnostic laboratory<sup>1</sup> for additional testing.

In the event that only 1 or 2 of the representative isolates could be confirmed as the pathogen of interest, CFU counts were adjusted proportionally prior to statistical analysis.

#### Statistical Analysis

Data were tabulated in a spreadsheet software program<sup>1</sup> and exported to a statistical software program<sup>2</sup> for analysis.

Pathogen load least squares means were calculated by treatment and compared over time using RMANOVA. Temperature and CIS data were dichotomized to 1 (rectal temperature  $\geq 104^\circ\text{F}$  (40.0°C); depression and/or respiratory score  $\geq 1$ ) or 0 (rectal temperature  $\leq 104^\circ\text{F}$  (40.0°C); depression and/or respiratory score = 0) and analyzed using Fisher's exact test. Body weight data were calculated as a percent change from weight on day 0 and analyzed using RMANOVA. Results were compared within treatment over time and among treatments at each time point.

Likelihood of death based on pathogen CFU/ml was computed for *M. haemolytica* and *P. multocida* using day 9 CFU data or the last available CFU value. Odds ratios and estimated 95% confidence intervals were calculated using logistic regression. Survival statistics were computed using Fisher's exact test. Results were considered significant at  $P < 0.05$ .

## Results

Thirty-six cohorts (28 full, 8 partial) were enrolled in the study, representing a total of 143 animals. Fifteen animals experienced an adverse outcome during the course of the study, which was defined as euthanasia for humane reasons or death due to natural causes. One ASYMP animal was treated, removed from the study, and excluded from statistical analysis due to development of clinical signs consistent with BRD during the 9-day observation period.

At the time of enrollment, *M. haemolytica* numbers (CFU/ml) in lung-derived samples were significantly greater ( $P < 0.05$ ) in cases (TIL10, TIL20, and POSCON) compared to ASYMP animals. On day 3, *M. haemolytica* numbers in TIL10 and TIL20 treatments were significantly reduced ( $P < 0.05$ ) compared to POSCON. By day 9, there was no difference ( $P > 0.05$ ) in *M. haemolytica* numbers between ASYMP, POSCON, and TIL10 treatments. Day 9 *M. haemolytica* numbers of the TIL20 treatment group were equivalent ( $P > 0.05$ ) to the ASYMP treatment and significantly reduced ( $P < 0.05$ ) compared to the TIL10 and POSCON treatments (Table 2). Across all treatments, for every 1-log increase in *M. haemolytica* numbers, likelihood of death increased by a factor of 1.29 (OR = 1.29, 95% CI: 1.16 to 1.44) ( $P < 0.05$ ) (Figure 1).

**Table 2.** Lung pathogen load (cfu/mL) change over time.†

| Variable              | ASYMP <sup>1</sup>   | POSCON <sup>2</sup>  | TIL10 <sup>3</sup>   | TIL20 <sup>4</sup>   |
|-----------------------|----------------------|----------------------|----------------------|----------------------|
| <i>M. haemolytica</i> |                      |                      |                      |                      |
| Day 0                 | 96.95 <sup>a**</sup> | 1195.43 <sup>b</sup> | 874.68 <sup>b</sup>  | 1708.75 <sup>b</sup> |
| 3                     | 65.09 <sup>a</sup>   | 857.60 <sup>c</sup>  | 18.45 <sup>*ab</sup> | 2.23 <sup>*b</sup>   |
| 6                     | 21.22 <sup>a</sup>   | 51.48 <sup>*a</sup>  | 18.02 <sup>*a</sup>  | 6.37 <sup>*a</sup>   |
| 9                     | 8.89 <sup>*abc</sup> | 80.54 <sup>*b</sup>  | 26.80 <sup>*ab</sup> | 1.71 <sup>*c</sup>   |
| <i>P. multocida</i>   |                      |                      |                      |                      |
| Day 0                 | 35.87 <sup>a</sup>   | 31.93 <sup>a</sup>   | 26.30 <sup>a</sup>   | 53.32 <sup>a</sup>   |
| 3                     | 61.63 <sup>a</sup>   | 63.43 <sup>a</sup>   | 2.93 <sup>*b</sup>   | 1.57 <sup>*b</sup>   |
| 6                     | 16.81 <sup>ab</sup>  | 110.43 <sup>a</sup>  | 14.22 <sup>ab</sup>  | 1.42 <sup>*b</sup>   |
| 9                     | 28.71 <sup>a</sup>   | 342.20 <sup>*b</sup> | 17.35 <sup>a</sup>   | 14.13 <sup>a</sup>   |

†Repeated measures analysis of variance (day 0 = time 0). Values reported above are geometric least squares means.

\*Within treatment, day 0 different from day 3, 6, or 9 at  $P < 0.05$ .

\*\*abc Within day, values with no common letters are significantly different at  $P < 0.05$ .

<sup>1</sup>Cattle in the ASYMP group were clinically normal (CIS = 0), had a rectal temperature  $< 103^\circ\text{F}$  (39.5°C), and did not receive antimicrobial therapy.

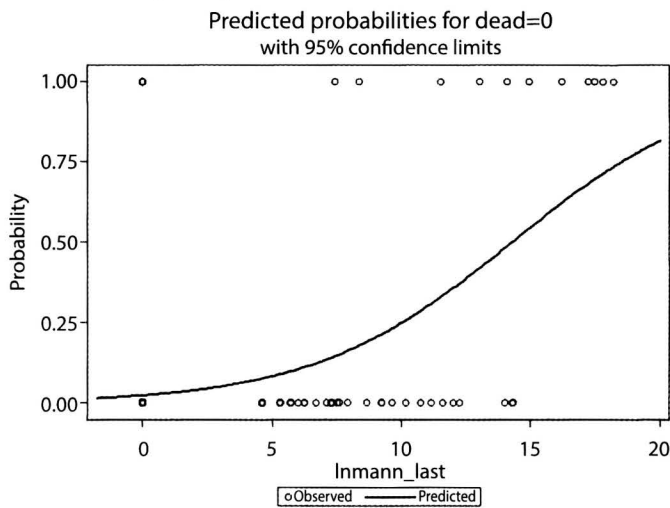
<sup>2</sup>Cattle in the POSCON group showed clinical signs of bovine respiratory disease (CIS  $\geq 2$ ), had a rectal temperature  $\geq 104^\circ\text{F}$  (40.0°C), and did not receive antimicrobial therapy.

<sup>3</sup>Cattle in the TIL10 group showed clinical signs of bovine respiratory disease (CIS  $\geq 2$ ), had a rectal temperature  $\geq 104^\circ\text{F}$  (40.0°C), and were treated with tilmicosin (Micotil® 300 Injection, Elanco Animal Health, Greenfield, IN) at a dose of 4.55 mg/lb (10 mg/kg) BW.

<sup>4</sup>Cattle in the TIL20 group showed clinical signs of bovine respiratory disease (CIS  $\geq 2$ ), had a rectal temperature  $\geq 104^\circ\text{F}$  (40.0°C), and were treated with tilmicosin at a dose of 9.1 mg/lb (20 mg/kg) BW.

*P. multocida* numbers in lung-derived samples were similar for all treatments on day 0. By day 3, *P. multocida* numbers were significantly less ( $P < 0.05$ ) in cattle receiving TIL10 and TIL20 treatments compared to those found in the

**Figure 1.** Likelihood of death with increasing *M. haemolytica* values in bronchial lavage samples.



Evaluation of survival versus CFU/mL: logistic regression analysis (death vs day 9 or last available CFU value)

| Variable              | Odds ratio | 95% Confidence interval | P-value |
|-----------------------|------------|-------------------------|---------|
| <i>M. haemolytica</i> | 1.29       | 1.16, 1.44              | <0.01   |
| <i>P. multocida</i>   | 1.01       | 0.91, 1.12              | 0.84    |

ASYMP and POSCON treatments. *P. multocida* numbers were significantly increased ( $P < 0.05$ ) in the POSCON treatment on day 9 compared to all previous time points, and significantly greater ( $P < 0.05$ ) than ASYMP, TIL10, and TIL20 treatments (Table 2). There was no discernable relationship between *P. multocida* numbers and likelihood of death (OR = 1.01, 95% CI: 0.91 to 1.12) ( $P > 0.05$ ) during the observation period (Figure 1).

Clinical impression scores were lower for ASYMP animals at all time points compared to POSCON and TIL10 treatments ( $P < 0.05$ ). However, by day 9, CIS scores were similar for TIL20 and ASYMP ( $P > 0.05$ ) (Table 3). Day 9 depression scores were decreased for TIL20 compared to TIL10 ( $P < 0.05$ ) (Table 3). Rectal temperature of POSCON, TIL10, and TIL20 was significantly greater ( $P < 0.05$ ) than ASYMP on day 0. By day 3, TIL20 rectal temperature was equivalent ( $P > 0.05$ ) to ASYMP and remained so on days 6 and 9. Rectal temperatures were similar for all treatment groups by day 9 ( $P > 0.05$ ) (Table 3).

Day 0 BW ranged from a minimum of 455 to 751 lb (206 to 341 kg). Body weight change as a percentage of day 0 BW was evaluated. Animals in the TIL10 and TIL20 treatments gained an average of 3.83% and 5.04%, respectively, of their day 0 BW over the 9-day observation period ( $P < 0.05$ ). Cattle in the POSCON treatment lost an average of 2.77% of their day 0 BW over the same period ( $P < 0.05$ ). For ASYMP animals, body weight was similar on days 0, 3, 6, and 9 ( $P > 0.05$ ) (Table 4).

**Table 3.** Temperature and clinical impression score (CIS) data by treatment and timepoint.

| Variable    | Day | ASYMP <sup>1</sup> | POSCON <sup>2</sup> | TIL10 <sup>3</sup> | TIL20 <sup>4</sup> |
|-------------|-----|--------------------|---------------------|--------------------|--------------------|
| Temperature | 0   | 0 <sup>a</sup>     | 100 <sup>b</sup>    | 100 <sup>b</sup>   | 100 <sup>b</sup>   |
|             | 3   | 4 <sup>a</sup>     | 65 <sup>b</sup>     | 23 <sup>c</sup>    | 7 <sup>ac</sup>    |
|             | 6   | 6 <sup>a</sup>     | 48 <sup>b</sup>     | 27 <sup>bc</sup>   | 18 <sup>ac</sup>   |
|             | 9   | 24 <sup>a</sup>    | 27 <sup>a</sup>     | 21 <sup>a</sup>    | 18 <sup>a</sup>    |
| Depression  | 0   | 0 <sup>a</sup>     | 100 <sup>b</sup>    | 100 <sup>b</sup>   | 100 <sup>b</sup>   |
|             | 3   | 0 <sup>a</sup>     | 59 <sup>b</sup>     | 17 <sup>c</sup>    | 7 <sup>ac</sup>    |
|             | 6   | 0 <sup>a</sup>     | 42 <sup>b</sup>     | 13 <sup>c</sup>    | 4 <sup>ac</sup>    |
|             | 9   | 2 <sup>a</sup>     | 43 <sup>b</sup>     | 24 <sup>b</sup>    | 0 <sup>a</sup>     |
| Respiration | 0   | 0 <sup>a</sup>     | 100 <sup>b</sup>    | 100 <sup>b</sup>   | 100 <sup>b</sup>   |
|             | 3   | 0 <sup>a</sup>     | 30 <sup>b</sup>     | 27 <sup>b</sup>    | 7 <sup>ab</sup>    |
|             | 6   | 0 <sup>a</sup>     | 38 <sup>b</sup>     | 17 <sup>b</sup>    | 14 <sup>b</sup>    |
|             | 9   | 0 <sup>a</sup>     | 43 <sup>b</sup>     | 17 <sup>bc</sup>   | 4 <sup>ac</sup>    |

\*Evaluation of the clinical score data: results were dichotomized to yes or no: temperature values  $\geq 104^\circ\text{F}$  ( $40.0^\circ\text{C}$ ) were scored as 1, depression and respiration scores  $\geq 1$  were scored 1. Differences between groups were assessed on each day. The values in this table represent the percent of animals with a score of 1 based on the above description.

\*\*abc Within a row, values with no common letters are significantly different by Fisher's exact test ( $P < 0.05$ ).

<sup>1</sup>Cattle in the ASYMP group were clinically normal (CIS = 0), had a rectal temperature  $< 103^\circ\text{F}$  ( $39.5^\circ\text{C}$ ), and did not receive antimicrobial therapy.

<sup>2</sup>Cattle in the POSCON group showed clinical signs of bovine respiratory disease (CIS  $\geq 2$ ), had a rectal temperature  $\geq 104^\circ\text{F}$  ( $40.0^\circ\text{C}$ ), and did not receive antimicrobial therapy.

<sup>3</sup>Cattle in the TIL10 group showed clinical signs of bovine respiratory disease (CIS  $\geq 2$ ), had a rectal temperature  $\geq 104^\circ\text{F}$  ( $40.0^\circ\text{C}$ ), and were treated with tilmicosin (Micotil® 300 Injection, Elanco Animal Health, Greenfield, IN) at a dosage of 4.55 mg/lb (10 mg/kg) BW.

<sup>4</sup>Cattle in the TIL20 group showed clinical signs of bovine respiratory disease (CIS  $\geq 2$ ), had a rectal temperature  $\geq 104^\circ\text{F}$  ( $40.0^\circ\text{C}$ ), and were treated with tilmicosin at a dosage of 9.1 mg/lb (20 mg/kg BW).

Survival of TIL10 (30/32, 93.75%) and TIL20 (28/30, 93.33%) treatments did not differ significantly ( $P > 0.05$ ) from ASYMP (48/48, 100%). Survival was significantly decreased ( $P < 0.05$ ) for POSCON (22/33, 66.67%) compared to other treatment groups. All deaths were attributed to BRD on the basis of lesions observed at necropsy.

### Discussion

Results of this study indicate tilmicosin administered to cattle with BRD at 9.1 mg/lb (20 mg/kg) results in greater pulmonary pathogen load reduction and equivalent or improved clinical response compared to a dose of 4.55 mg/lb (10 mg/kg). The effect of dose on *M. haemolytica* concentrations following treatment was apparent on day 9, when cattle receiving 9.1 mg/lb (20 mg/kg) BW of tilmicosin harbored a significantly lower pathogen load than those receiving 4.55 mg/lb (10 mg/kg) BW. Depression scores on day 9 were likewise reduced in cattle treated with 9.1 mg/lb (20 mg/kg) BW of tilmicosin compared to cattle receiving 4.55 mg/lb (10 mg/kg) BW. However, clinical outcomes, including survival percentage and BW change at the end of the 9-day observation period, were equivalent between the 2 dose levels ( $P > 0.05$ ). Other indicators of treatment response, including rectal temperature and respiratory scores, were also similar ( $P > 0.05$ ).

Clinical outcomes reported here support the findings of previously published studies evaluating the effects of tilmicosin therapy on BW, rectal temperature, and CIS scores.<sup>1,6,7</sup> Bodyweight change following treatment has been demonstrated to be an effective measure of clinical response in feedlot cattle treated for BRD. In 1 retrospective study, cattle that gained weight following treatment were significantly less likely to be repulped compared to those that lost weight following therapy.<sup>3</sup> The current study was not designed to evaluate the effects of dose on subsequent repull rates; however, cattle treated with tilmicosin gained weight over the 9-day

observation period, whereas untreated controls lost a mean of 2.77% of their day 0 BW over the same period ( $P < 0.05$ ).

The economic implications of administering tilmicosin as BRD therapy at a dose of 9.1 mg/lb (20 mg/kg) BW compared to 4.55 mg/lb (10 mg/kg) BW remain to be determined. Although it is known that the higher dose doubles treatment cost, other long-term effects may have additional economic implications for cattle owners and veterinarians. Metaphylactic studies have demonstrated no statistical difference in mean profit per head when comparing cattle receiving tilmicosin at either 4.55 mg/lb (10 mg/kg) BW or 9.1 mg/lb (20 mg/kg) BW at arrival processing.<sup>4</sup> Additional studies would be required to quantify differences in economic returns over the entire feeding period attributable to tilmicosin dosage used for BRD therapy.

### Conclusions

Tilmicosin administered at 9.1 mg/lb (20 mg/kg) results in greater pulmonary pathogen load reduction and equivalent or improved clinical response compared to a dose of 4.55 mg/lb (10 mg/kg) in high-risk feedlot cattle suffering from naturally occurring BRD.

### Endnotes

- <sup>a</sup>Micotil® 300 Injection, Elanco Animal Health, Greenfield, IN
- <sup>b</sup>Cydetin® Injectable, Boehringer Ingelheim Vetmedica, Inc., St. Joseph, MO
- <sup>c</sup>Bovi-Shield Gold® 5, Zoetis, New York, NY
- <sup>d</sup>Covexin® 8, Schering-Plough Animal Health Corp, Omaha, NE
- <sup>e</sup>Cavalry® 9, Schering-Plough Animal Health Corp, Omaha, NE
- <sup>f</sup>Revalor® XS, Merck Animal Health, Summit, NJ
- <sup>g</sup>Rumensin®, Elanco Animal Health, Greenfield, IN
- <sup>h</sup>Tylan®, Elanco Animal Health, Greenfield, IN
- <sup>i</sup>GLA M500 Series, GLA Agricultural Electronics, San Luis Obispo, CA

**Table 4.** Comparison of body weight as a percent change from day 0 weight.‡

|       | ASYMP <sup>1</sup>  | POSCON <sup>2</sup> | TIL10 <sup>3</sup> | TIL20 <sup>4</sup> |
|-------|---------------------|---------------------|--------------------|--------------------|
| Day 0 | 0%                  | 0                   | 0                  | 0                  |
| 3     | -0.32 <sup>ab</sup> | -2.32 <sup>*a</sup> | 1.34 <sup>bc</sup> | 1.57 <sup>c</sup>  |
| 6     | 0.41 <sup>a</sup>   | -2.65 <sup>*b</sup> | 3.14 <sup>*c</sup> | 3.55 <sup>*c</sup> |
| 9     | 0.88 <sup>a</sup>   | -2.77 <sup>*b</sup> | 3.83 <sup>*c</sup> | 5.04 <sup>*c</sup> |

‡Repeated measures analysis of variance

\*Within treatment, day 0 different from day 3, 6, or 9 at  $P < 0.05$

<sup>abc</sup>Within day, values with no common letters are significantly different at  $P < 0.05$ .

<sup>1</sup>Animals in the ASYMP group were clinically normal (CIS = 0), had a rectal temperature  $< 103^{\circ}\text{F}$  ( $39.5^{\circ}\text{C}$ ), and did not receive antimicrobial therapy.

<sup>2</sup>Animals in the POSCON group showed clinical signs of bovine respiratory disease (CIS  $\geq 2$ ), had a rectal temperature  $\geq 104^{\circ}\text{F}$  ( $40.0^{\circ}\text{C}$ ), and did not receive antimicrobial therapy.

<sup>3</sup>Animals in the TIL10 group showed clinical signs of bovine respiratory disease (CIS  $\geq 2$ ), had a rectal temperature  $\geq 104^{\circ}\text{F}$  ( $40.0^{\circ}\text{C}$ ), and were treated with tilmicosin (Micotil® 300 Injection, Elanco Animal Health, Greenfield, IN) at a dosage of 4.55 mg/lb (10 mg/kg) BW.

<sup>4</sup>Animals in the TIL20 group showed clinical signs of bovine respiratory disease (CIS  $\geq 2$ ), had a rectal temperature  $\geq 104^{\circ}\text{F}$  ( $40.0^{\circ}\text{C}$ ), and were treated with tilmicosin at a dosage of 9.1 mg/lb (20 mg/kg) BW.

<sup>j</sup>Microsoft Office Excel 2008 for Mac, Microsoft Corp, Redmond, WA

<sup>k</sup>Pyrex® solid glass beads, Corning, Inc., Tewksbury, MA

<sup>l</sup>Caine Veterinary Teaching Center, University of Idaho, Caldwell, ID

<sup>m</sup>SAS, Version 9.2, SAS Institute Inc., Cary, North Carolina, USA

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## Juggling Act — Complete protection must guard against the many factors causing BRD

What exactly lies behind the last decade's stubborn increase in BRD feedlot deaths, despite all the advancements in technology? Purdue's Mark Hilton lists a few suspects:

- Younger, less immune cattle going into feedlots
- Higher exposure to the viruses that contribute to BRD because of larger feedlot pen numbers
- More cattle being bought and sold more than once along the marketing chain
- Record-high feeder prices drawing more and more unweaned, unvaccinated cattle into the market<sup>1</sup>

Each of those factors shares a common underlying pattern: What typically awaits those ill-prepared cattle is a potent one-two viral/bacterial punch on the cattle immune system that will leave 16 percent of them sick and 1.6 percent of them dead.<sup>2-4</sup>

While respiratory viruses can cause BRD on their own, they also can compromise the immune system that normally protects cattle against bacteria, allowing those otherwise harmless bacteria to attack their host and cause severe cases of BRD.

When un-immunized cattle are exposed to bovine viral diarrhea (BVD), parainfluenza3 (PI<sub>3</sub>), infectious bovine rhinotracheitis (IBR), bovine respiratory syncytial virus (BRSV) and possibly bovine coronavirus, their immune systems can be weakened.<sup>5,6</sup> Once the immune system is compromised, bacteria, including *Mannheimia haemolytica* and *Pasteurella multocida*, typically harmless common inhabitants of the respiratory tract, can suddenly turn pathogenic.<sup>7</sup>

### Why single vaccination fails

Once those bacteria take hold in the lung, they are typically responsible for the severe inflammation and pneumonia that eventually leaves cattle drowning in their own bodily fluids. Those pathogenic bacteria damage the calf through a number of avenues, most notably, "leukotoxins," or cellular poisons that specifically attack the calf's white blood cells, along with other molecular tools that help them stick to and invade cells, and hide from or confuse the immune system.<sup>8</sup>

These bacteria weaken the calf's immature immune-defense system by confusing the signaling chemicals and the cellular receptors of the immune system,<sup>9</sup> confounding the structures that ingest and destroy bacteria, and otherwise suppressing the immune function.<sup>10,11</sup> The end result: The calf's over-taxed system loses the critical balance between the inflammatory response necessary to eliminate the organisms and heal the damage and an excess response that destroys the delicate lung tissue around them.<sup>6</sup>

Because of this "multi-factorial" aspect of BRD infection and disease progression, producers overestimate the protection they have when they rely on a single BRD vaccine at weaning, says South Dakota State University veterinary professor Chris Chase. "We know there's a lot of stress going on in that process of weaning and shipping," he says, "and given my preference, I think you should always vaccinate in front of the stressor rather than after."

In theory, that means producers should be giving a first vaccine 30 days before weaning, followed by another at weaning. But, of course, in practice, that first treatment often gets ignored. Chase says rather than rely on only one treatment at weaning, it's better to move the first injection back onto the younger calf, so the at-weaning dose becomes a booster.<sup>12</sup>

A 2009 study demonstrated Chase's advice in practice. In that study, young calves still nursing the cow were vaccinated with a modified-live respiratory vaccine at as young as 1 month old, followed by revaccination at weaning. When given an oil-adjuvanted killed vaccine five months later, they consistently showed a greater antibody response — a "priming effect" that's associated with better protection against BRD.<sup>13</sup>

Clearly, Chase says, there are ways to make vaccination against BRD work by adapting any of a number of vaccine protocols to your herd's diseases, labor supply, facilities, ability to handle risk, history and management.

### 'Priming' the immune system

Elanco technical services veterinarian Brett Terhaar agrees. "Producers should partner with their veterinarians to determine the best way to incorporate new vaccine technology into herd-health protocols designed to fight BRD."

"When we vaccinate, we're priming the immune system, setting up calves so they can protect themselves before the stress of weaning and shipping," Terhaar says. In order to protect against the bacterial pathogens that cause the worst damage, vaccines must contain an inactivated version of that leukotoxin — a "leukotoxoid."

"Vaccinated calves will produce antibodies against the damaging leukotoxin," Terhaar says, which will prevent the leukotoxin from attaching to and destroying protective white blood cells. Dependable levels of antigen are critical, he says. "When a vaccine product without a leukotoxoid relies solely on stimulated antigen growth, needed levels of protection may not be reached consistently, making the calf vulnerable," Terhaar says.

But, the leukotoxoid alone is not enough. The calf needs to develop antibodies to additional parts of the bacteria, which also attack the immune system. "You can't just give a leukotoxoid and have good protection," Terhaar says. "There's a lot of different components to the bacteria that we want the calf to make antibodies to." Those antigens also need to be included in an effective vaccine. That protection is crucial, and that's what Titanium<sup>®</sup> 5 + PH-M offers. It contains an *M. haemolytica* leukotoxoid and delivers an effective immune response against the viruses and both types of bacteria most often associated with BRD<sup>14,15</sup> — BVD 1 and 2, IBR, BRSV, PI<sub>3</sub>, *Mannheimia haemolytica* and *Pasteurella multocida* — to help the calf fight health challenges it is likely to face.

The label contains complete use information, including cautions and warnings. Always read, understand and follow the label and use directions.

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