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An Evaluation of the Field Efficacy of Tildipirosin for Control of Bovine Respiratory Disease in Feedlot Calves in Bulgaria

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Abstract: Bovine respiratory disease (BRD) is one of the most common and economically important disease affecting feedlot industry throughout the world. The economic significance of this condition are high morbidity and mortality, decreased weight gains, reduced food utilization, low meet quality and additional therapeutic and prophylactic measures. The hypothesis of this study was that the use of metaphylactic protocol based on the risk to develop BRD would reduce morbidity and mortality. For this purpose, the aims of this study were to evaluate the effect of tildipirosin on the incidence of BRD in feedlot cattle. A total of 106 male beef calves were enrolled in the study. Calves were allocated randomly in control group (54 animals) and treatment (52 animals) group. The first group received subcutaneous injection of placebo while the second was treated with SC injection of tildipirosin. The observed BRD incidence was 35.2, and 9.6% for the calves in the control and treatment group, respectively (P = 0.012). These results suggest that the tildipirosin metaphylaxis tend to decrease the incidence of BRD in the first four weeks of the fattening period in beef cattle. In conclusion, metaphylactic protocols, based on the administration of tildipirosin in the high risk period can be used for management of BRD.

Keywords: Bovine respiratory disease; metaphylaxis; tildipirosin; beef calves

INTRODUCTION

The bovine respiratory disease (BRD) complex is an economically important disease in beef cattle resulting in serious impact on health and welfare (Larson, 2005; Young and Woolums, 2014). BRD is the most common disease among feedlot cattle throughout the world. It is responsible for 75% of all morbidity and 50 to 70% of all finishing mortality (Galyean et al., 1999; Loneragan et al., 2001). BRD is a multifactorial syndrome, which etiology includes interactions between various infectious agents, environmental stressors, management practices and susceptibility of the host. Most viral pathogens involved in etiology, such bovine herpesvirus-1 (BHV-1), bovine respiratory syncytial virus (BRSV), bovine parainfluenza-3 virus (BPI-3v) and bovine viral diarrhea virus (BVDV), are ubiquitous in cattle populations (Martin et al., 1989; Booker et al., 1999). Bacterial pathogens involved such as *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*, have been shown to be commensals of the upper respiratory tract of both healthy and diseased cattle (DeRosa et al., 2000; Highlander, 2001). Thus, the onset of the disease will be dependent on risk factors, bacterial load, preceding respiratory viral infection and level of immunity. In feedlots, stress factors are extremely important in the etiology and induction of BRD especially in the initial period after commingling of calves. Most BRD morbidity occurs in the first month after arrival in feedlot operation (Buhman et al., 2000).

Prevention and control of BRD relies on implementation of herd health strategies designed to reduce stress, optimize nutrition and management, and generate immunity to specific viral and bacterial pathogens. Metaphylaxis at beginning of the fattening period, is commonly used management practice, to minimize the bacterial pathogen load and BRD incidence in a high-risk population (Nickell et al., 2010). Macrolides are one of the commonly used antimicrobials to control BRD. They inhibit essential protein biosynthesis by virtue of their selective binding to bacterial ribosomal RNA and act by blocking the prolongation of the peptide chain. Tildipirosin is a 16-membered semi-synthetic macrolide used to reduce disease incidence in high-risk population. It is rapidly distributed to lung tissue and bronchial fluid, followed by slow elimination, which is important because of the time-dependent therapeutic effect (Menge et al., 2012).

The objective of this field trial was to evaluate the effect of a metaphylactic treatment using tildipirosin in the incidence and mortality of BRD, in feedlot during the period of 42 days following commingling of the male beef calves.

MATERIALS AND METHODS

Farm information

Cow-calf operation system consisting of a total of 346 cows and bulls, year round calving cycle. Each year, 292 ±23 calves were born, and calves are weaned at around 5 month of age. Farm history from the record keeping logbook reveals that respiratory diseases are more common in the first four to five weeks after commingling in feedlot. Earlier results from on-farm seroepidemiology for BHV-1, BVDV, BRSV and BPI-3v showed a high seroprevalence in the population.

The study was conducted from May to June 2022, at a commercial beef cattle feedlot, located in North Bulgaria. A total of 106 healthy bull beef calves at mean age of 147 ± 24 days and initial body weight of 197.3 ± 18.4 kg were enrolled into the study. Most of them were Limousin breed (70.8%) and the rest were Aberdeen Angus breed (29.2%). Bull calves are weaned by abrupt removal from their dams and transported by truck with a trailer to the feedlot, which creates a stressful situation. They also face overcrowding, unfamiliar surroundings, noise, staff and procedures. Beef calves are housed in 8 dirt-floor partly covered (a mono-slope roof), single row pens with an open feed alley. In each pen 12 – 14 calves are placed. No other adult ruminants were present in the same barns and no direct or aerosol contacts were assumed to be possible between the calves from study group and other susceptible animals.

Feed and water

Beef calves are fed a balanced ration to meet energy and protein requirements. They received grain, corn silage, soybean meal, mineral salts, and had free access to hay and straw. Feed bunk length vary from 250 mm/head to over 300 mm/head. Water trough length vary from 120 mm/head to over 180 mm/ head and fresh water is freely available.

Study design and treatment

Calves enrolled in the study were randomly allocated into two different groups: control group (CTR) 54 animals and treatment group (TRT) 52 animals. Calves from CTR group received single SQ injection of placebo (sterile saline 0.9%), while the animals from TRT group received single SQ injection of tildipirosin (Zuprevo 18%, MSD Animal Health). Tildipirosin is administered subcutaneously to cattle at a single dose of 4 mg/kg body weight. Both groups were treated from one of the researchers in the team by using new needle for injection of each bull. The dose was calculated for each bull by passing through a scale when getting off the trailer. Upon arrival at the feedlot, all of the calves received also a multivalent clostridial bacterin-toxoid and were dewormed with doramectin. No vaccinations against respiratory pathogens have been conducted to date.

Case definition

BRD was defined when the following clinical signs were detected: depression, anorex-

ia, respiratory symptoms (cough, ocular or/ and nasal discharge, respiratory distress, open mouth breathing, extended head and neck, and noise when breathing), and rectal temperature >39.6 °C (DART). Case definition was based on the DART system (Pharmacia Upjohn Animal Health), modified later by Step et al. (2008). Each case was recorded, and following the diagnosis of BRD, animals were treated according to farm protocols by using florfenicol (dose 40 mg/kg, SC) and flunexin meglumine (dose 1.1 to 2.2 mg/kg, IV).

Laboratory tests

According to the adopted model of action, lung tissue samples from the dead calves were obtained and sent to the laboratory. Necropsy was performed, as soon as possible after the death of the animal, and tissue samples were chilled and transported promptly to the laboratory. For isolation of *M. haemolytica* and *P. multocida*, samples from lung tissue were plated on to a blood agar plate (Catry et al., 2006) and were incubated for 24 h at 37 °C. For *H. somni*, samples were plated on to a blood agar plate and incubated at 37 °C for 24–48 h with 10% CO2. The plates were then examined for presence of growth and colony morphology, size, shape, and hemolysis. Bacterial isolates were identified as described in Bergey's Manual of Determinative Bacteriology (Holt et al., 1994) and Manual of Clinical Microbiology (Murray et al., 2003), on the basis of colony appearance, Gram staining, cellular morphology, presence of haemolysis and biochemical behaviour (catalase, oxidase).

Commercial antigen capture sandwich ELISA test kit was used according to the manufacturer's instructions for post-mortem diagnosis of BoHV-1, BVDV, BRSV, and BPI-3 in lung tissue lysates (BIOX Diagnostics, Belgium).

Statistical analysis

The x^2 analysis (chi-square) method was used to investigate the effect of tildipirosin treatment on morbidity in male beef calves. Significant differences between experimental (TRT) and control (CTR) groups were calculated using One Way ANOVA analysis at $p < 0.05$. The obtained data were processed with statistical software IBM SPSS Statistics 26.0 (NY, USA).

RESULTS

During this study, 24/106 (22.6%) of the cattle evaluated had clinical manifestations of BRD with lower frequency reported in metaphylactic group. BRD incidence was 35.2, and 9.62% for beef calves enrolled in the CTR, and TRT, respectively (P = 0.012) (Figure 1). The high-risk period in the study was determined up to day 21, where 13/19 (62.5%) of the calves were affected all of them from the control group. In TRT group, no diseased calves were recorded until day 22. Statistically significant differences were found between the mean values of the diseased calves in the experimental (0.24) and control (0.90) groups for the studied period, (P = 0.013). The results of the One Way ANOVA analysis are presented in Table 1. The coefficient of determination is $R^2 = 0.145$, i.e. about 14.5% of the variations in the studied parameter *Number of sick calves* during the studied period are the result of the influence of the antibiotic treatment. This confirms the moderate relationship between tildipirosin treatment and reduction of respiratory diseases in calves over the study period. Cramer's V coefficient (0.393) indicated that the effect of tildipirosin treatment on morbidity of calves was moderate and statistically significant.

Tildipirosin metaphilaxis reduced the hazard ratio for BRD in TRT group compared to CTR group (HR= 0.26, P-value = 0.000062). (Figure 2).

During the study period only one bull calf (N # 42 Limousine breed) from CTR group died - case fatality rate 5.2% (1/19). Gross evaluation of the lungs revealed pulmonary lesions indicative for BRD cranioventral bronchopneumonia, emphysema and lung edema. Laboratory investigations revealed *Mannheimia haemolytica, Bovine herpesvirus-1* and *Bovine respiratory syncytial virus.*

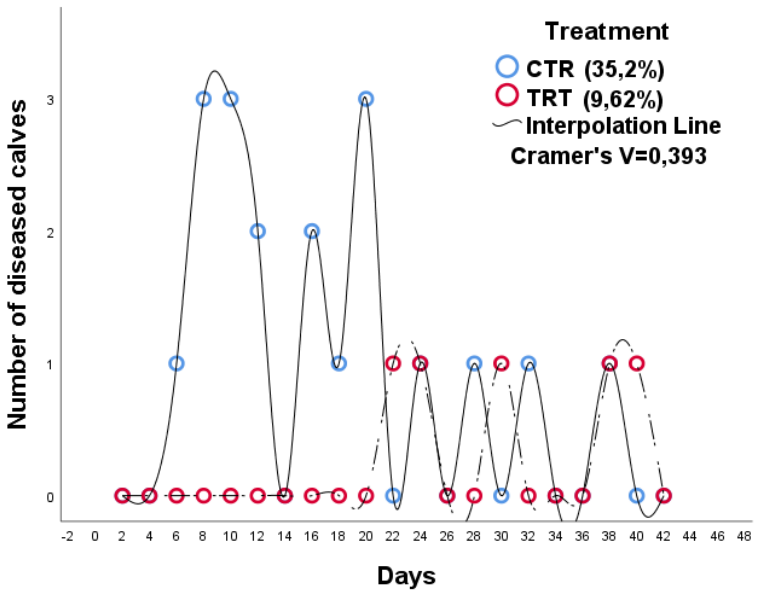

Figure 1. Time distribution of BRD in the first 42 on feed.

Table 1. One Way ANOVA of the observed parameter Number of the diseased calves in both groups during the experimental period.

	$\bar{x} \pm SD$	Sig. (p)	R^2
CTR (n= 54)	0,90±1,091 [a]	0,013	0,145
TRT (n= 52)	0,24±0,436 [a]		

** Same superscripts within the same column represent significant differences at the level of significance p < 0.05; SD – Standard deviation; R^2 – Coefficient of determination; n – number of the observations*

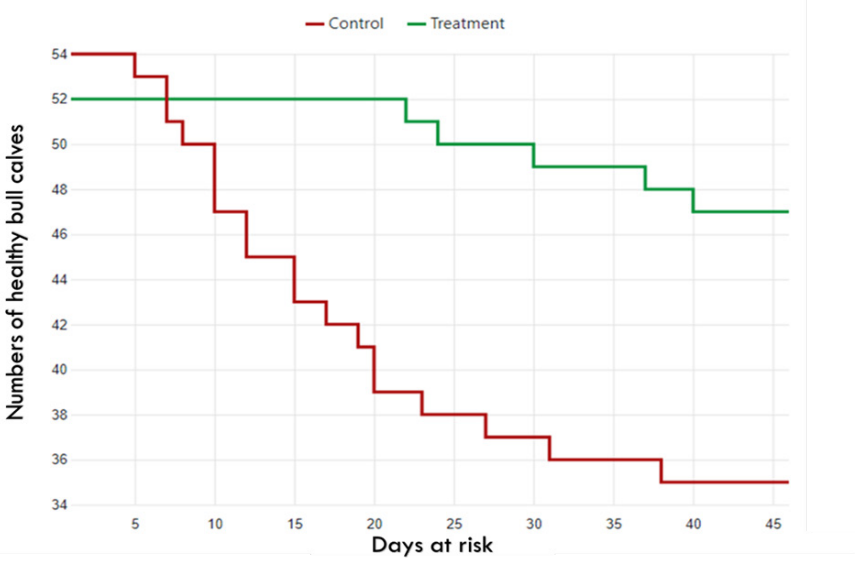

Figure 2. Effect of mataphylactic treatment with tildipirosin on the interval of time from arrival to diagnosis of BRD in feedlot calves during the study period.

DISCUSSION

The assessment of the epidemic situation of the farm, based on the retrospective study of the cases in the previous two years, defined as high risk for BRD the period of the first 21 days after the commingling of the animals. For a time, duration equal to the observed period of 42 days, an incidence of BRD of 22.6% was found, with most cases 62.5% occurring in the first 21 days. This is consistent with other results, for example in USA, Edwards (1996) reported higher incidence of BRD during the first 42 days on feed. According to Baptista et al. (2017), in Brazil, 69.3% of the cases occurred during the first 15 days on feed, while almost all (95.8%) cases occurred during the first 30 days on feed. Thompson et al. (2006) observed that 87% of all BRD treatments had occurred by 35 days after arrival. During a 5-year survey, Babcock et al. (2009) found that 74% of morbidity in a commercial feedlot occurred within the first 42 days on feed. Although, the highest incidence is reported in the initial fattening period, variations in the timing of peak new case occurrence are possible due to the multifactorial etiology of BRD. The compilation of a series of stressors including abrupt weaning, and transportation, as well as relocation and placement in a new environment, overcrowding and competition, unfamiliar noises, food, workers and procedures multiply the risk of illness (Step et al., 2008; Sanderson et al., 2008 Wilson et al., 2017). In this negative period, stress can compromise the effect of vaccines used to control BRD in calves. Assessment of temporal patterns of BRD and the concentration of most cases in the early fattening stage is an important point in herd health management to influence the decision for metaphylaxis when disease rates rise above the expected level. Based on this, prophylaxis by antibiotic metaphylaxis early in the fattening period will reduce morbidity and mortality due to bacterial pathogens (Nickell et al., 2010).

During the first three weeks of the observation period, no disease was detected in the calves of the treated group, which could be explained by the higher concentrations of the antibiotic in the lung and bronchial fluid. In bronchial fluid, the concentration of tildipirosin reached 3.0 μg/g at 10 h, maintained a plateau of about 3.5 μg/g between day 1 and 3, and slowly declined to 1.0 at day 21 (Menge et al., 2012). The determined MIC90 for *Mannheimia haemolytica* and *Pasteurella multocida* is 1μg / mL (Menge et al., 2012). According to our results metaphylactic treatment with tildipirosin reduced the hazard ratio for BRD (HR=0.26), which means that calves in the TRT group at any individual time along here are 74% less likely to experience an event than the calves in the CTR group. A similar study evaluating the metaphylactic effect of oxytetracycline found a reduced hazard ratio (HR=0.39) and extended 7 days the interval of time from arrival to the diagnosis of BRD in all the calves becoming sick (Fazzio et al., 2015). Tildipirosin in pre-weaned dairy calves has been observed to lower the hazard of being affected with BRD and/or otitis (Teixeira et al., 2017). In experimentally infected with *Histophilus somni* calves, treated with tildipirosin had lower BRD clinical score and less lung consolidation compared to calves that had received tulathromycin metaphylaxis or saline control treatment (Confer et al., 2016). In another study calves that received tildipirosin pre-challenge with *Mannheimia haemolytica* had fewer lung lesions and lower clinical scores than calves that had received tulathromycin or saline. (Amrine et al., 2014). These results are quite different from those of Celestino and colleagues (2020) done in Holstein calves in pre-weaning period. They reported that metaphylaxis did not decrease the incidence of BRD, which might be due to the low disease incidence in their study.

Only one death case was occurred during the study, probably due to the daily monitoring of animals, thorough clinical examination and early treatment. This confirms the opinion that DART-based therapy is a reliable tool to control BRD (Love et al., 2014). In our opinion, the study of the effectiveness of tildipirosin in a relatively small number of animals needs to be extended, to include large groups of susceptible calves, both

beef and dairy. However, it is important to note that the interpretation of these observations must take into account that the calves included in the study were not vaccinated. Worldwide practices for managing BRD on commercial farms include reducing stress, optimizing management, general vaccination, and mass antibiotic treatment (Fulton, 2009). Despite the development and improvement of vaccines, uncontrollable stressors can dysregulate humoral and cellular immune responses and can lead to disease. This makes metaphylaxis a reliable tool in the prevention of respiratory diseases in beef calves during the period of increased stress. As a result, from this study tildipirosin mass treatment was efficient in reducing BRD related morbidity rates. Globally, there is a tendency to reduce the use of antimicrobial agents, with the aim of reducing the antibiotic pressure on bacteria and selecting resistant strains. In intensive animal husbandry, the use of antimicrobial agents is often the only alternative to overcome health and economic problems associated with bacterial infections. Antimicrobial coverage as mass treatment also aids in reducing the number of chronics and mortalities in a group, thus having a significant positive effect on animal welfare (Sweiger and Nichols, 2010). Word et al. (2020) reported that, metaphylaxis did not increase total antimicrobial use on a mass basis or total therapeutic applications, although total number of applications was increased when metaphylaxis was included.

CONCLUSION

In evaluating the practical value of the results of this field trial, it should be taken into account that the bulls did not receive bacterins containing *Mannheimia haemolytica* and/or *Pasteurella multocida* as BRD prevention. In poorly managed herds in the periods of elevated stress, antimicrobial metaphylaxis remains the most accessible and fastest way to protect animals from suffering and ensure their well-being.

REFERENCES

Amrine, D. E., White, B. J., Larson, R. L. & Mosier, D. A. (2014). Pulmonary lesions and clinical disease response to Mannheimia haemolytica challenge 10 days following administration of tildipirosin or tulathromycin. *Journal of Animal Science*, *92*(1), 311-319.

Babcock, A. H., White, B. J., Dritz, S. S., Thomson, D. U. & Renter, D. G. (2009). Feedlot health and performance effects associated with the timing of respiratory disease treatment. *J. Anim. Sci*., 87, 314-327.

Baptista, A. L., Rezende, A. L., de Almeida Fonseca, P., Massi, R. P., Nogueira, G. M., Magalhães, L. Q. & Saut, J. P. E. (2017). Bovine respiratory disease complex associated mortality and morbidity rates in feedlot cattle from southeastern Brazil. *The Journal of Infection in Developing Countries*, *11*(10), 791-799.

Booker, C. W., Guichon, P. T., Jim, G. K., Schunicht, O. C., Harland, R. J. & Morley, P. S. (1999). Seroepidemiology of undifferentiated fever in feedlot calves in western Canada. *The Canadian Veterinary Journal*, *40*(1), 40.

Buhman, M. J., Perino, L. J., Galyean, M. L., Wittum, T. E., Montgomery, T. H. & Swingle, R. S. (2000). Association between changes in eating and drinking behaviors and respiratory tract disease in newly arrived calves at a feedlot. *American Journal of Veterinary Research*, *61*(10), 1163-1168.

Catry, B., Decostere, A., Schwarz, S., Kehrenberg, C., de Kruif, A. & Haesebrouck, F. (2006). Detection of tetracycline-resistant and susceptible Pasteurellaceae in the nasopharynx of loose group-housed calves. *Veterinary research communications*, *30*, 707-715.

Celestino, M. L., Fernandes, L., Menta, P. R., Paiva, D., Ribeiro, T. L., Silva, T., ... & Machado, V. S. (2020). The effect of metaphylactic use of tildipirosin for the control of respiratory disease in long-distance transported dairy calves. *Frontiers in Veterinary Science*, *7*, 632.

Confer, A. W., Snider, T. A., Taylor, J. D., Montelongo, M. & Sorensen, N. J. (2016). Clinical disease and lung lesions in calves experimentally inoculated with Histophilus somni five days after metaphylactic administration of tildipirosin or tulathromycin. *American Journal of Veterinary Research*, *77*(4), 358-366.

DeRosa, D. C., Mechor, G. D., Staats, J. J., Chengappa, M. M. & Shryock, T. R. (2000). Comparison of Pasteurella spp. simultaneously isolated from nasal and transtracheal swabs from cattle with clinical signs of bovine respiratory disease. *Journal of clinical microbiology*, *38*(1), 327-332.

Edwards, A. (1996). Respiratory diseases of feedlot cattle in central USA. *The Bovine Practitioner*, 5-7.

Fazzio, L. E., Giuliodori, M. J., Galvan, W. R., Streitenberger, N. & Landoni, M. F. (2015). A metaphylactic treatment with double dose oxytetracycline reduces the risk of bovine respiratory disease in feedlot calve. *Revista veterinaria*, *26*(2), 89-92.

Fulton, R. W., Briggs, R. E., Payton, M. E., Confer, A. W., Saliki, J. T., Ridpath, J. F., ... & Duff, G. C. (2004). Maternally derived humoral immunity to bovine viral diarrhea virus (BVDV) 1a, BVDV1b, BVDV2, bovine herpesvirus-1, parainfluenza-3 virus bovine respiratory syncytial virus, Mannheimia haemolytica and Pasteurella multocida in beef calves, antibody decline by half-life studies and effect on response to vaccination. *Vaccine*, *22*(5-6), 643-649.

Galyean, M. L., Perino, L. J. & Duff, G. C. (1999). Interaction of cattle health/immunity and nutrition. *Journal of Animal Science*, *77*(5), 1120-1134.

Larson, R. L. (2005). Effect of cattle disease on carcass traits. *Journal of Animal Science*, *83*(suppl_13), E37-E43.

Loneragan, G. H., Dargatz, D. A., Morley, P. S. & Smith, M. A. (2001). Trends in mortality ratios among cattle in US feedlots. *Journal of the American Veterinary Medical Association*, *219*(8), 1122-1127.

Magalhães, L. Q., Baptista, A. L., Fonseca, P. D. A., Menezes, G. L., Nogueira, G. M., Headley, S. A., ... & Saut, J. P. E. (2017). Use of metaphylactic protocols based on the risk to develop bovine respiratory diseases in feedlot cattle. *Ciência Rural*, *47*, e20161110.

Martin, S. W., Bateman, K. G., Shewen, P. E., Rosendal, S. & Bohac, J. E. (1989). The frequency, distribution and effects of antibodies, to seven putative respiratory pathogens, on respiratory disease and weight gain in feedlot calves in Ontario. *Canadian Journal of Veterinary Research*, *53*(3), 355.

Menge, M., Rose, M., Bohland, C., Zschiesche, E., Kilp, S., Metz, W., ... & Nürnberger, M. (2012). Pharmacokinetics of tildipirosin in bovine plasma, lung tissue, and bronchial fluid (from live, nonanesthetized cattle). *Journal of veterinary pharmacology and therapeutics*, *35*(6), 550-559.

Nickell, J. S. & White, B. J. (2010). Metaphylactic antimicrobial therapy for bovine respiratory disease in stocker and feedlot cattle. *Veterinary Clinics: Food Animal Practice*, *26*(2), 285-301.

Sanderson, M. W., Dargatz, D. A. & Wagner, B. A. (2008). Risk factors for initial respiratory disease in United States' feedlots based on producer-collected daily morbidity counts. *The Canadian Veterinary Journal*, *49*(4), 373.

Step, D. L., Krehbiel, C. R., DePra, H. A., Cranston, J. J., Fulton, R. W., Kirkpatrick, J. G., ... & Confer, A. W. (2008). Effects of commingling beef calves from different sources and weaning protocols during a forty-two-day receiving period on performance and bovine respiratory disease. *Journal of Animal Science*, *86*(11), 3146-3158.

Sweiger, S. H. & Nichols, M. D. (2010). Control methods for bovine respiratory disease in stocker cattle. *Veterinary Clinics: Food Animal Practice*, *26*(2), 261-271.

Fulton, R. W. (2009). Bovine respiratory disease research (1983–2009). *Animal health research reviews*, *10*(2), 131-139.

Teixeira, A. G. V., McArt, J. A. A. & Bicalho, R. C. (2017). Efficacy of tildipirosin metaphylaxis for the prevention of respiratory disease, otitis and mortality in pre-weaned Holstein calves. *The Veterinary Journal*, 219, 44-48.

Thompson, P. N., Stone, A. & Schultheiss, W. A. (2006). Use of treatment records and lung lesion scoring to estimate the effect of respiratory disease on growth during early and late finishing periods in South African feedlot cattle. *Journal of animal science*, *84*(2), 488-498.

Wilson, B. K., Richards, C. J., Step, D. L. & Krehbiel, C. R. (2017). Beef species symposium: best management practices for newly weaned calves for improved health and well-being. *Journal of Animal Science*, *95*(5), 2170-2182.

Young, A. E. & Woolums, A. R. (2014). Proceedings of the Bovine Respiratory Disease Symposium 2014: New Approaches to Bovine Respiratory Disease Prevention, Management, and Diagnosis. *Animal Health Research Reviews*, *15*(2), 119-119.

Love, W. J., Lehenbauer, T. W., Kass, P. H., Van Eenennaam, A. L. & Aly, S. S. (2014). Development of a novel clinical scoring system for on-farm diagnosis of bovine respiratory disease in pre-weaned dairy calves. *PeerJ*, *2*, e238.

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