EVALUATION OF TWO METHODS TO PREVENT BOVINE RESPIRATORY

DISEASE IN GROWING CATTLE

A Thesis

by

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ABSTRACT

Bovine Respiratory Disease (**BRD**) is the leading cause of morbidity and
mortality in the cattle feeding industry. High impact and cost of BRD necessitates
development of preventative mechanisms to improve animal health, performance, and
well-being and to augment the sustainability of beef production. Two potential
mechanisms to prevent disease were investigated: through metaphylactic therapy (or the
on-arrival mass medication of a group of high-risk cattle to control BRD) and through
manipulation of dietary energy intake.

A trial was conducted to determine the effects of on-arrival metaphylaxis in beef
cattle for controlling BRD and the subsequent effects on health and performance. Male
calves in a randomized complete block design (n=198) received ceftiofur crystalline free
acid (**EXC**), tilmicosin phosphate (**MIC**), or were not treated (**CON**). Significant
differences were not observed in morbidity rates ($P = 0.14$) between cattle on the MIC
($46.4 \pm 4.32\%$) or EXC treatments ($56.5 \pm 4.32\%$). Both the MIC and EXC treatments
effectively reduced overall morbidity and delayed onset of clinical illness in newly
received beef cattle. Furthermore, this reduction in overall morbidity was achieved with
minimal increase in total antimicrobial usage. While overall performance outcomes were
not different, animal health was improved with metaphylaxis.

A second trial was conducted to determine the effects of limit-feeding growing
steers on immune function. Thirty-two steers were fed the same ration at one of three
intake levels (low, medium, or high DMI). All steers were vaccinated on study d-0 with
a five-way modified live vaccine, which acted as an immunological challenge to

measure immune function. Energy intake affected serum neutralizing antibody response to vaccines, and therefore overall immune function, in growing cattle. Future research should establish an ideal window of energy intake for growing cattle where both performance and health are optimized.

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"And whatever you do, whether in word or deed, do it all in the name of the Lord Jesus, giving thanks to God the Father through him." –Colossians 3:17

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CHAPTER I

INTRODUCTION AND REVIEW OF LITERATURE

Introduction

Bovine Respiratory Disease (**BRD**) is the leading cause of morbidity and mortality in the cattle feeding industry, affecting feedlot cattle almost five times more often than the next most commonly reported disease (USDA-APHIS, 2001). In 1999, feedlots in 12 states reported an average BRD incidence of 14.4% (USDA-APHIS, 2000a), although 97.8% of cattle processed in a feedlot were vaccinated against BRD in the same year (USDA-APHIS, 2000c). Cost of treatment for a single case of respiratory disease in 2013 was $23.60 (USDA-APHIS, 2013). Accounting for production losses such as labor, decreased feed intake, and reductions in growth adds to the cost of BRD. Mortalities and chronically ill cattle that require multiple treatments push this cost estimate up. These costs far exceed the average cost of treating less common diseases such as lameness and digestive disorders. High impact and cost of BRD necessitates development of preventative strategies to improve animal health, performance, and well-being, and to augment the sustainability of beef production. Two potential methods to prevent disease will be discussed: prevention through metaphylactic therapy (or the on-arrival mass medication of a group of high risk cattle to control BRD) and through dietary manipulation.

Diagnosis of BRD is typically made by subjective observation. Cattle displaying symptoms are typically depressed or lethargic, have labored breathing or nasal discharge, and refrain from drinking or eating (Duff and Galyean, 2007). Cattle with prolonged cases of respiratory disease that go undiagnosed may begin to display emaciated body condition. Perino and Apley (1998) developed a scoring system to clinically describe BRD by a scoring an animal from 0 to 4 with increasing severity, where 0 describes a normal animal and 4 describes a moribound animal that is unable to rise. Scores of 1-3 describe increasing severity of animals that are depressed, weak, and have labored breathing or an altered gait. Such a scoring system is useful because it applies a quantitative approach to a subjective evaluation. They recommend animals assigned a clinical score ≥ 1 and have a rectal temperature $\geq 40°C$ be treated for respiratory disease. Duff and Galyean (2007) similarly recommend treatment when cattle displaying symptoms have a rectal temperature $\geq 39.7°C$. Although treatment protocols differ between studies, cattle are typically treated for respiratory disease based on clinical observation and rectal temperature.

Many factors contribute to BRD development, and pathogenic causes include both viral and bacterial agents (Callan, 2002). Newly arrived, lightweight cattle may experience various preweaning and postweaning stressors including transportation, management, and nutritional stress (Duff and Galyean, 2007). Stress negatively affects the immune system, measured by an increase in the total number of circulating white blood cells following transport, corresponding with an increase in plasma cortisol level (Murata et al., 1987). Increases in specific types of circulating white blood cells, such as

neutrophils, indicates that an immune response is occurring. Increases in plasma cortisol, a glucocorticoid secreted via the hypothylamic-pituitary axis, indicate that the animal is stressed, which may affect immune function. Swanson and Morrow-Tesch (2001) described in a review the immunological response to cattle transport stress and concluded that the immune system is suppressed during stress. Immune decline, in addition to commingling and exposure to pathogens, can increase the risk of BRD development. Although risk factors and stressors are well widely described, an industry-wide definition of "high risk" cattle has not been made concrete. Using known attributes of an incoming group of cattle to assign a level of risk (i.e., expected percent morbidity) to the group. Feedlots most commonly base this prediction on distance traveled and shrink, or the amount of body weight lost during transport (USDA-APHIS, 2000b).

Dry matter intake can decrease by up to 45% in morbid cattle, and it takes 10-17 d for feed intake to return to normal once an animal has been successfully treated (Chirase et al.,1991). Previous research on BRD has shown that both DMI and ADG are good indicators of overall health in growing animals. Healthy calves have more frequent feeding bouts and spend 33% more time at the bunk than morbid calves (Daniels et al., 2000). The same authors reported sick cattle lost weight, while healthy calves gained 0.78 kg/d and were 20 kg heavier than sick cattle after 21 d; sick cattle lost 0.03 kg/d. Morck et al. (1993) reported that healthy cattle gained 16 kg more than cattle requiring a first treatment for BRD, and cattle requiring a first BRD treatment gained 14 kg more than cattle requiring additional BRD treatments. Blood et al. (1996) reported calves gaining 0 to 5% of initial body weight during the first treatment regimen were 2.7 times

less likely to be pulled for a second treatment compared to calves that lost weight. Additionally, sick cattle gaining more than 5% of their bodyweight after treatment were 11 times less likely to be repulled than cattle losing weight. Regarding ADG as an indicator of BRD, the Texas A&M Ranch to Rail program reported that animals suffering from health complications during the finishing period gained an average of 1.2 kg while healthy animals gained 1.4 kg (McNeill, 2000). Although a definitive test does not exist for the diagnosis BRD, DMI and ADG may provide indicators of an animal's overall health.

Once an animal becomes sick with BRD, the economic costs can carry through to harvest. Gardner et al. (1999) reported that final body weight for steers diagnosed and treated for BRD during the finishing period averaged 9 kg less compared to healthy cattle, resulting in 7.5 kg lighter hot carcass weight. Additionally, cattle with active lung lesions and active lymph nodes at harvest (indications that respiratory disease was occurring at harvest) had 27.9 kg lighter HCW and 1.8% lower dressing percentage. This suggests that illness during life can negatively affect the value of animal even after harvest.

There are many economic incentives to prevent BRD. In 2000, the Texas A&M Ranch to Rail program reported the leading cause of death to be pneumonia at 67% of mortalities. Morbid steers in the study returned an average of $123.86 less than healthy cattle. Only $26.78 of this reduction came from medicine and treatment costs, while $97.08 was lost due to reduced efficiency and overall animal performance (McNeill, 2000). Permanent changes in the animal following BRD coupled with a decrease in

animal value imply that prevention of BRD is more beneficial than treatment once the animal becomes ill.

Diagnosis of respiratory disease

Recent advancements in technology may allow for either early detection or a more quantitative approach to predicting and diagnosing BRD. Ideally, a chute side test would be available to ascertain the risk of an individual animal developing BRD. Alternatively, quantitative assessment could be developed to determine if metaphylaxis would be economically beneficial in a specific group of cattle. Multiple challenges have inhibited development of metaphylactic thresholds or decision points, despite the inherent value of such a tool to the beef industry. An initial challenge is identifying the causative agents for BRD, a complex viral and bacterial disease that is impacted by various environmental factors. Bacterial pathogens found to contribute to BRD include *Mannheimia (Pasteurella) haemolytica* and *Mycoplasma bovis* (Ellis, 2001; Confer, 2009). A second challenge is the lack of an industry definition for "high risk" or a more exact way to quantify a percentage of cattle within a group that will get BRD. Finally, even when BRD is treated therapeutically, it is almost impossible to verify BRD. Such challenges, and a need for a more accurate way to diagnose BRD, have made it difficult to decide whether metaphylaxis should be used in a specific group of animals.

Narrow spectrum antibiotics targeting specific bacterial species are typically more effective, and minimize the chance of broad antimicrobial resistance, according to the United States Food and Drug Administration (2014). Therefore, identifying the pathogen or causative agent of BRD symptoms within a specific group of cattle is

advantageous, allowing for specificity of treatment. Laboratory tests performed on nasal or transtracheal swabs or blood samples are feasible for identifying a specific causative agent of BRD (DeRosa et al., 2000). However, the isolates often can only be detected in an acutely ill animal; therefore, this information may act as a diagnostic tool but not as a means of prediction. Additionally, some level of these pathogens may reside in healthy animals not having succumbed to the previously described stressor. Therefore, isolation of such pathogens may not be enough to confirm BRD. These and other tests are rarely used in practice due to slow reporting time, high cost, and inaccuracies. Therefore, using a broad spectrum antibiotic is typically the preferred method of treatment as pinpointing a specific causative agent to treat the disease is not currently feasible.

Subjective diagnosis of BRD has long been called into question. Wittum et al. (1996) reported that in a group of 469 feedlot steers, 35% were treated for respiratory disease at some point between birth and slaughter. However, 78% of treated and 68% of untreated cattle had pulmonary lesions at slaughter, indicating that BRD, especially subacute BRD, may be more prevalent than previously considered. Additionally, cattle that had pulmonary lesions also had a 0.08 kg reduction in ADG. This is similar to the results of Schneider et al. (2009), who reported that 8.2% of cattle were treated for BRD during the feeding period, while 61.9% had lung lesions at the time of harvest. This is a particularly important consideration if cattle are being sold on a carcass merit basis rather than a live basis, thereby further increasing the value of both disease prevention and rapid treatment.

Chute-side technology with the ability to accurately and rapidly diagnose BRD would have tremendous value. Allen et al. (1991) used nasopharyngeal swabs and a bronchoalveolar lavage via an endoscope into the trachea to isolate bacteria from live cattle. These observations were used to assign a risk level for developing BRD. Respiratory tracts of sick cattle harbored more species of bacteria than BRD free cattle. However, this was not statistically significant, indicating such a test may not lead to an accurate diagnosis. *Pasteurella multicoda* and *Mannheimia haemolytica* were isolated more frequently from the respiratory tracts of cattle showing symptoms of BRD than from non-morbid animals. In contrast, DeRosa et al. (2000) suggested potential for efficacy of the nasal swab procedure, reporting that transtracheal and nasal swabs that were bacteriologically positive identified the same bacterial species 96% of the time. Matched pairs were genetically identical 70% of the time. Accordingly, nasal swab cultures can successfully identify the causative agent of BRD in a specific calf 70% of the time. Bacteria most frequently isolated were *Manheimma haemolytica* and *Pasteurella multicoda*. Among the *M. haemolytica* isolates, all but 2.1% of the isolates were from the same two ribotype profiles, suggesting its involvement in the cause and transmission of BRD. Isolated bacteria from other isolates in this study almost always had different ribotypic profiles, meaning that they were genetically different, yet they were similarly susceptible to each antibiotic tested. *In vitro* susceptibility of each bacteria isolated to a certain antibiotic resulted in similar susceptibilities for ceftiofur and tilmicosin regardless of bacteria ribotype, securing the place of each product in the broad spectrum category. The weakness of the process, however, lies in that the

nasopharyngeal and bronchial swabs were only able to detect bacteria from acutely sick animals, meaning that such a method can be used as a diagnostic tool but not as a predictor of morbidity risk.

Decreasing antimicrobial use is a widely discussed topic. The World Health Organization (**WHO**) in 2011 created a list of antimicrobials ranked by their importance in human medicine. They concluded that the four most important classes of antibiotics in human medicine were fluoroquinolones, third and fourth generation cephalosporins, and macrolides. Each of these classes includes an antimicrobial that is currently used in veterinary medicine to control or treat BRD. Previously, WHO (1998) expressed concern regarding antibiotic use in food animals, specifically fluoroquinolone antibiotics. Enrofloxacin, a bactericidal antibiotic in the fluoroquinolone class, is used to treat BRD by destroying causal bacteria and has been reported to be more cost effective and more efficacious in preventing BRD relapses and mortalities than ceftiofur (Abutarbush et al., 2012), making this an important antibiotic class for treating BRD. In 2011, the federal Food and Drug Administration reported that cephalosporins were the second most commonly reported class of antibiotic sold in the United States (FDA, 2010). Excede, a product discussed below with the active ingredient ceftiofur crystalline free acid, is classed as a second or third generation cephalosporin.

Theoretically, if the predicted level of morbidity and treatment failure rates in a group of arriving cattle is expected to be high, the possibility may exist to decrease total antimicrobial use by controlling an outbreak of BRD. Therefore, it stands to question whether less total antimicrobials are used in metaphylactic therapy, or in highly stressed

cattle that do not receive metaphylaxis and must be treated when subsequent illness occurs. Research is also needed to determine a definition for exactly how high of percentage morbidity would be required for the total antimicrobial use in a negative control group to exceed that of a metaphylaxis group, or if such a decrease is even possible. Additionally, if a specific class of antimicrobial could be ranked as "less important" in human medicine, potential would exist to develop a protocol to treat BRD that minimizes use of antibiotics that are critical to human medicine.

Metaphylaxis

Metaphylaxis is the on-arrival mass medication of a group of highly stressed, newly received calves for the control of BRD. When deciding to use metaphylaxis, the level of disease risk must be sufficient to offset the initial cost. As it is impossible to predict exactly how many cattle will become sick without metaphylaxis, evaluating incoming cattle and assessing if metaphylaxis will be advantageous is a challenge. A group of cattle can be assessed and a level of risk established based on the known "risk factors" previously outlined. From these parameters, an estimated prediction of BRD morbidity is derived.

To create a basis for knowledgeable decision making, literature regarding the efficacy of tilmicosin phosphate or ceftiofur crystalline free acid as metaphylaxis products to reduce BRD morbidity was collected. Basic principles in studies discussed in this review include the use of a "morbidity score" as a basis for determining health of individual animals and treating animals with a rectal temperature $\geq 39^{\circ}$C. This follows the proper study design for clinical feedlot trials to minimize observational bias (Perino,

1998). It is important to follow these guidelines for multiple reasons: to minimize observational bias when deciding to pull and treat morbid cattle and to create a sound trial design that can be utilized when looking at data across multiple metaphylaxis studies. Existent data using tilmicosin phosphate or ceftiofur crystalline free acid are not homogeneous in that data collection differs between studies. For example, studies use different threshold for treatment, while others use divergent dosages. Additionally, there is no standard for moratorium periods, the amount of time following metaphylaxis before an animal can be treated for BRD symptoms. Moratorium periods range from 1 to 8 d. Differences in protocol affects both the total morbidity and number of d until peak morbidity is observed in treatment groups, making comparisons across data sets difficult.

Although previously collected metaphylaxis data is heterogeneous, value exists in consolidating existent data and predicting a result of using a specific metaphylactic product on newly received beef calves. For the purpose of this review, results of twelve studies using tilmicosin phosphate and six studies using ceftiofur crystalline free acid were consolidated and used to create a prediction equation for morbidity reduction when either of these products is utilized for metaphylaxis. Criteria for inclusion were that the study must include a negative control (or untreated group) to provide a baseline for evaluation of percentage change in morbidity. Each of the studies included used either a 6.6 mg/kg dose of ceftiofur crystalline free acid, or a 10 mg/kg dose of tilmicosin phosphate. Morbidity (%) from each study was plotted as the percentage improvement in the treatment group over the negative control group in the same study. Results for tilmicosin phosphate are displayed in Figure 1.1, using 12 studies. Only 6 studies using

ceftiofur crystalline free acid were available, therefore the line could be more robust if future research continues to test the efficacy of this product (Figure 1.2).

For the purposes of these models, morbidity is defined as an estimation of a percentage of cattle that will become ill with respiratory disease. Previously specified risk criteria for newly received cattle may allow for an approximation of morbidity or internal data may be used to predict morbidity. Once a prediction of expected morbidity has been made, the percentage reduction in morbidity if metaphylaxis using tilmicosin phosphate or ceftiofur crystalline free acid is implemented can be calculated (Figures 1.1 and 1.2). Calculation of percentage reduction in morbidity allows the subsequent calculation of the medicinal cost of a particular group of cattle, which may be contrasted with the cost of metaphylaxis. This series of calculations allows a producer to make the most informed decision possible. Additional data would allow more accurate prediction by including treatment failure rates, or the percentage of cattle that would require treatment multiple times. Additional data would also allow similar decision support tools to include performance improvements and total antibiotic usage to provide a more accurate decision support system when choosing whether to implement metaphylaxis and what specific products to use.
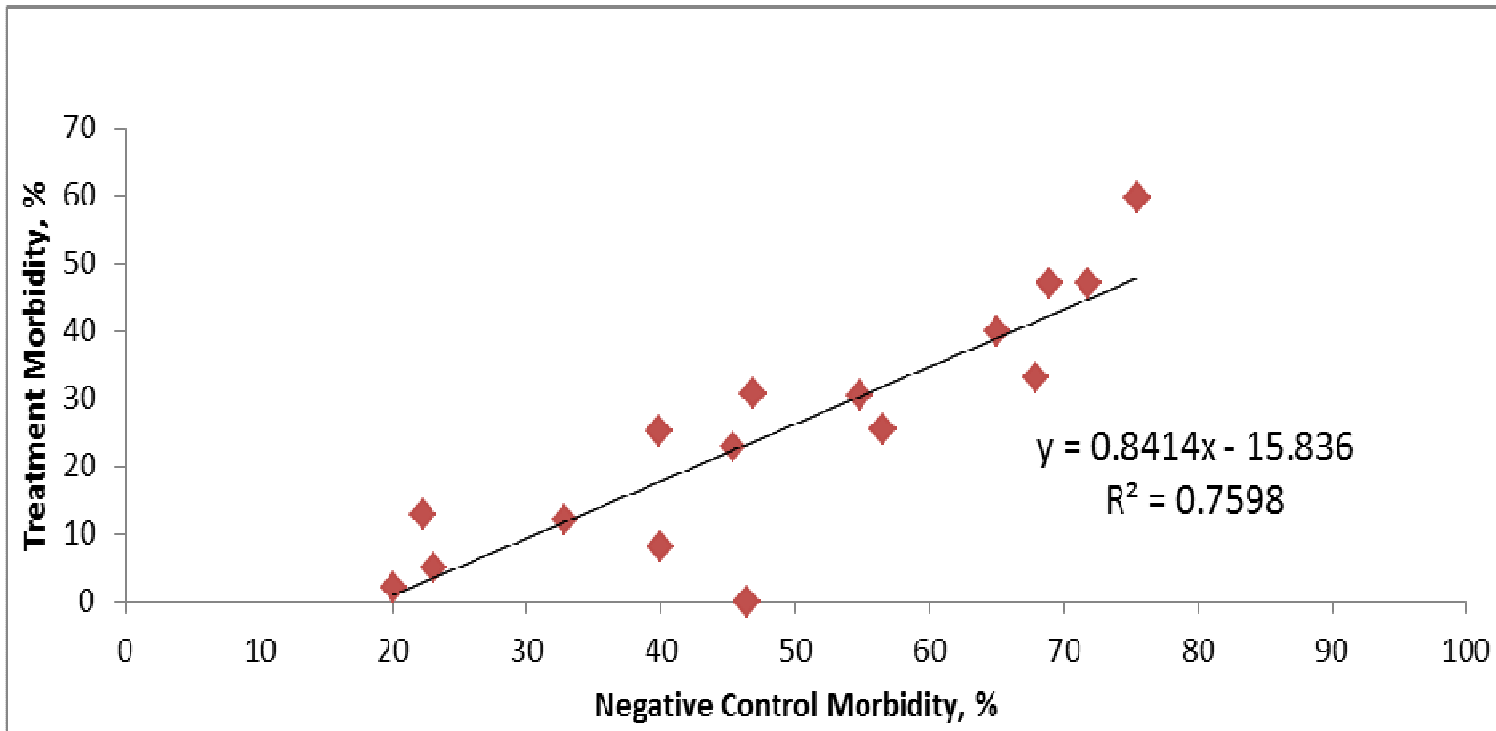
Figure 1.1: Percentage reduction in morbidity for cattle given a tilmicosin phosphate injection on arrival, compared to a negative control (untreated) group.
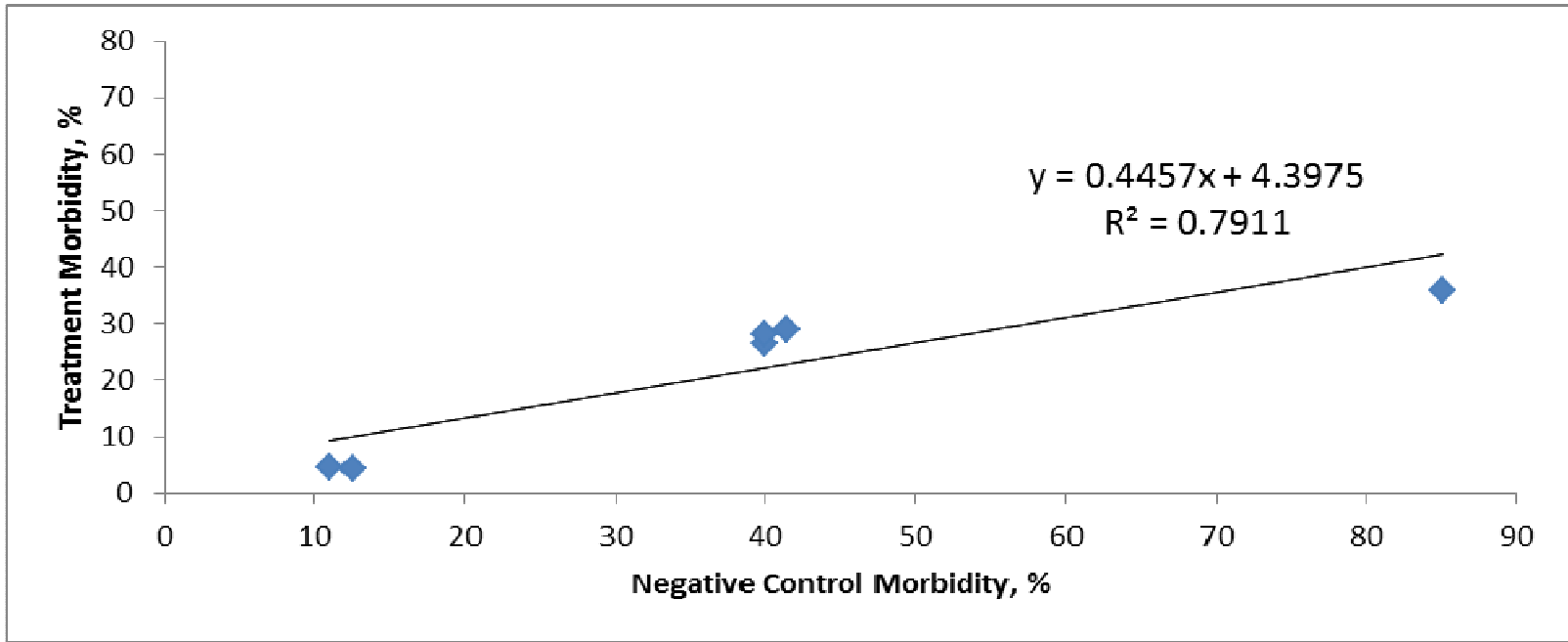
Figure 1.2: Percentage reduction in morbidity for cattle given a ceftiofur crystalline free acid injection on arrival, compared to

a negative control (untreated) group

Response to tilmicosin phosphate vs. ceftiofur crystalline free acid

Reduction in morbidity is well documented in newly received cattle provided either ceftiofur crystalline free acid or tilmicosin phosphate on arrival. Current literature does not consistently support an improvement in the performance of growing cattle due to the implementation of a metaphylactic regimen.

Due to longer-standing FDA approval and earlier release to the market, more published data exists for tilmicosin phosphate than for ceftiofur crystalline free acid. Bremer et al. (2007) compared ceftiofur crystalline free acid when given either on-arrival or at revaccination 16-27 d following arrival. Incidence of BRD was highest when cattle were given ceftiofur at revaccination, although only 2.8% higher than the negative control group. Cattle given ceftiofur on-arrival had the lowest morbidity, 4.7% versus 11% for the negative control. However, there were no differences between any treatment group in ADG or final BW. Ceftiofur crystalline free acid was most effective at controlling BRD when given on-arrival. Mass-medication with ceftiofur at revaccination was most likely ineffective because cattle had already experienced morbidity due to BRD prior to being given ceftiofur. Also in this study, cattle with lighter initial BW were more likely to be subsequently diagnosed with BRD, suggesting initial BW is a risk factor worth considering higher risk.

Benton et al. (2008) reported that a ceftiofur crystalline free acid injection on arrival compared to a negative control group decreased BRD morbidity from 12.5% to 4.4%. Cattle given the ceftiofur injection had a 0.07 kg greater ADG compared to the negative control; final body weight and feed efficiency were not affected. Maximum

number of first treatment BRD pulls occurred between 0-10 d after arrival for the negative control group, while the ceftiofur group expressed peak BRD symptoms between d-21-25. However, this may have been affected by an 8 d moratorium period for the group that received ceftiofur on-arrival.

Encinias et al. (2006) reported that a ceftiofur crystalline free acid injection on arrival compared to a negative control reduced morbidity from 85.1% to 35.8%. Furthermore, ADG of the treated group tended to be greater than the control group by 0.22 kg. Johnson et al. (2008) tested ceftiofur crystalline free given on-arrival, prompted by pen morbidity, prompted by a decline in feed intake, or on-arrival compared to a negative control group. Ceftiofur on-arrival did not change ADG or efficiency. However, morbidity was reduced by 15%, from 42 to 27%. This study included a cost analysis on each treatment group and a numerical reduction in mortality (from 3.4 to 0.9%) was not a sufficient reduction to make on-arrival metaphylaxis more cost effective than treatment based on displayed BRD symptoms. However, this result was calculated using treatment product and cattle costs in 2006, and the same result may not be obtained using these costs today. Additionally, total antimicrobial use was greater in cattle given ceftiofur on-arrival. Each of these studies used the same dose of ceftiofur crystalline free acid, 6.6 mg/kg of BW. Although there is a clear reduction in morbidity when ceftiofur crystalline free acid is administered on-arrival, more research is needed to determine the direct effects of an on-arrival injection of ceftiofur crystalline free acid on performance of growing cattle.

Tilmicosin phosphate has been used in production settings for longer than ceftiofur crystalline free acid and therefore more published data are available. As discussed previously with ceftiofur crystalline free acid, the ideal timing of metaphylaxis to control BRD has been tested. In two studies comparing tilmicosin phosphate given either prior to shipping or on-arrival, Duff et al. (2000) reported conflicting results. In one study, morbidity was 1.7% less when cattle were given tilmicosin phosphate pre-shipping as compared to on-arrival, while the second study reported that a pre-shipping tilmicosin injection resulted in 11.2% greater morbidity. Overall, both studies reported a significant decrease in the on-arrival treatment as compared to the negative control group (25% and 32.5%, respectively). Although the results were variable, they imply that pre-arrival mass medication with tilmicosin phosphate was equal or less effective as on-arrival medication. Frank and Duff (2000) similarly reported variable results between cattle given tilmicosin phosphate pre-shipping or on-arrival, compared to a negative control. Cattle given tilmicosin phosphate pre-shipping in the first study had a 5% reduction in morbidity while pre-shipping injection resulted in an 11% greater morbidity in the second study. Similar to Duff et al. (2000), these studies showed that on arrival metaphylaxis resulted in a 22% or 32% reduction in morbidity as compared to a negative control group. Both results imply that tilmicosin phosphate, when given as metaphylactic therapy for the control of BRD, is most effective when given on-arrival.

Tilmicosin phosphate has also been investigated for use post-arrival. Klemesrud et al. (1997) compared a negative control group to groups receiving tilmicosin phosphate on-arrival or 6 d following arrival. The authors reported that morbidity did not differ

when cattle were treated on-arrival (13%) or on day 6 (14%). However, increased labor

costs and increased animal stress associated with bringing the cattle up for treatment on

d-6 make this an undesirable process. The authors also reported that on-arrival

medication decreased morbidity by 9% compared to the negative control group.

Similarly, Schumann et al. (1991) compared tilmicosin phosphate given on-arrival or 3 d

following arrival to a negative control group. On-arrival medication resulted in a

reduction of morbidity from 20% in the negative control group to 2%, while morbidity

for the group given tilmicosin 3 d later was reduced to 1%. Both of the medicated groups

had 0.18 kg greater ADG compared to the negative control, resulting in a 10.5 kg greater

BW at the end of the 60 d feeding period. These results also suggest that on-arrival

treatment is the "ideal" option.

Two studies compared treatment with injectable tilmicosin phosphate on-arrival

to a negative control group (Galyean et al., 1995). In one of these trials, morbidity was

reduced from 46.4% to 0% when cattle were housed in confinement pens. Both ADG

and DMI were unaffected by the on-arrival injection. The other study housed cattle on

pasture, where tilmicosin led to a decrease in BRD from 32.8% to 12.1%. Again, ADG

was unaffected by tilmicosin phosphate. Brazle et al. (1997) also reported a decrease in

morbidity when tilmicosin phosphate was given on-arrival to both bulls (15.8%) and

heifers (25.3%). Tilmicosin phosphate led to 6.9% decrease in bull and a 5.4% decrease

in heifer mortality. However, in contrast to Galyean et al. (1995), this study reported that

ADG was 0.08 kg higher when heifers were given metaphylaxis with tilmicosin

phosphate, although the ADG for bulls was not different. Final BW was not reported in

the study results but would be the best indicator of whether this increase in ADG was worth the cost of metaphylaxis.

Daniels et al. (2000) compared metaphylaxis using tilmicosin phosphate or florfenicol to a negative control group. Statistical analysis was not completed to directly compare the tilmicosin group to the negative control; however, they reported a 16.3% decrease in morbidity and a 3.5% reduction in mortality over the negative control group when tilmicosin phosphate was used. Average daily gain was improved by 0.15 kg. The control group had higher percentage morbidity and mortality compared to the combined metaphylaxis groups; however, no significant differences were observed in any of these parameters when tilmicosin phosphate was compared to florfenicol. Healthy calves in the study gained 0.78 kg/d more and were 20 kg heavier than sick cattle after 21 d, while sick cattle lost weight on average. Accordingly, increased performance after metaphylaxis administration may be the result of an improvement of overall health status as opposed to a direct result of the product, as healthy cattle tend to perform better than morbid cattle.

Morck et al. (1993) compared tilmicosin phosphate or oxytetracycline given on-arrival with a negative control and reported that morbidity decreased by 22% when tilmicosin phosphate was used and by 14% when oxytetracycline was used. Average number of d to first treatment was extended from 10.5 to 14.5 d when tilmicosin was given compared to a negative control. Cattle that remained healthy throughout the study gained 16 kg more than cattle requiring a first BRD treatment. Additionally, cattle requiring first BRD treatment gained 14 kg more than cattle requiring further BRD

treatment. Cattle administered tilmicosin gained 4 or 6 kg more than cattle in the negative control group or cattle given oxytetracycline, respectively. Tilmicosin phosphate was more efficacious than oxytetracycline when used as a metaphylactic product for the control of BRD morbidity, although it is important to consider that tilmicosin phosphate is generally more expensive.

Guthrie et al. (2004) reported that morbidity decreased from 56% to 25% when tilmicosin phosphate was used for metaphylaxis. There was no difference in treatment failure rates between the metaphylaxis and control groups, meaning the retreatment or repull rate for cattle already treated once for BRD were similar between the two groups. Although they reported no significant difference in DMI or efficiency, cattle given metaphylaxis gained approximately 0.08 kg/d more than the negative control for the first 102 d of the study. Similarly, Schumann et al. (1990) reported that cattle given metaphylaxis gained 0.21 kg per day more than a negative control group, and that feed efficiency was improved by 18%. Vogel et al. (1998) also reported a 0.11 kg increase in ADG when tilmicosin phosphate was given on-arrival compared to a negative control, resulting in 21.8 kg heavier final BW after the 211 day feeding period. Additionally, this study reported a 6% improvement in feed efficiency in the tilmicosin on-arrival group. All of the studies discussed used tilmicosin phosphate at 10 mg/kg BW dose.

Few studies have directly compared the efficacy of tilmicosin phosphate and ceftiofur crystalline free acid. Booker et al. (2006) compared ceftiofur crystalline free with either a 3 or 7 day moratorium period to tilmicosin phosphate with a 3 day moratorium period. Initial BRD treatment rate did not differ in cattle given ceftiofur or

tilmicosin on-arrival and eligible to be treated for BRD 3 d after arrival. However, BRD mortality was 2.9% higher and overall mortality was 3.5% higher in the tilmicosin group compared to the ceftiofur group that underwent a 3 day moratorium. Feed efficiency did not differ between treatment groups; however, ADG was 0.3 kg greater in the ceftiofur group. Step et al. (2007) also reported no significant difference between cattle treated with ceftiofur or tilmicosin on-arrival for morbidity or ADG. Both of these studies did not include a negative control group, making it difficult to determine a baseline level for morbidity or to compare these studies to other metaphylaxis studies using this product. Because of this, these studies were not included in the regression analysis previously discussed.

Each of the studies discussed suggests that a reduction in morbidity can be expected when cattle are given metaphylaxis with either of these products, while data demonstrating performance improvements due to the administration of these products is limited. However, there are known benefits to performance, carcass quality, health costs, and animal well-being when disease is avoided (Larson, 2005). Future research regarding metaphylaxis should produce an industry standard definition for "high-risk" and continue to research means to decide when metaphylaxis is economically advantageous for a specific group of cattle.

Energy concentration in growing cattle diets

Beef cattle that undergo multiple stressors, such as transport and commingling, are at risk of becoming morbid (Duff and Galyean, 2007). Currently, it is unknown whether receiving diet contributes to stress and thereby negatively affects immune

function (Galyean, 1999). Although dietary energy is required for the immune system to function properly (Tizard, 2004), limited data has shown that excess dietary energy could also lead to a compromised immune system (Galyean, 1999). Nutritional manipulation may therefore provide a non-invasive strategy for mitigating disease and improving animal health.

When young, lightweight cattle (typically 400-550 lb) arrive at a feedyard or backgrounding operation, emphasis is typically placed on growth (Peel, 2003). In order to accomplish this growth, these cattle may undergo an increase in dietary energy concentration, either as a supplement to forage or as a total mixed ration in a confinement setting. High-energy diets consist of readily fermentable carbohydrates that may act as an additional stressor and suppress immune function (Owens et al., 1998). Vasconcelos and Galyean (2007) reported the average NE_g concentration of a finishing diet to be 1.5 Mcal/kg, which they say reflects low roughage concentration. There are three potential ways that energy acts as a stressor: 1) level of ME intake (Mcal/d), 2) concentration of ME (Mcal/kg), or 3) source of ME (starch versus fiber).

Diet manipulation during the growing phase may provide a simple and non-invasive approach to improve animal well-being, while reducing antibiotic use and the cost of treating sick animals through BRD prevention. Research is needed to determine if receiving period nutrition can be manipulated for the optimization of both animal health and performance. A recent and so far under-investigated management strategy to prevent immune suppression is to limit dietary energy during the growing phase, potentially alleviating an additional stress during the receiving period. If limiting dietary

energy intake or concentration is found to decrease incidence of disease, additional savings may be realized through lower feed costs during the receiving period.

Energy restriction in multiple species has been related to improved immune function. In aged rodents, caloric restriction increased lymphocyte proliferation and expression of interleukin-2 (**IL-2**) as compared with rats fed energy *ad libitum* (Pahlavani, 2000). This is important because IL-2 is a cytokine signaling molecule that regulates lymphocyte proliferation, and lymphocytes are responsible for the immune system's response to a specific infection. Binding activity of nuclear factor of activated T-cell transcription, a component in IL-2 transcription, also increased in calorie restricted rats. Stabel et al. (2003) naturally infected dairy cows with *Myobacterium paratuberculosis* while feeding either an *ad libitum* diet or an *ad libitum* diet plus additional energy added through a ruminal cannula. Control cows not receiving supplemental energy had greater lymphocyte proliferation responses to all T cell mitogens studied, suggesting an increase in immune response over cattle receiving higher energy levels. In beef cattle, Lofgreen et al. (1981) reported that cattle fed a 75% concentrate diet tended to have more total sick d than those fed hay alone (324 vs. 248 d, respectively). This data suggests a relationship between dietary energy intake and immune function.

Restricted dietary energy during the growing phase has minimal impact on finishing performance or the final carcass characteristics, and potentially improves efficiency during the finishing phase (Felix et al., 2011). Steers were fed to gain 0.9 or 1.4 kg of BW/d from diets containing 65% of either dried distillers grains with solubles

or corn during the 98 d growing phase. During the finishing phase, cattle that were limit fed (fed to gain 0.9 kg BW/d) from either energy source grew 14% faster and were 8% more efficient than cattle fed to gain 1.4 kg BW/d. Cattle that were limit fed also had 0.105 cm decrease in backfat and a decrease USDA yield grades, and a 2.5 cm^2 greater longissimus muscle area. Limit feeding energy during the growing phase, regardless of source, may positively impact finishing performance and carcass characteristics.

Few studies have been designed to investigate if changes in energy intake are connected with morbidity. Results regarding source of energy have been variable. Calves fed 38% of ME from starch had a 9% lower morbidity rate and tended to require fewer antimicrobial treatments than calves fed 48% of ME from starch when ME concentrations were the same (Berry et al., 2004b). However, there was no morbidity change when calves were fed a high or low energy diet, implying that source of energy may play a larger role in immunological changes than energy concentration.

The immunological competence of a specific animal may be quantified when exposed to an immunological challenge. Individual acute phase protein responses are measured to model variation in disease response between animals. In a study limit-feeding the same high concentrate diet and evaluating breed differences in acute phase protein response to an endotoxin challenge, dietary energy restriction affected rectal temperatures, serum cortisol concentration, and TNF-α concentration independent of breed (Carroll et al., 2011). Endotoxin challenge may have caused a redistribution of dietary energy to the immune system, thereby decreasing the dietary energy available to be used for performance (such as gain). Because the authors did not measure

performance responses after the challenge, it is difficult to determine if limit feeding the steers was detrimental to their immunological response due to this redistribution of energy. An inclusion of the time required to return to performance parameters equivalent to before the challenge would determine if limit-feeding the steers negatively affected their ability to elicit an immunological response.

Humoral immunity is a subdivision of acquired immunity that is mediated by the secretion of antibodies from B lymphocytes to defend against a specific antigen (Tizard, 2004). Exposure to antigens, as occurs during vaccine administration, helps an animal acquire humoral immunity. Theoretically, interference with this acquisition due to diet or other stress factors would interfere with vaccine efficacy. Many of the studies discussed are based on measuring humoral immunity through lymphocyte-derived cytokines. To our knowledge, no data have been published to quantify effects of divergent energy levels on the humoral immune response of growing cattle through antibody response, specifically immune response to a vaccine. Doing so would provide insight into the role of nutrition on vaccine efficacy, as well as contribute to the body of knowledge suggesting that dietary energy concentration could affect the immune system.

Limited research has suggested that humoral immunity and diet may be linked. Chen et al. (2013) described immune response in diet-induced obese (**DIO**) mice. Mice fed a high calorie diet had increased concentrations of the pro-inflammatory cytokines tumor necrosis factor-α and interferon-γ after immunocytes were cultured with the mitogens lipopolysaccharide and concanavalin A. An increase in production of these cytokines is a known trigger for inflammation and generally symbolizes a suppressed

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humoral immune response. Additionally, when both groups were given a Hepatitis B (**HB**) vaccine, anti-HBs antibody production was significantly less in DIO mice that were still receiving a high-calorie diet compared to control mice. Antibody production was still significantly less than control mice when vaccine dose was doubled in DIO mice. These findings indicate that both cellular and humoral immune responses are affected by high calorie diets and obesity. Further research is needed to gain insight into the direct effect of the high calorie diets on the immune system.

Energy concentration in growing rations can affect all phases of beef cattle production, from growing and finishing to carcass quality. Too little dietary energy intake is known to negatively affect the immune system (Tizard et al., 2004), while research is not sufficient to conclude if too much dietary energy could also carry negative effects. Current research is also not sufficient to make a conclusion about the ideal window of energy concentration during the growing phase to optimize both cattle performance and cattle health during both the growing and finishing phases. If an optimal window could be found, benefits would be seen from both an economic standpoint and an animal health standpoint.

EFFECT OF METAPHYLAXIS ON PRODUCTION RESPONSES AND

ANTIMICROBIAL USAGE IN HIGH-RISK STEERS

Overview

A trial was conducted to determine the effects of on-arrival metaphylaxis in beef cattle for controlling bovine respiratory disease (**BRD**) and determining subsequent effects on health and performance. Male calves in a randomized complete block design (n=198, arrival weight= 231 kg ± 2.4) received either 3.3 ml/100 kg (6.6 mg/kg) ceftiofur crystalline free acid (**EXC**), 4.4 ml/100 kg (13.2 mg/kg) tilmicosin phosphate (**MIC**), or were not treated (**CON**). Cattle receiving metaphylaxis had 25.2% lower morbidity rates than CON ($P = 0.01$; 51.5 versus 76.7%). Significant differences were not observed in morbidity rates ($P = 0.14$) between MIC ($46.4 \pm 4.3\%$) or EXC treatments ($56.5 \pm 4.3\%$). Of cattle requiring BRD therapy, the CON group displayed symptoms approximately 5 d earlier than cattle in the metaphylaxis group ($P = 0.01$). Cattle displaying BRD symptoms in the MIC group required treatment 3 d earlier than those in the EXC group ($P = 0.02$, 8 versus 12 d, respectively). Metaphylaxis improved ADG (1.63 versus 1.28 kg/d; $P = 0.06$) and G:F (0.29 versus 0.22, $P = 0.01$) during the first 14 d compared to CON, but differences between EXC and MIC were not significant ($P > 0.40$) during the first 14 d. Despite differences at 14 d, no differences were observed in ADG ($P = 0.20$) or G:F ($P = 0.18$) between CON and treatment groups

across the 42 d trial. Total antimicrobial usage was 6.03 vs. 6.16 of g active ingredient per animal for CON vs. metaphylaxis ($P = 0.88$), and 5.99 vs 6.33 for MIC vs EXC ($P = 0.74$). These results suggest that both tilmicosin phosphate and ceftiofur crystalline free acid effectively reduce overall morbidity and delay onset of clinical illness in newly received beef cattle. Furthermore, this reduction in overall morbidity was achieved with minimal increase in total antimicrobial usage. While overall performance outcomes were not different, animal health was improved with metaphylaxis.

Introduction

Bovine respiratory disease (**BRD**) is the leading cause of morbidity and mortality in feedlots in the United States (NAHMS, 2013). An estimated 16.2% of cattle placed in feedlots experience symptoms of respiratory disease at some point in the feeding period. Of the cattle displaying symptoms, 87.5% are treated, increasing the costs associated with BRD. Dry matter intake decreases of 50% or more are reported in cattle with BRD and it takes 10-14 d to return to normal following treatment (NRC, 2000). Post weaning transportation stress, receiving period management, and nutrition coupled with pre-weaning management and nutrition may each play a role in the development of this disease (Duff and Galyean, 2007).

Metaphylactic therapy is on-arrival mass medication of a group of newly received calves for the control of BRD. Several factors contribute to the development of BRD, including viral and bacterial agents. The bacterial species most commonly associated with BRD is *Manheima (Pasturella) haemolytica* (R.J. Callan et al., 2002).

Both ceftiofur crystalline free acid and tilmicosin phosphate are labeled for control of BRD associated with this species.

Metaphylactic therapy is often an effective means of decreasing BRD incidence in a group of highly stressed, newly received calves (Duff and Galyean, 2007). Tilmicosin phosphate on arrival resulted in a 22% lower morbidity rate and an 18% increase in ADG in one group as compared to a negative control (Galyean et al., 1995). Ceftiofur on arrival compared to a negative control decreased BRD morbidity by 14% (Johnson et al., 2008). Our objective is to evaluate the effects of tilmicosin phosphate and ceftiofur crystalline free acid on morbidity and performance of newly received cattle. We will also evaluate the effects of these metaphylactic products on total antimicrobial usage and animal health and well-being.

Materials and methods

The experimental protocol was approved by the Institutional Animal Care and Use Committee at Texas A&M University.

Three treatments were evaluated in a receiving cattle system: 1) control receiving no arrival treatment (**CON**), 2) ceftiofur crystalline free acid (Excede, Pfizer Animal Health) on arrival at 6.6 mg/kg (**EXC**), 3) tilmicosin phosphate (Micotil, Elanco Animal Health) on arrival at 13.2mg/kg (**MIC**). Doses were selected to provide a cost-neutral evaluation of each product, and both doses fall within the labeled range for effectiveness. Male calves (n=198) were purchased from an order buyer in Caldwell, Texas and shipped to the Texas A&M Agrilife Research Beef Cattle Systems Center, Burleson County, Texas. Twenty-four bulls were included in the study; the remaining

174 cattle were steers. Cattle were shipped by truck in two groups with each group arriving 14 d apart, the first 91 cattle arrived on February 26 and the remaining 107 arrived on March 12, 2013. Arrival weights ranged from 223 to 239 kg, with an average of 231 kg. Cattle were stratified by weight and randomly assigned a treatment such that each treatment group had a similar average pen weight. Each treatment group was randomly assigned to a pen, for a total of 12 pens and 4 replications per treatment. Animal health personnel and the veterinarian were blind to treatments. Housing facilities were open air, dirt floor pens, 10 measuring 10×20 m and 2 measuring 12×26 m. Cattle arrived in the late afternoon and were allowed to rest overnight in the pens. On the following day, cattle underwent initial processing where they were identified by a number with an eartag (tag did not indicate treatment to prevent bias). Cattle received MIC or EXC. They were then vaccinated with labeled dosage of: a 7-way clostridial (Barr-Vac 7, Boehringer Ingelheim) and a modified live virus vaccine (Pyramid 5) and 1 mL/50kg Moxidectin (Cydectin, Boehringer Ingelheim) and were implanted with a Component TEG with Tylan implant (Elanco Animal Health). A consulting veterinarian visited once weekly to assess overall health and confirm correct diagnosis of BRD symptoms.

Pens were monitored daily by two animal health personnel, who were blind to treatment. Animals diagnosed with anything other than BRD were removed from the pen and treated according to the consulting veterinarian, and were returned to the pen after treatment. Per the standard industry clinical trial design, (Perino, 1998) cattle suspected of BRD received a morbidity score of 0-4 based on signs of BRD including: labored

breathing, nasal or ocular discharge, lethargic or depressed behavior, or emaciated body condition. Cattle given a score of 0 displayed no signs of illness and 1-4 showed increasingly severe signs. Cattle with an illness score of 1-4 were pulled from pens, symptoms were assessed and rectal temperatures recorded, and the animal was treated if the rectal temperature was ≥ 40.6° C. At first pull, cattle were treated with 12.5 mg/kg enrofloxacin (Baytril, Bayer Animal Health), cattle not responding within 48 h were removed and treated a second time with 40 mg/kg florfenicol (Nuflor, Merck Animal Health), and cattle not responding within 96 h received a third treatment with 19.8 mg/kg oxytetracycline (Bio-Mycin, Boehringer Ingelheim). After medical treatments cattle were returned to their respective pens. A fourth pull was considered "chronic" and the steer was no longer pulled from the pen. Cattle in both the EXC and MIC groups underwent a three day moratorium following initial treatment on study day 0, and therefore were not eligible to receive Enrofloxacin for BRD symptoms until study day 4.

A receiving diet (Table 2.1) including 100 mg·hd^{-1}·d^{-1} of monensin (Rumensin, Elanco Animal Health) was delivered once daily and fed to allow for *ad libitum* intake. Ration samples were collected from each bunk at feeding, composited into one sample and subsequently analyzed to determine DM, CP, ADF, and NDF. Cattle were provided unrestricted access to water at all times. Performance responses measured included ADG and morbidity. Both were calculated as a mean for each pen.

Body weight was measured individually on d 0, 14, 28, and 42 to determine ADG and G:F. Morbidity was measured as a percentage of calves in each treatment group that required treatment for symptoms of BRD. Efficiency (G:F) was calculated as

the amount (kg) an animal gained over an experimental time period divided by the

average of the amount fed to the pen·hd^{-1}. All data were analyzed as a randomized

complete block design using the Mixed procedure in SAS version 9.3, with pen as the

experimental unit and arrival group as a block effect. Orthogonal contrasts

(metaphylaxis versus control, or EXC versus MIC) were used to compare among

treatments.

Table 2.1: Composition of the receiving ration.

Feedstuff	Percentage (as fed basis)
Cracked Corn	31.80
Dried Distillers Grains	24.40
Alfalfa	18.15
Oat Hay	18.15
Molasses	5.00
Premix	2.50
Dry Matter, %	88.7
--------------------% DM--------------------	
CP	15.5
NDF	32.1
ADF	21.4

Results and discussion

Morbidity due to respiratory disease for cattle given metaphylaxis was 25.2%

lower than the control group ($P = 0.01$; 51.5 versus 76.7%, Table 2.2). Mortality rate

was 0% for all treatments (data not shown). Brazle et al. (1997) and Duff et al. (2000)

also reported a 25% improvement in morbidity over a negative control in cattle

administered tilmicosin phosphate on arrival, while Frank and Duff (2000) reported a

34% improvement in cattle treated with tilmicosin phosphate on arrival. Encinias et al.

(2006) reported a 49.3% improvement in morbidity over a negative control in cattle

administered ceftiofur crystalline free acid on arrival.

Table 2.2: Morbidity and average number of d (after arrival) until first pull.

	Treatment[1]				Contrast P – Values[2]	
Item	CON	EXC	MIC	SEM	CON vs TRT	EXC vs MIC
Morbidity, %	76.7	56.5	46.4	4.3	0.01	0.14
Calves treated						
Twice, %[3]	36.3	29.7	17.9	5.8	0.12	0.19
Thrice, %[3]	15.3	12.7	1.4	4.4	0.16	0.11
Success rate[4], %	53.2	47.1	61.4	8.2	0.92	0.25
Days to first pull[5]	5	12	8	1.1	0.01	0.02

[1]Treatment: CON, no metaphylaxis at arrival; EXC, 6.6 mg/kg ceftiofur crystalline free acid at arrival; MIC, 13.2 mg/kg tilmicosin phosphate at arrival.
[2]Contrast P – Values: CON vs TRT, control vs EXC plus MIC.
[3]Calves treated twice or thrice: Includes calves treated for BRD symptoms only.
[4]Success rate: number of morbid animals in a pen (animals treated once for BRD), minus the number treated greater than one time for BRD, divided by the number morbid in a pen.
[5]Days to first pull: average number of d until an animal required BRD treatment. EXC and MIC groups underwent a three day moratorium following metaphylactic treatment on study day 0.

Morbidity in this experiment was higher than expected. Previous experiments

evaluating tilmicosin phosphate or ceftiofur crystalline free acid as metaphylactic

products reported morbidity rates for the control groups varying between 32% (Duff et

al., 2000) and 56.5% (Guthrie et al., 2004). Based on these data, morbidity rates for

control cattle in this study were expected to be approximately 40%. Notably, Brazle

(1997) reported average morbidity rates of 76% in negative control groups across two

experiments. This author attributed the high morbidity to the stress the freshly weaned

calves underwent when they were held at the auction barn for 48 hours or more and heavy rain both at the auction barn and at study facilities. Encinias et al. (2006) also reported a high morbidity rate (85% in a negative control group), as well as a reduction of morbidity in the group given ceftiofur crystalline free acid on-arrival (36%). Analogous to the current study, Encinias et al. (2006) also reported 0% mortality in all treatment groups.

An average of 7% of metaphylaxis cattle and 15% of control cattle required a third antibiotic treatment, suggesting that some individual morbidity cases persisted. Therefore, it is possible that symptoms were caused by a virus rather than a bacterial pathogen. Viral agents are known contributors to BRD. The exact amount of time each calf spent at the auction barn is unknown, although it is known to be less than a week. Cattle were most likely not transported long distances, although they met other criteria for being "high-risk" cattle in that they were lightweight, young, and commingled. Despite this, high morbidity rates observed (76.7% in the control group) were not expected. However, animal health personnel heavily pulled animals that were suspected to be infected with BRD, which may have contributed to a higher morbidity rate.

The average number of d to first pull was 5 d greater in cattle given metaphylaxis as compared to the control (10 versus 5 d; $P < 0.01$), and 4 d greater in the EXC group than in the MIC group (12 versus 8 d; $P = 0.02$). These results support label indications of efficacy for each drug. "Success rate", or the number of cattle diagnosed with BRD that responded to the first antimicrobial treatment, did not differ between cattle given metaphylaxis and CON ($P = 0.92$). This result is similar to Duff et al. (2000), who

compared an on-arrival tilmicosin phosphate injection to a negative control and found no difference in the percentage of steers that required more than one BRD treatment. These data suggest that cattle given metaphylactic treatment may not differ in chronicity of bacterial diseases compared to a negative control group after being treated once for BRD.

Performance differences were limited between groups (Table 2.3). During the first 14 d, ADG tended to be greater for cattle given metaphylaxis than for the control (1.63 versus 1.28 kg·hd^{-1}·d^{-1}; P = 0.06). Similarly, feed efficiency was greater for cattle given metaphylaxis during d 0-14 (0.29 versus 0.22 kg; P = 0.01). However, these differences were not maintained during the remaining 28 d, and there was no difference in final body weight on day 42 or feed efficiency over the entire 42 day feeding period. Dry matter intake did not differ between treatments during the 42 day feeding period. However, intake was measured across the entire pen; therefore, a decrease in intake by individuals was not able to be observed.

Performance response to metaphylactic treatment with these two products has varied between existing experiments. In one experiment, Galyean et al. (1995) reported that calves treated with tilmicosin phosphate on arrival tended to gain more and be more efficient during the first 14 d, but no differences remained at the end of the 28 day period in intake, feed efficiency, or ADG. Benton et al. (2008) reported no significant differences in intake or final body weight of cattle either given ceftiofur crystalline free acid on-arrival or in a negative control group, although ADG was greater for the group given ceftiofur. Similarly, Duff et al. (2000) reported no difference in DMI, ADG, or

G:F ratio in calves treated or not treated on arrival with tilmicosin phosphate. These results, along with data from the current study, suggest that changes in performance measured as ADG or feed efficiency with metaphylactic treatment may be limited. As results have varied between experiments, positive performance response could be the direct result of a decrease in overall morbidity. Early clinical identification and treatment of disease may also minimize the negative impacts of morbidity and thus minimize performance differences.

There was no difference in DMI between treatment groups in this study, and previous data suggesting changes in DMI due to metaphylaxis is varied. In a study evaluating the intake of healthy and morbid cattle in a GrowSafe System, Sowell et al. (1999) reported that healthy steers spent more time at the feed bunk than morbid steers. However, significant differences were not observed in a second trial. When evaluating tilmicosin phosphate or florfenicol as metaphylactic products and measuring intake in a GrowSafe System, Daniels et al. (2000) found no differences in DMI in cattle given metaphylaxis compared to a negative control in one trial. In another trial, the same authors reported that calves given metaphylaxis had approximately 2 more feeding bouts per day than a negative control group. Duff et al. (2000) found that DMI was 0.26 kg/steer greater in the first 7 d in cattle receiving tilmicosin phosphate on arrival compared to a negative control, but that there was no difference in DMI during the entire 35 day feeding period.

Table 2.3: Performance traits for cattle treated or not treated with metaphylaxis.

Item	Treatment[1]			SEM	Contrast P-Value[2]	
	CON	EXC	MIC		TRT vs CON	EXC vs MIC
No. of calves	67	64	67			
BW, kg						
D 0	232	233	229	2.4	0.66	0.27
D 42	300	305	302	4.9	0.62	0.65
ADG, kg/d						
D 0-14	1.28	1.63	1.62	0.13	0.06	0.95
D 14-28	1.90	1.95	2.03	0.14	0.61	0.71
D 28-42	1.66	1.59	1.58	0.12	0.65	0.95
D 0-42	1.61	1.73	1.74	0.07	0.20	0.87
Gain:Feed						
D 0-14	0.22	0.28	0.30	0.02	0.01	0.41
D 14-28	0.25	0.25	0.26	0.02	0.86	0.74
D 28-42	0.20	0.18	0.17	0.01	0.19	0.60
D 0-42	0.22	0.23	0.23	0.01	0.21	0.80
Intake, kg/d						
D 0-14	5.87	5.93	5.43	0.39	0.70	0.39
D 14-28	7.48	7.71	7.80	0.26	0.40	0.80
D 28-42	8.48	8.76	9.19	0.25	0.14	0.27
D 0-42	7.28	7.47	7.47	0.19	0.42	0.98

[1]Treatment: CON, no metaphylaxis at arrival; EXC, 6.6 mg/kg ceftiofur crystalline free acid at arrival; MIC, 13.2 mg/kg tilmicosin phosphate at arrival.
[2]Contrast P – Values: CON vs TRT, control vs EXC plus MIC.

Total antibiotic use was calculated based on the grams of active ingredient given with each treatment (Table 2.4) and was averaged across each treatment group. This calculation included the metaphylactic drug where applicable. There was no difference in total antibiotic use between the metaphylaxis or CON treatments (6.16 versus 6.03 g; $P = 0.88$) or between the EXC and MIC groups (5.99 versus 6.33 g; $P = 0.74$). However, fluoroquinolone use was lower in groups receiving metaphylaxis and requiring only a first treatment than in the control group that required only one treatment to recover (1.44

versus 2.13 g; $P = 0.01$). It is likely that this result is due to 76% of cattle in the negative

control group requiring a first treatment compared to 51% of cattle in the metaphylaxis

group that required a first treatment. Additionally, the relative concentration of the first

treatment product (enrofloxacin) may contribute to these differences. Enrofloxacin,

when given in labeled dose, contains more active ingredient than either tilmicosin

phosphate or ceftiofur crystalline free acid. Therefore, cattle given metaphylactic

treatment and subsequently requiring no antibiotic treatment used less total antibiotic

than individuals in the control group that required a Baytril treatment. High morbidity in

this study was a driver of high total antibiotic use in all groups. Such a calculation

should be made in future studies that observe lower morbidity rates in order to determine

if a difference in antimicrobial usage exists.

Table 2.4: Total antibiotic use, calculated based on g of active ingredient given within each treatment.

	Treatment[1]				Contrast P – Value[2]	
	CON	EXC	MIC	SEM	TRT vs. CON	EXC vs. MIC
Total Antibiotic Use[3]	6.03	6.33	5.99	0.70	0.88	0.74
Enrofloxacin Use (1st Treat)	2.13	1.58	1.30	0.17	0.01	0.26
Florfenicol Use (2nd Treat)	3.29	2.69	1.62	0.51	0.11	0.58
Oxytetracycline Use (3rd Treat)	0.62	0.56	0.07	0.20	0.24	0.11

[1]Treatment: CON, no metaphylaxis at arrival; EXC, 6.6 mg/kg ceftiofur crystalline free acid at arrival; MIC, 1 mg/kg tilmicosin phosphate at arrival.
[2]Contrast P – Values: CON vs TRT, control vs EXC plus MIC.
[3]Total antibiotic use: includes g of active ingredient given via metaphylaxis (includes 6.6 mg/kg ceftiofur crystalline free acid or 10 mg/kg tilmicosin phosphate given on-arrival, where applicable).

CHAPTER III

EFFECTS OF A LIMIT-FEEDING REGIMEN ON THE IMMUNE FUNCTION OF

GROWING STEERS

Overview

A trial was conducted to determine the effects of limit-feeding growing steers on

immune function. Thirty-two steers (average BW= 262 kg ± 3.9) were fed the same

ration at one of three intake levels: 4.5 (**LOW**), 5.7 (**MED**), or 6.8 kg·hd^{-1}·d^{-1} (**HIGH**).

All steers were vaccinated on study d 0 with a five-way modified live vaccine, which

acted as an immunological challenge to measure immune function. Blood samples were

collected on study d 0 prior to vaccination and every 7 d following to measure antibody

titers and hematological measurements to quantify animal response to the vaccine. By

design, ADG (0.50, 0.95, and 1.14 kg/d for the LOW, MED, and HIGH steers,

respectively) and 28 d BW of steers increased linearly ($P < 0.04$) as intake level

increased. Steers fed MED and HIGH had the greater gain to feed than LOW (0.19 and

0.12, respectively), with a tendency towards a quadratic response ($P = 0.11$). While there

was no treatment × day interaction for serum neutralizing antibody titers ($P > 0.3$), a day

effect was observed for all antibody responses measured ($P < 0.01$). Bovine herpes

virus-1 serum neutralizing antibody concentrations (log$_2$) decreased linearly (2.64, 2.12,

and 1.49; $P = 0.03$) as energy intake increased. Bovine viral diarrhea virus type-1b

serum neutralizing antibody concentrations (log$_2$) responded quadratically ($P = 0.03$) by

increasing from LOW to MED then decreasing from MED to HIGH (6.93, 7.36, and

6.36). Hematological measures, including white blood cell, hemoglobin, and mean corpuscular volume counts, did not differ between treatment groups ($P \geq 0.65$), although fibrinogen concentration was responded quadratically and was highest for the MED treatment group (434.9, 467.1, and 388.5 mg/dL, $P = 0.01$). These results suggest that energy intake does affect antibody response to vaccines, and overall immune function, in growing cattle. Future research should establish an ideal window of energy intake for growing cattle where both performance and health are optimized.

Introduction

Humoral immunity is a subdivision of acquired immunity that is mediated by the secretion of antibodies from B lymphocytes to defend against a specific antigen (Tizard, 2004). Exposure to antigens, as occurs during vaccine administration, helps an animal acquire humoral immunity. Humoral immunity and diet have been linked when mice fed a high calorie diet to induce obesity had lower serum neutralizing antibody concentrations in response to a Hepatitis B vaccine (Chen et al., 2013). Further research is needed to gain insight into the direct effect of energy intake on immune function.

High-energy diets consist of readily fermentable carbohydrates that may act as an additional stressor to already stressed growing cattle and thus suppress immune function. An adequate level of dietary energy is required for proper immune function (Tizard, 2004). However, limited data has shown that excess dietary energy can lead to a compromised immune system (Galyean, 1999). Nutritional manipulation may therefore provide a non-invasive strategy for mitigating disease and improving animal health and well-being.

Production of growing cattle depends on vaccines to stimulate immune function, prevent epidemic disease, and maintain animal well-being (Peel, 2003). The most common vaccinations given to cattle placed in feedyards include bovine viral diarrhea virus (**BVD**) vaccine and bovine herpes virus-1 (**BHV-1**) vaccine (USDA-APHIS, 2013). The objective of this study is to determine if limit-feeding growing cattle positively contributes to immune function and assists in disease prevention, by administering a proxy immunological challenge through the most common vaccinations given in US feedlots. Such information would contribute to the investigation of an ideal concentration of dietary energy to optimize both animal health and performance.

Materials and methods

The experimental protocol was approved by the Agricultural Animal Care and Use Committee at Texas A&M Agrilife Research.

Thirty-two male calves were born, weaned, and moved to a Calan Gate barn at the Texas A&M Agrilife McGregor Research Center, McLennon County, Texas. Steers had previously been vaccinated: at approximately 60 d of age, calves were given 2 mL of a 7-way clostridial vaccine (Clostri-Shield 7, Novartis Animal Health); at approximately 170 d of age, calves were revaccinated with 2 mL of the same vaccine and 5 mL of an inactivated product (Vira-Shield 6, Novartis Animal Health); and at approximately 190 d of age, calves were given 2 mL of a multivalent modified-live vaccine (BRD Shield, Novartis Animal Health). At the beginning of the feeding period, steers weighed between 200 and 312 kg, with an average initial BW of 262 kg. Steers were trained to the Calan Gate barn for 10 d prior to study d-0. Steers were fed 5.44

kg·hd⁻¹·d⁻¹ as-fed of the same receiving ration used for the duration of the study during the training period (Table 3.1). Steers were then stratified by weight and assigned to treatment such that each treatment group had a similar average initial BW. Steers were then assigned to a pen such that each pen had a similar average initial BW. Steers were placed on three dietary treatments on d-0. Treatments were: 1) low dietary intake (4.5 kg·hd⁻¹·d⁻¹; **LOW**) 2) medium dietary intake (5.7 kg·hd⁻¹·d⁻¹; **MED**), or 3) high dietary intake (fed 6.8 kg·hd⁻¹·d⁻¹; **HIGH**). These intakes allowed for predicted ADG of 0.57, 0.91, and 1.25 kg·hd⁻¹·d⁻¹, respectively. Cattle were provided unrestricted access to water at all times. A receiving diet was delivered once daily at 0800. By study design, DMI was limited in each treatment group beginning on study d-0. Orts were weighed and sampled once per week. Ration samples were collected at feeding every 7 d and subsequently analyzed to determine DM, CP, NDF, ADF, and TDN. Ort samples were also analyzed.

On study d-0, cattle were given a second dose, 2 mL (revaccination) of the five-way modified live vaccine (BRD Shield, Novartis Animal Health) containing BVD type-1 and BVD type-2, infectious bovine rhinotracheitis (**IBR**, caused by BHV-1), bovine parainfluenza type 3, and bovine respiratory syncytial virus. Blood was collected on d 0, 7, 14, 21, and 28 from the jugular vein into both a 10 ml Vacutainer tube containing 18 mg of K2-EDTA for hematological measurements via a partial blood count and a 10 ml Vacutainer tube containing a clot activator and gel for serum neutralizing antibody titer analysis. Hematological measurements quantified were white blood cell count, red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular

hemoglobin, mean corpuscular hemoglobin concentration, and fibrinogen. Serum

neutralizing antibody concentrations measured were bovine herpes virus-1 (**BHV-1**) and

bovine viral diarrhea virus type-1b (**BVD-1b**). These were selected because both were

included in the vaccine given on study d-0, and BVD-1b is the predominant BVD

subtype reported in calves with respiratory disease (Fulton et al., 2002). Blood was

transported on ice from McGregor, Texas to College Station, Texas. Blood containing

the clotting agent was then centrifuged to obtain serum and transferred into 1.5 ml

microtube. Both whole blood and serum samples were then hand delivered to the Texas

Veterinary Medical Diagnostic Laboratory, College Station, Texas for analysis. Five

whole blood samples clotted prior to delivery (four from d-0 and one from d-7);

therefore, hematological measurements could not be made and those samples were

excluded from statistical analysis.

Body weight was measured individually on d-0, 7, 14, 21, and 28 to determine

ADG and efficiency. Efficiency (gain to feed) was calculated as the amount (kg) an

animal gained over the experimental time period divided by feed consumed. All data

were analyzed using the repeated measures procedure in SAS 9.4 for Microsoft

Windows (SAS Inst., Cary, NC). Terms in the model were treatment, day, and treatment

× day interaction, with animal (treatment) serving as the subject. The LSMEANS option

was used to calculate treatment means. Orthogonal polynomial contrasts (linear and

quadratic) were used to partition treatment sums of squares. Terms in the intake and

performance model were treatment with animal (treatment) serving as the subject. The

LSMEANS option was used to calculate treatment means. Orthogonal polynomial

contrasts (linear and quadratic) were used to partition treatment sums of squares.

Table 3.1: Composition of the ration.

Feedstuff	Percentage (as fed basis)
Cracked Corn	38.0
DDG	25.5
Cottonseed Hulls	30.0
Molasses	4.0
Premix	2.5
Dry Matter, %	90.1
--------------------% DM--------------------	
CP	10.2
NDF	38.9
ADF	29.8
TDN	65.3
ME (Mcal/kg)[1]	2.36
NE_m (Mcal/kg)[1]	1.76
NE_g (Mcal/kg)[1]	0.82

[1]ME, NE_m, and NE_g were calculated based on TDN values

Results and discussion

Intake was linearly increased ($P < 0.01$) as per the design of the study (Table

3.2). Steers consumed slightly less than projected, with the LOW, MED, and HIGH

treatments consuming 4.05, 5.1, and 6 kg·hd^{-1}·d^{-1}, respectively. Steers consumed less

than expected due to both selection against various components of the diet. Crude

protein intake was lower than expected for all treatment groups due to lower than

expected CP content of the ration (10.2% versus 13% formulated). Also by design, ADG

and final BW increased linearly ($P < 0.01$, Table 3.3) as DMI increased. Steers in the

MED or HIGH treatment groups had greater gain to feed during the 28 d study period

than steers in the LOW treatment group (0.19 vs. 0.12; quadratic, $P = 0.11$). On study d-

0, average initial BW was the same for each treatment group ($P = 0.83$). Body weight

then increased linearly over the 28 d study period as DMI increased (276, 286, and 297

kg; $P = 0.04$).

Table 3.2: Average actual nutrient intake per animal per day.

	Treatment[1]				Contrast P – Value[2]	
Item, kg/d	Low	Medium	High	SEM	Linear	Quadratic
DMI	4.05	5.10	6.00	0.27	0.01	0.03
CP	0.42	0.52	0.61	0.01	0.01	0.73
NDF	1.50	1.90	2.25	0.03	0.01	0.56
ADF	1.05	1.33	1.72	0.03	0.01	0.11
TDN	2.69	3.39	3.98	0.02	0.01	0.08
ME	7.12	8.91	10.56	0.06	0.01	0.07

[1]Treatment: Low (fed 4.5 kg·hd^{-1}·d^{-1}); Medium (fed 5.7 kg·hd^{-1}·d^{-1}); High (fed 6.8 kg·hd^{-1}·d^{-1}).
[2]Contrast P – Value: Linear, linear effect of intake level; Quadratic, quadratic effect of intake level.

Table 3.3: Growth and performance of steers.

Item	Treatment[1]			SEM	Contrast P – Value[2]	
	Low	Medium	High		Linear	Quadratic
BW, kg						
Day 0	262	259	265	7.13	0.73	0.62
Day 7	262	266	278	7.17	0.12	0.63
Day 14	266	271	285	7.35	0.06	0.57
Day 21	274	283	295	7.20	0.04	0.86
Day 28	276	286	297	7.20	0.04	0.93
ADG, kg/d	0.50	0.95	1.14	0.07	0.01	0.16
G:F	0.12	0.19	0.19	0.01	0.01	0.11

[1]Treatment: Low (fed 4.5 kg·hd^{-1}·d^{-1}); Medium (fed 5.7 kg·hd^{-1}·d^{-1}); High (fed 6.8 kg·hd^{-1}·d^{-1}).

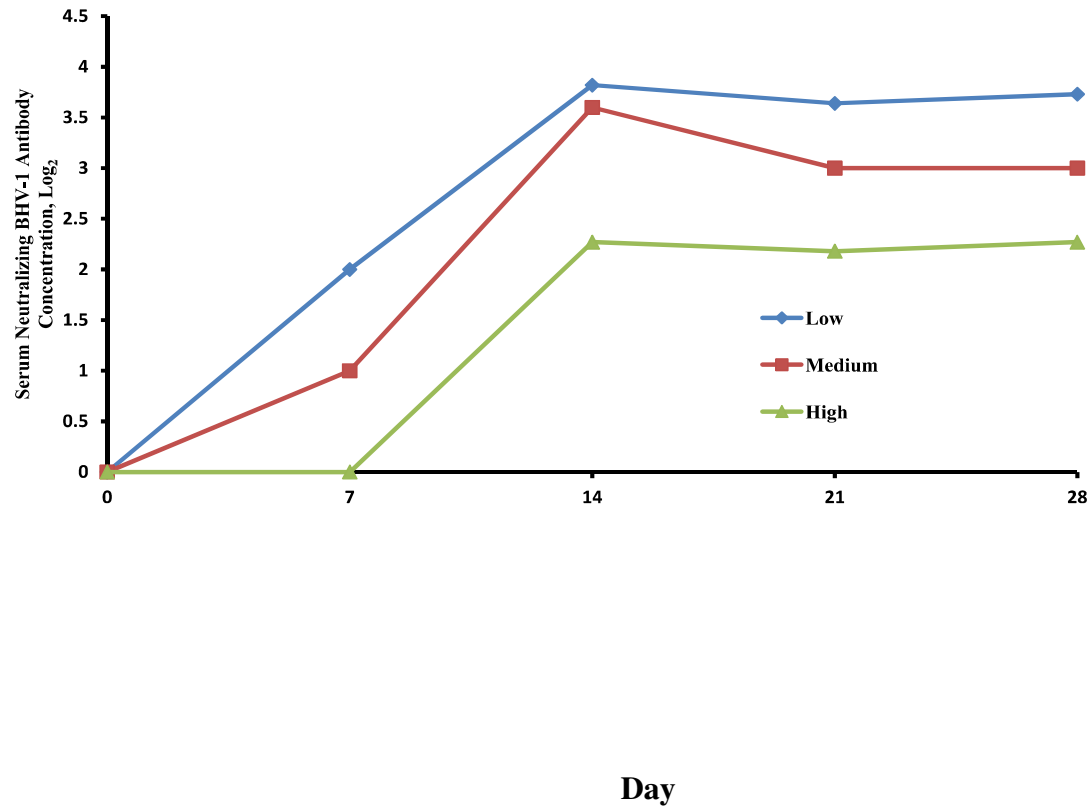[2]Contrast P – Value: Linear, linear effect of intake level; Quadratic, quadratic effect of intake level.

Day

Figure 3.1: Bovine herpesvirus-1 (BHV-1) serum neutralizing antibody titers of cattle provided either Low (fed 4.5 kg·hd^{-1}·d^{-1}); Medium (fed 5.7 kg·hd^{-1}·d^{-1}); or High (fed 6.8 kg·hd^{-1}·d^{-1}) dry matter intake. Treatment × day $P = 0.25$.
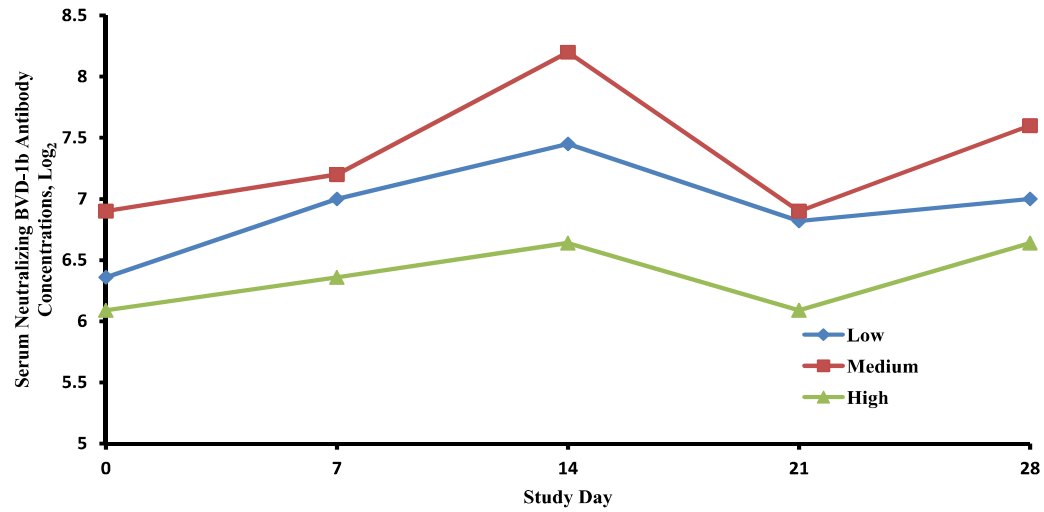
Figure 3.2: Bovine viral diarrhea virus (BVD-1b) serum neutralizing antibody titers of cattle provided either Low (fed 4.5 kg·hd^{-1}·d^{-1}); Medium (fed 5.7 kg·hd^{-1}·d^{-1}); or High (fed 6.8 kg·hd^{-1}·d^{-1}) dry matter intake. Treatment × day $P = 0.36$.

There were no treatment × day interactions for serum neutralizing antibody titers ($P = 0.25$). There was a significant day effect ($P < 0.01$). On study d-0, all cattle were seronegative for BHV-1 (serum antibody titer < 2) and positive for BVD-1b (serum antibody titer ≤ 9). Steers on the low intake treatment had the greatest concentrations of BHV-1 serum neutralizing antibody concentrations on every day of the study after d-0, while HIGH treatment had the lowest (Figure 3.1). In contrast, MED cattle had the greatest BVD-1b serum neutralizing antibody concentrations (log_2) on each day of the study while HIGH treatment had the lowest (Figure 3.2). Cattle fed the MED treatment also had the greatest BVD-1b serum neutralizing antibody concentration on study d-0 prior to vaccination or beginning of treatment, which may have affected the response. Future research should increase the DMI to see if a quadratic response exists at higher total energy intake for BHV-1 serum neutralizing antibody concentrations. If such a response is found to exist, DMI can be adjusted to limit-feed growing cattle in order to optimize immune function regarding these two parameters.

Concentrations (log_2) of serum neutralizing antibodies for BHV-1 decreased linearly ($P = 0.03$) as DMI increased (2.64, 2.12, or 1.49, Table 3.4). In contrast, concentrations (log_2) of serum neutralizing antibodies for BVD-1b responded quadratically as intake increased ($P = 0.03$). Seroconversion for BVD-1b antibody concentrations increased as intake increased from the LOW to MED treatment groups then decreased as intake increased from the MED to HIGH treatment groups. To our knowledge, no previous data exists to determine immune function using a vaccine as an immunological challenge in growing beef cattle. Results from the current study are

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similar to Chen et al. (2013), who described immune function in mice fed a high calorie diet to induce obesity. When diet-induced obese mice were given a Hepatitis B (**HB**) vaccine, anti-HBs serum neutralizing antibody production was significantly less in obese mice receiving a high-calorie diet compared to control mice. Antibody production remained significantly less than control mice when the vaccine dose was doubled in obese mice, implying a connection between caloric intake and antibody production. Future studies should increase intake level and measure serum neutralizing BHV-1 antibody concentrations again to determine if a quadratic response would occur at a higher level of energy intake.

Biological value of vaccination lies in increasing serum neutralizing antibody concentrations in response to exposure to BHV-1, as this response is essential in recovery from infection or exposure to viral pathogens (Babiuk, 1996). Serum neutralizing antibodies function by neutralizing the extracellular virus, preventing virus attachment to the host cell. They also assist polymorphonuclear neutrophils in antibody dependent cytotoxicity, a process within cell mediated immunity that limits the spread of an infection by lysing a target cell (Tizard, 2004). In this study, exposure to a modified live BHV-1 virus occurred when the vaccine was given on study-d 0; therefore, an increase in the concentration of serum neutralizing antibodies after vaccination can be associated with a positive change in the seroconversion point in the current study. Such a change suggests an improvement in immune function.

Table 3.4: Serum antibody and hematological measurements.

Item	Treatment[1]			SEM	Contrast P – Value[2]	
	Low	Medium	High		Linear	Quadratic
BHV-1, Log_2[3]	2.64	2.12	1.49	0.35	0.03	0.90
BVD-1b, Log_2[4]	6.93	7.36	6.36	0.27	0.13	0.03
WBC, μL[5]	9766	9594	10466	506	0.31	0.98
RBC, M/μL[6]	9.45	8.97	9.06	0.27	0.30	0.40
HGB, d/dL[7]	14.70	11.64	12.44	1.5	0.26	0.29
HCT, % [8]	35.96	33.44	34.05	1.05	0.19	0.22
MCV, fL[9]	38.20	37.40	37.40	0.73	0.42	0.65
MCH, pg[10]	12.52	13.02	13.59	1.42	0.31	0.37
MCHC, g/dL[11]	47.19	34.91	36.36	5.09	0.11	0.27
Fibrinogen mg/dL	434.9	467.1	388.5	15.6	0.03	0.01

[1]Treatment: Low (fed 4.5 kg·hd^{-1}·d^{-1}); Medium (fed 5.7 kg·hd^{-1}·d^{-1}); High (fed 6.8 kg·hd^{-1}·d^{-1}).

[2]Contrast P – Value: Linear, linear effect of intake level; Quadratic, quadratic effect of intake level.

[3]IBR: Infectious Bovine Rhinotracheitis (IBR) serum titers.

[4]BVD-lb: Bovine Viral Diarrhea type 1b (BVD-1b) serum titers.

[5]WBC: White blood cell count.

[6]RBC: Red blood cell count.

[7]HGB: Hemoglobin.

[8]HCT: Hematocrit.

[9]MCV: Mean corpuscular volume.

[10]MCH: Mean corpuscular hemoglobin.

[11]MCHC: Mean corpuscular hemoglobin concentration.

Hematological measures were not different ($P > 0.19$, Table 3.4) between treatment groups except for fibrinogen concentration. There was a significant day effect for red blood cell concentrations (**RBC**), hematocrit concentrations (**HCT**), and mean corpuscular volume (**MCV**);($P < 0.01$, data not shown). A treatment × day interaction occurred for RBC and HCT ($P < 0.03$). Serum fibrinogen concentration decreased quadratically as DMI increased ($P < 0.01$, Figure 3.3). This result is in contrast to Berry et al. (2004b) who measured the response of acute phase proteins to different dietary energy and starch concentrations and found no differences in serum fibrinogen concentration. Fibrinogen, an acute phase protein, is considered an inflammatory marker and concentrations are typically increased when exogenous threats are presented to the immune system (Conner, 1988). The result may have been affected by serum fibrinogen concentration being lowest on d-0, prior to vaccination or the beginning of treatments, for the HIGH treatment group. As the fibrinogen response is similar to the BVD-1b antibody production response, it is also possible that the MED treatment group better identified and responded to the immune threat. Future research should further investigate the relationship of fibrinogen with stress and morbidity, and energy intake.
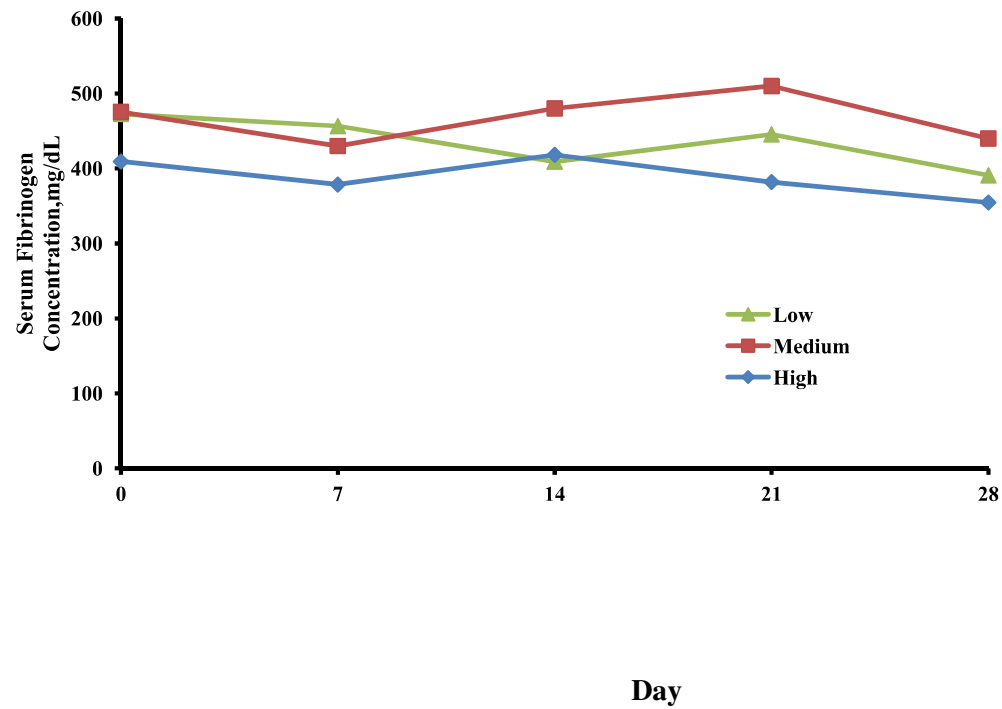
Figure 3.3: Serum fibrinogen concentrations of cattle provided either Low (fed 4.5 kg·hd^{-1}·d^{-1}); Medium (fed 5.7 kg·hd^{-1}·d^{-1}); or High (fed 6.8 kg·hd^{-1}·d^{-1}) dry matter intake. Treatment $P < 0.01$. Treatment × day $P = 0.68$.

While results of the current study are the first known to use a vaccine as a challenge to quantify immune function, other researchers have investigated a connection between dietary energy and immune function via other measurements. The current study fed 1.76 Mcal/kg of ME to all treatment groups (7.12, 8.91, or 10.56 Mcal/d of dietary energy intake$\cdot$hd$^{-1}\cdot$d^{-1}). Lofgreen et al. (1981) also investigated changes in immune function based on dietary energy intake and reported that cattle fed lower levels of dietary energy, (6.62 or 8.31 Mcal/d of ME, calculated based on the reported DE) had 76 more total sick days that cattle fed 11.37 or 12.15 Mcal/d of ME. Possibly, such a wide range of energy intake allowed for a greater total number of sick days to appear in the calves. However, steers in Lofgreen's work were not all fed the same ration, indicating that the change in ME source may be involved in the increase in total number of sick days.

Several studies have investigated dietary energy concentration as a means of affecting morbidity and immune function (Berry et al., 2004a, Lofgreen et al., 1975). Berry et al. (2004a) fed two different dietary energy levels as well as two different dietary energy concentrations in a 2 × 2 factorial, allowing a low energy diet similar to the diet used in the current study that was 2.35 Mcal/kg of ME, as well as a high energy diet that was 2.6 Mcal/kg of ME. There was no difference in morbidity of calves based on total dietary energy intake; however, there was a tendency for calves fed a greater percentage of ME from starch to become morbid with respiratory disease. Lofgreen et al. (1975) fed rations with increasing levels of ME from 2.25 to 2.84 Mcal/kg, and reported that total calves requiring treatment and total number of treatments per calf increased as

energy level in the ration increased in two of three experiments. In the third experiment, numerically fewer calves that were fed the high energy ration required treatment than those fed the low energy ration. Each of these studies fed a narrow range of dietary ME intake relative to the current study and Lofgreen et al (1981).

In the current study, all calves were fed the same ration; therefore, energy intake was adjusted by changing DMI. Intake of all other nutrients followed energy and the results of the current study cannot be solely attributed to a change in energy intake alone. Although previous research has suggested that dietary energy intake is associated with immune function (Galyean, 1999), it is unknown if other dietary factors also play a role in cattle health. In the current study, CP intake increased linearly ($P = 0.01$) as DMI increased. Nissen et al. (1989) reported a linear increase in number of calves that responded to a BHV-1 vaccine as metabolizable protein intake increased. This result is in contrast to that of the current study, where serum neutralizing BHV-1 antibody concentrations decreased linearly as DMI (and therefore CP intake) decreased.

Existent data is insufficient to clearly elucidate the connection between dietary energy and immune function. While changes in immune markers, such as acute phase proteins, did not reveal a direct connection and no change in morbidity (Berry et al., 2004a), a wider range of energy differences revealed a change in morbidity (Lofgreen et al., 1981). As limit-feeding during the growing phase does not negatively affect feedlot performance or carcass characteristics (Felix et al., 2011) future research should feed a wider range of energy intake and measure immune markers to determine an ideal "window" of energy intake where both health and performance are optimized.

CHAPTER IV

CONCLUSIONS

Bovine respiratory disease is the primary cause of morbidity and mortality in feedyards. Prevention of respiratory disease has the potential to improve economic returns, carcass quality, and animal health and well-being. Metaphylactic therapy is an effective means to reduce morbidity in highly stressed, newly received cattle that are more susceptible to illness. Further investigation is needed to find non-invasive means to prevent respiratory disease and to determine the relationship between dietary energy concentration and morbidity.

Results of the current study along with previous reports indicate that tilmicosin phosphate or ceftiofur crystalline free acid given as metaphylactic treatment to newly received calves decreases the percentage of calves requiring treatment for BRD. According to the current data, this decrease in animal health and well-being may be achieved with minimal effect on total antimicrobial usage. Overall weight gain of cattle given either product did not improve over cattle not given metaphylaxis. There was no difference in the efficacy of the two products for decreasing morbidity or increasing performance.

The current study established a connection between receiving period nutrition and immune function through nutritional effect on antibody production in response to vaccine exposure. Future research should provide a wider range of intake levels than the current study to test for a quadratic response for BHV-1 serum neutralizing antibody

production, and should evaluate the effects of energy source and concentration on

immune function.

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