COMPARATIVE EFFICACY OF METAPHYLAXIS AND RESPIRATORY VACCINATION IN HIGH-RISK, NEWLY RECEIVED FEEDLOT CATTLE

by

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ABSTRACT

Our objective was to compare metaphylaxis with tulathromycin (META) and vaccination with a pentavalent modified-live virus respiratory vaccine (MLV) in high-risk feedlot calves. Beef bulls (n = 372) and steers (n = 106) were blocked by truck load, stratified by initial BW (234 ± 1.32 kg), health status and sex, and randomly assigned to treatments arranged in a 2 × 2 factorial: 1) no META or MLV; 2) META administration on d 0 (**META**), 3) MLV administration on d 0 with revaccination on d 14 (**MLV**), and 4) META and MLV administration (**META+MLV**). Interactions and main effects were analyzed within a generalized complete block design using a mixed statistical model with 10 pen replicates/treatment. Body weight and feed refusals were recorded on d -1, 0, 14, 28, 55 and 56 to determine interim and overall (d 0 to 56) gain performance, dry matter intake, and gain to feed ratio. A subset (n = 256) was affixed with a 3-axis accelerometer ear-tag to quantify activity and rumination time. A 7-d post-metaphylactic interval was implemented for META and BRD cases were determined by treatment-blinded, trained investigators. Interactions were tested first, followed by the main effects of META and VAC if the interaction for a given dependent variable was non-significant ($P > 0.05$). The META groups had greater ADG from d 0 to 14, 14 to 28, and overall ($P \leq 0.01$). Body weight on d 14, 28, and 56 was increased ($P < 0.01$) for calves in the META group with a 13.52 kg increase on d 56. For each interim period and overall, DMI was greater ($P < 0.01$) for META, but not MLV ($P \geq 0.11$). The BRD morbidity rate was less for META

(18.5 vs. 51.2%; $P < 0.01$); however, it was not improved for MLV ($P = 0.37$). Increased daily rumination time was observed for META ($P < 0.05$). A META × day interaction existed ($P = 0.01$) for daily rumination time and greater rumination minutes occurred for META groups from d 9 to 20 and on d 22, 24, 26, 27, and 29 ($P < 0.05$). Health and performance of high-risk feedlot cattle was improved by META, but not MLV.

Key words: bovine respiratory disease, health, metaphylaxis, modified-live virus vaccination

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Chapter I: Review of the Literature

Introduction

Bovine Respiratory Disease Complex

Bovine respiratory disease (BRD) is a complex, multifaceted disease that impacts an estimated 19% of cattle placed in U.S. feedlots and is responsible for 70 to 80% of morbidity and 60 to 70% of feedlot mortality (USDA-APHIS, 2011). The beef marketing system predisposes cattle to physical and psychological stress that can induce physiological stress. Physical stress occurs when there is any kind of bodily or physical injury and events that can be generated by water deprivation, physical trauma, commingling, and transportation (Tarrant, 1990). Alternately, psychological stress is fear-based stress that can be induced by chute restraint, handling, or novel environments (Grandin, 1997), while physiological stress causes disruption of biological homeostasis such as inflammation or infection (Dragoş and Tănăsescu, 2010). Chronic stress is defined as a stressor that impacts an animal for greater than 24 hours (h), and is typically immunosuppressive (Trevisi and Bertoni, 2009). Weaning is an example of a chronic stress event that causes weight loss and immunosuppression, thus resulting in an increased risk of morbidity or mortality (Step et al., 2008). Many cow-calf producers sell calves at auction the same day they are weaned because it is less labor and morbidity risk when compared to calves that are pre-weaned and kept on the ranch for 45 d or more. In a commercial feedlot, 1,444 beef calves were used to determine the differences in health and performance between preconditioned and non-preconditioned calves (Seeger et al., 2008). These outcomes were observed from 3 treatment groups, 493 unweaned calves with unknown health history, 664 calves weaned 45 d before to shipment and received

vaccination at weaning, and 287 calves weaned 45 d before shipment and feedlot commercial health protocol was followed upon feedlot arrival. The calves that were not preconditioned required more days on feed (161 vs 147 d). The non-preconditioned cattle also had a lower average daily gain (ADG; 1.49 vs 1.77 kg) and greater morbidity throughout the feeding period (26.29 vs 13.01%) compared to the pre-conditioned calves (Seeger et al., 2008). Another element that adds to the pathogenesis of BRD is commingling at auction barns. The average cow herd size in the U.S. is 47.4 bovine animals, and because of gender and weight differences, cattle are frequently sold individually at auction barns where commingling occurs (USDA-APHIS, 2011). Commingling is a psychological stressor and the primary method by which cattle are introduced to new antigens or pathogens they have yet to develop immunity against (Sanderson et al., 2008). Therefore, BRD is a multifaceted disease with viral infection(s) predisposing the cattle to bacterial infection by causing damage to lung clearance mechanisms, such as cilia, and by taxing the immune system allowing bacteria to invade the lungs (Carlos-Valdez et al., 2016; Ellis, 2009).

Viral pathogens associated with bovine respiratory disease

Common viruses associated with BRD include bovine viral diarrhea virus (BVDV) type 1 and 2, infectious bovine rhinotracheitis virus (IBRV), bovine respiratory syncytial virus (BRSV), and bovine parainfluenza-3 virus (PI3V). Bovine viral diarrhea virus has a synergistic effect with other BRD pathogens such as *Mannheimia haemolytica* (Potgieter et al., 1985), PI3V (Fulton et al., 2000), BRSV, IBRV (Richer et al., 1988) and is categorized into biotypes and genotypes. The BVDV biotypes consist of non-

cytopathic, and cytopathic mechanisms, where cytopathic biotypes result in epithelial cell expiration. The genetic variation of BVDV is categorized by genotypes, type 1 or 2 (Goyal and Ridpath, 2008) and can cause mild or severe infections that result in enteritis, immunosuppression, fatal mucosal disease, and reproductive disorders (Duffell and Harkness, 1985; Liebler et al., 1995; Kelling et al., 2002).

A persistently infected (PI) calf is immunotolerant to BVDV and continuously sheds BVDV throughout its entire life, but may not exhibit any clinical symptoms unless they contract mucosal disease that is generally fatal (Caswell and Archambault, 2007; Donis, 1995; Goyal and Ridpath, 2008; Thurmond et al., 2008). The number of initial respiratory treatments in feedlot cattle was 43% greater in cattle exposed to an animal PI with BVDV compared to those not exposed to a PI animal (Loneragan, 2005). It is questionable if high-risk cattle should be PI BVDV tested upon arrival to identify and remove any PI calves that will continuously shed BVDV. A PI BVDV bovine comes about when a non-PI cow contracts a congenital infection with BVDV during the first trimester of pregnancy and the calf is born a PI calf. Occurring less often, a PI cow produces a calf that is also a PI because the fetus recognizes intra-cellular BVDV viral DNA as self and therefore the virus becomes part of the genome (Liebler-Tenorio et al., 2008; McClurkin et al., 1984). In the host animal, BVDV causes immunosuppressive effects, such as decreasing T and B lymphocyte concentrations, chemotaxis, cytokine production, and impairment of mucosal bacterial clearance mechanisms (Bolin et al., 1985; Pollreisz et al., 1997). Bovine viral diarrhea virus works synergistically with bacterial pathogens and has been found in cattle with pneumonia along with *Mannheimia hemolytica* (*MH;* Fulton et al., 2000), *Pasteurella multocida* (*PM*), *Mycoplasma bovi*

(*MB;* Haines et al., 2001), *Histophilus somni* (*HS*), Bovine herpesvirus-1 (BHV-1; Biuk-Rudan et al., 1999), PI-3 (Fulton et al., 2000), and BRSV (Brodersen and Kelling, 1999).

Bovine herpesvirus-1, also known as IBRV and causes a disease referred to as "rednose" because of the distinctive plaque formations that develop in the naris. Other clinical signs of BHV-1 infection include upper respiratory tract disorders, nasal discharge, conjunctivitis, genital disorders, and gaunt appearance (Muylkens et al., 2007). Bovine herpesvirus-1 is commonly transmitted via nose to nose contact and less commonly via airborne and aerosol transmission (Mars et al., 2000). Bovine herpesvirus-1 encodes 3 proteins that inhibit specific components of immunity UL49.5, Glycoprotein G, bICP0. Protein UL49.5 down-regulates major histocompatibility complex (MHC) class I molecules by blocking the transporter associated with antigen processing (Koppers-Lalic et al., 2001). Glycoprotein G inhibits chemokine activity by preventing their interaction with cellular receptors (Costes et al., 2005). Transactivator protein, bICP0, obstructs interferon cytokine signaling (Henderson et al., 2005). Bovine herpesvirus-1 has an incubation period of 2 to 6 d and establishes lifelong latency following an acute infection where it resides in the trigeminal ganglia and germinal center of pharyngeal tonsils (Jones, 2003). Physiological stress may cause recrudescence of BHV-1 (Pastoret et al., 1980). Twenty calves previously challenged with BHV-1 and with a pre-existing antibody titer against BHV-1 were administered 40 mg of dexamethasone at 0600 h on d 0 to 2. Nasal swabs were collected daily from d 0 to 12 and analyzed by virus isolation testing. All cattle had BHV-1 in nasal swabs at least one sample day indicating that physiological stress can cause reactivation of BHV-1 (Seiver et al., 2019).

Bovine respiratory syncytial virus (BRSV) is an enveloped ssRNA virus that replicates in the nasal epithelium and later disperses throughout the upper respiratory tract (Valarcher and Taylor, 2007). Bovine respiratory syncytial virus has an incubation period of 2 to 6 d and its virulence factors include fusion proteins that make syncytium formation. Clinical indications of BRSV infection include reduced sperm quality, induced febrile response, reduced phagocytosis and opsonization by alveolar macrophages, inhibited mucociliary clearance mechanisms, and bronchial and bronchiolar epithelial necrosis (Castleman et al., 1985; Hodgins et al., 2002). These BRSV induced factors also aid in immune dysfunction, allowing for opportunistic bacteria to proliferate.

Bacterial pathogens associated with bovine respiratory disease

Mannheimia haemolytica (MH), previously known as *Pasteurella haemolytica,* is a gram-negative, non-spore forming and non-motile, opportunist, commensal bacteria that resides in the nasopharynx and tonsillar crypts (Clawson and Murray, 2014). *Mannheimia haemolytica* has 12 capsular serotypes with serotype A1 being the most commonly associated with BRD cases throughout the feedlot receiving period (Hodgins and Shewen, 2004). During immune dysfunction or suppression, the commensal relationship between host and bacteria is disrupted allowing bacteria, such as *MH*, to proliferate (Highlander, 2001). Virulence factors include an outer capsule that aids in attachment, outer membrane proteins that protect the bacterium from immune responses, a lipopolysaccharide complex that causes edema, acute inflammation, and a leukotoxin (Lee et al., 2007; Rice et al., 2007). The endotoxin serves as a chemoattractant for inflammatory cells and leukotoxin causes degranulation of neutrophils and tissue mast

cells resulting in fibrinous pleuropneumonia associated with *MH* (Saban et al., 1997). A 7-year study from 1994 through 2002 collected *MH*, *PH* and *HS* isolates from lung tissue or swabs from necropsies of calves that were 16 to 18 months of age and were diagnosed with pneumonia. There was a total of 842 bacterial isolates collected, with *MH* as the most abundant, followed by *PM,* and then *HS* (46.3, 34.7, and 19.0% respectively; Welsh et al., 2004).

Pasteurella multocida is a gram-negative bacteria that has 5 capsular serotypes and 16 serotypes based on lipopolysaccharide antigens. The outer membrane protein of *PM* can cause hemorrhagic septicemia and pneumonic pasteurellosis in cattle. It has several virulence factors such as a polysaccharide capsule that aids in resisting phagocytosis, adherence to a host with fimbriae adhesion ligands, and sequestration of iron, leaving it unavailable for immune response. Serotypes strains B and E are predominantly responsible for hemorrhagic septicemia, with A3 as the most common serotype found in BRD. According to Welsh et al. (2004), *PM* is the second most common bacteria isolated in the lungs of cattle that died because of bovine pneumonia. It is a commensal bacterial that resides in the mucous membrane of the oropharynx.

Histophilus somni, previously referred to as *Haemophilus somnus,* is a gram-negative commensal bacteria that resides in the nasopharynx and colonizes in the lower respiratory tract (DeRosa et al., 2000). *Histophilus somni* can generate histamine that aids in tissue inflammation and has an exopolysaccharide that is released from its surface to form biofilms, or groups of bacteria that adhere together (Corbeil, 2007). The immunoglobulin binding protein has cytotoxic activities against endothelial cells by mediating contractions that allows the pathogen to enter the blood (Pan et al., 2014).

Uncomplicated infections of *HS* can result in fibrinopurulent bronchopneumonia, and when associated with BRD complex, results in abscessing laryngitis, fibrinous pericarditis, incoordination, and sudden death related to cardiovascular muscle necrosis (DeRosa et al., 2000).

Mycoplasma bovis does not have a traditional cell wall, but instead possesses a tri-layered membrane that makes it difficult for commonly used antimicrobials to destroy (Maunsell et al., 2011). Once *MB* enters the respiratory system, it can migrate through the epithelial cells and become systemic. Bacteremia caused by *MB* can occur within a day of bacterial infection thus explaining symptoms of arthritis and otitis (Caswell and Archambault, 2007). *Mycoplasma bovis* related lung lesions can vary from minor lung consolidation to necrotic bronchopneumonia and can also cause enlargement of bronchi or bronchi branches. When cattle were infected with *MB* and then challenged with *MH*, it resulted in more severe disease suggesting a synergistic relationship (Gourlay et al., 1989).

Antimicrobial Metaphylaxis For the Control of BRD

Efficacy of antimicrobial metaphlaxis to control BRD

Antimicrobial metaphylaxis is defined as the timely mass medication of a group of animals to eliminate or minimize an expected outbreak of disease (CDC, 2019; Ives and Richeson, 2015). Antimicrobial metaphylaxis is used by 50.4% of all U.S. feedlots and 39% of all cattle entering a feedlot will receive an antimicrobial metaphylaxis during initial processing (USDA-APHIS, 2011). The American Association of Bovine

Practitioners defines metaphylaxis as “the administration of an antimicrobial to an individual animal with a subclinical infection to reduce the risk of the infection becoming clinically apparent, spreading to other tissues or organs, or being transmitted other individuals” (Smith et al., 2009). Metaphylaxis is typically used in feedlot calves that are classified as high-risk and do not have known pre-arrival health information. High-risk calves are typically light-weight and experience a series of stressors as they move through the beef cattle marketing system. High-risk calves are typically not backgrounded and not castrated, vaccinated or weaned before marketing (Daniels, 2000; Fike, 2017; Steph et al., 2008). Furthermore, high-risk calves are generally purchased at an auction market where they are highly commingled, transported and introduced to a novel environment (Tarrant, 1990; Stephenson, 2002). There are many diverse antimicrobials available for the control of BRD and an abundance of research depicting the efficacy of antimicrobial metaphylaxis in reducing BRD related morbidity and mortality in high-risk calves (Baptiste and Kyvsgaared, 2017; Kilgore et al., 2005; Wellman and O’Connor, 2007; Ives and Richeson, 2015). The majority of respiratory disease-related morbidity typically arises within the first 14 d of feedlot arrival (Richeson et al., 2009). Determining clinical signs of BRD is subjective and can require training and experience to become consistent and accurate at recognizing sick cattle. It can also be difficult to recognize sick cattle because cattle are prey animals; therefore, when they feel threatened, they typically conceal clinical signs. Wittum et al. (1996) recognized the difficulty of identifying cattle affected with BRD. Feedlot calves were evaluated for BRD morbidity by trained feedlot personnel and resulted in 8.17% morbidity. Subsequently, calves were harvested to record lung lesions, resulting in 62% of all the calves having

lung lesions at harvest. Similarly, 469 steers were found to have at least one lung lesion at harvest, and only 35% received treatment for respiratory disease throughout their lifetime. At harvest, 72% of the calves had lung lesions and 68% went undetected for signs of respiratory disease and were never treated (Wittum et al., 1996). Antimicrobial metaphylaxis aids in reducing the subjectivity of diagnosing BRD and has repeatedly resulted in improved morbidity. Kilgore et al. (2005) used tulathromycin and tilmicosin for the control of BRD in 1,239 high-risk calves. Calves were allocated to 1 of 3 treatments, saline (0.02 ml/kg of BW), tulathromycin (2.5 mg/kg of BW), and tilmicosin (10 mg/kg BW). The saline-treated calves had the highest morbidity rate followed by tilmicosin and tulathromycin (58, 28.7, and 13.2%, respectively). In the saline-treated group, 78% of BRD related morbidity occurred within the first 5 d of arrival processing, further validating that administration of metaphylaxis upon arrival could aid in reducing morbidity. A nasopharyngeal swab collected from treatment failures of the saline-treated calves revealed the most commonly isolated bacteria to be *MH* (63.3%), followed by *Mycoplasma* species (54.4%). Abell et al. (2017) reported BRD morbidity results from 29 studies with 7 different antimicrobials in a meta-analysis of metaphylaxis for control of BRD. From d 1 to close out of the feeding period, tulathromycin had the smallest odds ratio (risk) for BRD morbidity followed by gamithromycin, tilmicosin, and ceftiofur. The overall results of the meta-analysis indicated that the cattle treated with an antimicrobial upon feedlot arrival had reduced odds ratio for BRD compared to control animals. Metaphylaxis is practical in feedlot situations because it mitigates the risk of missing a sick animal that might benefit from an antimicrobial. All animals are administered an antimicrobial at initial processing and a post-metaphylactic interval of 3 to 10 d is

prescribed. Therefore, this reduces handling and stress from pull and treat protocols up to the expiration of the moratorium and may allow time for self-cure to occur before the need to administer antimicrobial treatment.

Antimicrobial-resistance concerns

Antimicrobial use in livestock has been under increasing public scrutiny due to increased awareness of antimicrobial-resistant bacteria when using medically important human antimicrobials in food animal production (CDC, 2019). The World Health Organization describes antimicrobial resistance as, "when microorganism's change in ways that render the medications used to cure the infections they cause ineffective" (WHO, 2017). Resistance can occur via natural resistance, genetic mutations, or most commonly, acquired resistance (Amat, 2019; Mandal and Paul, 2019). The Center for Disease Control has listed four core actions to prevent antimicrobial resistance: preventing infections and the spread of infections, tracking resistant patterns, improving the use of antimicrobials, and developing new antimicrobials and diagnostic tests (Stephenson, 2002). The first multidrug-resistant bacteria relating to BRD causing bacteria was reported by Chang and Carter (1976). Throughout a 3-year period, *MH* and *PM* isolates from clinical cases of BRD were investigated for resistance to streptomycin, penicillin, tetracycline, and chloramphenicol using a Kirby-Bauer test. It was reported that *PM* and *MH* resulted in 79.1 and 96.1% resistance to at least one of these drugs, respectively. A more recent study by Snyder et al. (2017) evaluated the antimicrobial resistance of *MH* against tulathromycin in auction derived, high-risk calves. Upon arrival, all calves received tulathromycin (2.5 mg/kg of BW) and a deep nasopharyngeal swab

(NPS) sample was collected. A second NPS sample was collected either before BRD treatment or 10 to 14 d after arrival. A Kirby-Bower test indicated the number of isolates that were susceptible, intermediate or resistant to ceftiofur, enrofloxacin, florfeinicol, gamithromycin, tilmicosin, and tulathromycin. From the arrival NPS, there were few isolates classified as resistant. Except for ceftiofur, there was a dramatic shift from susceptible to intermediated and resistant concluding that MH can become multi-drug resistant. This study did not contain a negative control, therefore, a relationship between antimicrobial metaphylaxis and antimicrobial resistance was not determined (Snyder et al., 2017). For the control of BRD in a truckload of cattle, the average required number of cattle to treat in order to prevent 1 acute case of BRD, is 5 (DeDonder and Apley, 2015). Therefore, in a group of 100 cattle, only 20 head on average will benefit from the administration of antimicrobial metaphylaxis (Baptiste and Kyvsgaard, 2017) which presents concerns for judicious use and promotion of bacterial resistance with metaphylaxis.

Targeted metaphylaxis

A novel alternative to metaphylaxis is targeted metaphylaxis that is defined by Dr. John Richeson as “an alternative disease control strategy, applied at the individual animal level, through means of a risk metric as a decision tool, thus reducing antimicrobial use and cost” (Richeson, 2019). Targeted metaphylaxis can improve health management, address antimicrobial resistance concerns, and demonstrate antimicrobial stewardship to the public. A chosen targeted metaphylactic strategy must be repeatable, accurate, have a positive return on investment, and produce a rapid result so the processing crew

workflow is not disrupted (Richeson et al., 2018). Accuracy is the capability to deliver a true measurement of the subsequent BRD risk, and precision is the capability to deliver a consistent test result (Timsit et al., 2018). Targeted metaphylaxis can use simple metrics such as chute entry order, on-arrival gender (Richeson et al., 2013), pre-existing ear-tags, BW in relation to cohorts (Pillen et al., 2016), rectal temperature (Galyean et al., 1995), or lung auscultations (Noffsinger and Brattin, 2014). It was hypothesized that a chute entry pattern during initial processing might depict behavioral patterns associated with BRD risk that could be used as a decision tool to administer targeted metaphylaxis. In an unpublished data set, chute entry order was recorded throughout 10 truckloads of cattle at the WTAMU Research Feedlot, with no correlation between chute entry order and incidence of BRD morbidity observed. Another possible risk metric is arrival gender (bull vs steer). Castration is a stress event that can negatively impact morbidity performance (Álvarez-Rodríguez et al., 2017). As calves become older, the stress of castration increases as indicated by Gretschneider (2005), who compared plasma cortisol concentrations of cattle castrated at less than 6 months of age to cattle greater than 6 months of age (Bretschneider et al., 2005). Daniels et al. (2000), combined data throughout 3 trials that each consisted of a duration of 21 d to determine how arrival gender status (bull vs steer) might affect morbidity and performance. When compared to cattle castrated upon arrival, cattle that arrived as steers had less morbidity (18.6 vs 35.8%) and increased ADG (0.21 vs. 0.53 kg). It has also been reported that stocker calves are 3.32 times more likely to be clinically diagnosed with BRD when they arrive as bulls and castrated during initial processing (Richeson et al., 2013). Similarly, when calves arrive at the feedlot with a pre-existing ear tag it is an indication that they have

been handled at least once before arrival. Although we do not know what was done to the calves when they were handled, it is possible they were exposed to better health management strategies when compared to calves that did not have an existing ear tag. Therefore, the presence of an ear-tag at arrival to subsequent facilities in the beef production chain could indicate reduced health risk and be a useful metric for targeted metaphylaxis, although this concept has not been previously evaluated. Several factors can influence cattle weight, such as age, genetic propensity for growth, or nutritional status. It is well documented that there is a negative correlation between increased weight and incidence of BRD (Hay et al., 2016a; Hay et al., 2016b; Sanderson et al., 2008; Cernicchiaro et al., 2013). As reported by the USDA National Animal Health Monitoring System, 21.2% of calves that weighed less than 317.51 kg developed BRD; whereas, only 8.8% of calves that weighed greater than 317.51 kg developed BRD (USDA-APHIS, 2011). Furthermore, records from 16 U.S. feedlots over a 7-year period were analyzed to determine if a correlation existed between the mean average arrival BW and mortality and culling. An inverse relationship was determined between arrival weight and mortality and culling; as arrival BW increased the occurrence of mortality and culling decreased. Lightweight calves, less than 181.89 kg, were 3.60 times more likely to die or be culled when compared to middleweight (181.89 to 270.79 kg) and heavyweight (greater than 270.79 kg) calves (Babcock et al., 2013). Rectal temperature is an objective measure that is frequently used to verify morbid cattle in production settings and therefore could potentially be useful for targeted metaphylaxis. However, rectal temperature can be influenced by weather (Rhynes and Ewing, 1973), animal temperament (Burdick et al., 2010), processing time (Galyean et al., 1995), and depth or technique of rectal probe

penetration (Burfeind et al., 2010). There is a temporal correlation between the rectal temperature and processing order; as the processing order number increases, rectal temperature increases (Galyean et al., 1995). There was no difference in BRD incidence detected when cattle that had a rectal temperature of ≤ 39.7°C were administered antimicrobial metaphylaxis compared to cattle that were mass treated (Galyean et al., 1995), which suggests utility for targeting antimicrobial metaphylaxis at initial processing. In another study utilizing 33 dairy cows, a rectal temperature probe was inserted at a depth of 11.5 cm or 6.0 cm to determine if rectal probe depth influences temperature. Rectal temperature was greater at a depth of 11.5 cm when compared to 6.0 cm (39.2 vs 38.8°C), so variation may exist between techniques. Lung auscultations may be a predictive measure for BRD. DeDonder et al. (2010) assigned lung auscultation scores (1 to 10) to 4,341 feeder cattle to determine if there was an association between lung lesions, prevalence of BRD morbidity, and lung auscultation score. As lung auscultation score increased from 2 to 6, the retreatment rate and case fatality rate increased. In a subset of 34 calves, lung auscultation score was determined antemortem, and an average lung lesion score was determined postmortem. There was a linear correlation between lung auscultation score and average lung lesion score (DeDonder, 2010). Similarly, Zeineldin et al. (2016) studied the potential for lung ultrasonography as an aid for diagnosing BRD in 135 high- risk feedlot calves. After visual observation throughout a 30-d period, 24 steers were BRD cases. Lung lesions were found in 70.83% of steers, via ultrasonography, that were predetermined to have a lung auscultation score between 2 to 5 (Zeineldin et al., 2016). Merck Animal Health (Madison, NJ) has introduced the Whisper stethoscope that quickly analyzes lung sounds and produces a

lung severity score through a computer software system. The Whisper stethoscope is a self-contained system that does not require consumables and removes subjectivity. However, the utilization of the Whisper stethoscope for targeted metaphylaxis is questionable because of the pathogenesis of BRD with bronchopneumonia as the end stage of BRD. Therefore, it is likely that the Whisper stethoscope functions as a better diagnostic tool rather than a predictive tool (Noffsinger et al., 2014). Some biological strategies to possibly predict BRD morbidity are biomarkers such as serum haptoglobin (Hp) concentrations (Richeson et al., 2013), non-esterified fatty acids (NEFA) concentrations (Faylon et al., 2015), nasal microbiome (Holman et al., 2015), and leukocyte profile (Richeson et al., 2013). The acute phase response (APR) occurs in response to homeostatic disturbances or inflammation. At the site of injury, activated cells release acute phase cytokines, IL-6, and TNFα, which induce changes in acute phase protein (APP; Heinrich et al., 1990). Haptoglobin is an APP synthesized in the liver by hepatocytes and is a non-specific indicator of inflammatory status (Heinrich et al., 1990). The APR usually begins on d 0 and returns to homeostasis by d 14. The commonly investigated APP in cattle includes Hp, serum amyloid A, fibrinogen, and ceruloplasmin (Paulina and Tadeusz, 2011). Haptoglobin is perhaps the most frequently quantified APP in cattle; Hp sequesters iron forming haptoglobin-hemoglobin complexes, leaving it unavailable for bacterial growth (Allison and Rees, 1957). An outflow of amino acids from skeletal muscles is directed to the liver during APR. Protein synthesis decreases and protein degradation increases due to lack of nutrients to synthesize amino acids. This can be attributed to the catabolic and anorectic effects of the APR (Johnson, 1997).

Haptoglobin is associated with tissue injury and inflammation. For example, Ball et al. (2018) conducted a study to evaluate the performance, behavior, and Hp concentrations of cattle receiving different castration methods. Beef bulls (n = 180) were randomly assigned to 1 of 3 treatments: Zinc injection, banding, and intact bulls. Whole blood was collected on d 0, 1, 3, 5, 7, and 14 to determine Hp concentration. On d 3, Zinc treated calves had greater Hp concentration (1,404,047 mg/dL) indicating greater pain and inflammation when compared to banded (421,508 mg/dL) and control bulls (360,427 mg/dL).

Several studies have resulted in elevated NEFA concentrations in high-risk cattle upon feedlot arrival. Non-esterified fatty acids along with glycerol make up triglycerides that are stored in adipose cells and used to evaluated energy balance in cattle. When ewes were fed 123% of the maintenance energy requirement, a NEFA concentration of 37 µ mol/L was measured. However, when ewes were underfed and only provided 22% of maintenance energy requirements, the NEFA concentration was 593 µmol/L, an increase of 1,500%; therefore, exhibiting NEFA concentrations increase with negative energy balance (Bonnet et al., 2000). When auction derived calves arrived at a stocker facility, the NEFA concentrations were greatest on d 0 and then decreased from d 0 to 14 suggesting the cattle arrived in a negative energy balance. Furthermore, research has indicated that cattle temperament can also influence NEFA concentration with temperamental cattle having greater NEFA concentrations compared to calm cattle (0.3 vs 0.20 mmol/L; Burdick et al., 2010). Hormones associated with activation of the hypothalamic-pituitary-adrenal (HPA) axis include corticosteroids, adrenocorticotropic hormone (ACTH) and catecholamines that have a positive influence on lipase which

promotes lipolysis of triglycerides. In the event of negative energy balance, triglycerides are cleaved by lipolysis into NEFA and glycerol and released into the blood. Glycerol is then available for glucose production by cells and because NEFA has hydrophobic tendencies, it attaches to albumin molecules and can be taken up by hepatocytes and esterified for further functions. Epinephrine is a catecholamine that is associated with the fight or flight response. Sechen et al. (1990) exogenously administered epinephrine to 4 Holstein cows at a rate of 0.4, 0.8, 1.2, and 1.6 µg/kg of BW once a day at 1900 h for 11 d. As the dosage of epinephrine increased, the plasma NEFA concentration increased. This demonstrates how a repeated stressor and the impact of the stressor can induce a negative energy balance in cattle (Sechen et al., 1990).

Immunologic Regulation and Response

Cells of the innate immune system

The immune system is categorized into two different subsystems based on their function. The innate immune system is often referred to as the non-specific immune system that has a fast and relatively non-specific response. Some of the cells associated with the innate immune system are monocytes, neutrophils, basophils, eosinophils, and natural killer (NK). The adaptive immune system recognizes specific antigens and specific immunity is acquired after exposure to a pathogen and is mediated by T and B lymphocytes (Dunkelberger and Song, 2010).

Leukocytes, or white blood cells, are involved in fighting infectious diseases and foreign invaders. They are produced via the hematopoietic process that occurs in bone

marrow (Jagannathan-Bogdan and Zon, 2013). Hematopoietic stem cells in the bone marrow differentiate into myeloid or lymphoid cells (Dzierzak and de Pater, 2016). Monocytes, neutrophils, basophils, and eosinophils are derived from myeloid cells, produced in lymphoid tissue. A multipotential hematopoietic stem cell, hemocytoblast, will differentiate into either a common myeloid progenitor or a common lymphoid progenitor (Rieger and Schroeder, 2012). The myeloid progenitor can then differentiate into several other cells including a myeloblast. The myeloblast will then become either a basophil, neutrophil, eosinophil, or monocyte that are all associated with the innate immune system. The monocyte will differentiate into a macrophage once it translocates into tissue (Jagannathan-Bogdan and Zan, 2013). If a stem cell differentiates into the lymphoid progenitor, it can either become a natural killer cell, which is a large granular lymphocyte associated with the innate immune system, or a small lymphocyte that will further differentiate into a T lymphocyte and a B lymphocyte that are part of the adaptive immune system (Rieger and Schroeder, 2012). The B lymphocyte will then further differentiate into plasma cells and produce antibodies (Rieger and Schroeder, 2012).

Neutrophils makeup 15 to 45% of the total leukocyte concentration and are known as the first line of defenders against various pathogens including bacteria, fungi, and protozoa (Jones and Allison, 2007; Roland et al., 2014). They have a relatively short "life", only surviving 1 to 2 d. Neutrophils do not recognize unique pathogens specifically but rather pathogen-associated molecular patterns (PAMPs) that allows them to combat a broad array of pathogens (Mayadas et al., 2014). The normal neutrophil to lymphocyte ratio in cattle is 0.5 (Weiss et al., 2010; Roland et al., 2014), but physiological stress can result in this ratio exceeding 1.0. Neutrophils can migrate

through blood vessels and move into the interstitial tissue, known as chemotaxis, and can arrive within minutes following injury or stress.

Monocytes are a white blood cell that makes up about 2 to 7% of white blood cell concentrations and the normal cattle reference range is between 25 to 840 cells/µl (Jones and Allison, 2007). Monocytes can differentiate into macrophages and dendritic cells (Serbina et al., 2008). Resident macrophages reside in the tissue and act promptly in the presence of foreign material, making them very useful in combating respiratory infections (McGill and Sacco, 2020). Monocytes are a large leukocyte that aids in phagocytosis and inflammatory cytokine production, and because of their inflammatory response, they can be used as an inflammatory marker. Roberts et al. (2015) evaluated the effect of surgical castration with or without meloxicam, a nonsteroidal anti-inflammatory drug. Bull calves (n = 30) were randomly assigned to 1 of 3 treatment groups: control, surgical castration without meloxicam, and surgical castration and meloxicam at 1mg/ kg BW. Whole blood samples were collected to analyze complete blood count. After castration (0.5 h), serum cortisol concentrations were elevated for both castrated treatment groups when compared to control calves indicating pain (24.13, 26.27, and 13.88 ng/mL, respectively). At h 2, cortisol concentrations were reduced for calves castrated with meloxicam when compared to castrated calves without meloxicam. This indicates that meloxicam can mitigate inflammation, which is associated with pain and stress (Johnson, 1997; Coetzee, 2011). Calves castrated without meloxicam had the greatest concentration of monocytes, followed by castration with meloxicam and control. During an inflammatory response, monocytes are recruited to the site of infection or injury to aid in the control of pathogen removal (Shi and Palmer, 2011).

Eosinophils, also known as acidophiles, are granulocytes, classified in the innate immune system and are involved in parasitic infections and allergic reactions (Roland et al., 2014). They can make up 0 to 20% of the total white blood cell concentration (Jones and Allison, 2007) and have an affinity for gastrointestinal tissue where they can survive up to two weeks (Rieger and Schroeder, 2012). During an episode of inflammation, cytokines such as IL-4, IL-5, and IL-3 help attract and increase the number of eosinophils to the inflammatory site (Lampinen, 2004). Eosinophils bind to parasites that are opsonized with IgG and IgE and secrete mediators on parasites destroying it, and then macrophages "clean up" the debris (McEwen, 1992). To evaluate cellular immune components, 22 calves were artificially infected with ticks (Engracia Filho et al., 2017). After 21 d, a 6 mm punch biopsy around the tick site was collected, and inflammatory cell counts were determined using histopathological evaluation. It was found that eosinophils made up 47.8% of the cells infiltrating the site of parasitic infection. Moreover, calves that had an acute inflammatory response induced by surgical castration had statistically less eosinophils over a 72-h period compared to control calves which suggest that eosinophils migrated from the blood to the site of inflammation (Roberts et al., 2015). Upon feedlot arrival, 6 mL of blood was collected from the jugular vein of 1,179 bulls and steers to determine if a correlation in hematologic variables or castration and the incidence of BRD existed. Calves that were castrated were 3.32 times more likely to contract BRD at least once or twice. Additionally, calves that had a greater concentration of red blood cells were 0.75 times more likely to be diagnosed with BRD. Red blood cells can be an indication of hydration status with increased concentrations indicating dehydration (Kaufman, 2017). Furthermore, calves with eosinophil levels less

than 540 cells/μL were 1.98 times more likely to become ill with BRD. It was proposed that cattle with lower eosinophil concentrations have a greater chance of experiencing BRD. The correlation between lower eosinophil concentration and BRD occurrence is not fully understood, but there are a few hypotheses that include eosinophil translocation to the site for mitigation of inflammation (Isobe et al., 2012). It has also been proposed that corticosteroids can suppress eosinophils (Soda et al., 1993). When rats were injected with 1mg of dexamethasone, it resulted in an 80% decrease of eosinphils within 24 h (Soda et al., 1993).

Natural Killer cells are a large, granular, cytotoxic lymphocytes that makes up approximately 2 to 10% of total white blood cells. They are the only lymphocyte that is considered part of the innate immune system and specializes in killing virus-infected cells. Natural killer cells will target any cell type that is missing an MHC class I molecule because MHC I is a distinct characteristic in normal functioning cells in the body and can produce antiviral cytokines such as interferon γ. Natural killer cells are missing the MHC I so they do not require activation to kill infected cells (Grzywacz et al., 2010). Two groups of five calves were administered a commercially available killed-virus vaccine for foot and mouth disease. Blood was collected for 7 d and analyzed using a cytolytic assay. The assay resulted in no increase in NK cell activity suggesting that NK cells do not play a role in adaptive immunity. However, when another group of calves were administered a live foot and mouth virus, the NK killing activity increased and remained elevated for approximately 6 d (Patch et al., 2014).

Macrophages are effector cells that phagocytize bacteria, viruses, and protozoans both inside and outside of cells with granular content. Once a monocyte leaves the

bloodstream and enters the tissue, it differentiates into a macrophage and acts as a protector of the innate immune system (Baumann and Gauldie, 1994). Macrophages can recognize a wide variety of pattern recognition receptors (PRR) that allow them to locate and destroy. Phagocytosis occurs when a phagocyte, neutrophil, or NK cell, recognizes microbes by using PAMPs or surface molecules aided by opsonization. The phagocyte membrane remodels to allow the cytoplasmic membrane to begin flowing around the microbe until it is completely engulfed. The lysosome and phagosome will fuse forming a phagolysosome, thus killing the microbe inside the vesicle. During an acute inflammatory response, monocyte production is increased and the amount of monocytes entering and leaving circulation is concomitantly increased (Van Furth, 2013).

Adaptive immune system

T-cells are a lymphocyte that is part of the adaptive immune system. Once a macrophage has engulfed and processed a pathogen, it presents the processed antigen to various T-cells until it finds the matching T-cell and MHC II receptor, thus activating the T-cell. Then, differentiation and clonal expansion of the T-cell occurs to either differentiate into an effector T-cell or a memory T-cell (Kumar et al., 2011). Effector T-cells are classified as T-helper cell 1 (TH1) or T-helper cell 2 (TH2). The TH1 is $CD8^+$, MHC class I restricted, and production is driven by INFγ. They tend to attack intracellular bacterial pathogens or virus-infected cells. It aids in the activation of cytotoxic T-cells. TH2 cells production and activity is stimulated by IL-4 and is $CD4^+$, MHC class II restricted and aids in humoral immunity and proliferation of B cells and antibody production (Kumar et al., 2011).

B-cells are part of the adaptive immune system and are responsible for humoral immunity. They originate in the bone marrow and conjugate in the spleen to mature (Den Haan et al., 2014). They can recognize a wide range of PAMPs, such as lipids, proteins carbohydrates, and nucleic acids. Binding of an antigen will cause the expression of IL-4 receptors on the surface of B-cells. IL-4 comes from the TH2 cells and signals the B-cell to proliferate via clonal expansion (Roth and Perino, 1998). Plasma cells produce numerous immunoglobulins that are specific to the original antigen that bound. Antibodies can attach to the surface of antigens to assist with phagocytosis through a process known as opsonization (Dunkelberger and Song, 2010). After an infection begins to subside, memory B-cells are produced. They can express either IgG, IgA, or IgE, and have a high affinity for the antigens. B-cells can differentiate into plasma cells that specialize in producing antibodies (Den Haan et al., 2014).

Stress and the immune response

There are various definitions of stress that have evolved throughout the decades. Selye published his first article about stress in 1936 where he referred to the phenomenon as, "the general alarm reaction of an organism" (Selye, 1936). In 1950, Selye coined the term stress and defined it as "the body's nonspecific reaction to a demand placed on it" (Selye, 1950). Stress can be classified in livestock as psychological, physical (Grandin, 1997), or physiological (Hughes et al., 2013). Psychological stress is any exogenous stressor that is processed by the brain and perceived as alarming by the animal, such as commingling, handling, or fear. Physical stress can include hunger, injury, trauma, or disease. Psychological and physical stress can lead to physiological stress which is any

stressor that disrupts homeostasis, such as inflammation or infection (Dragoş and Tănăsescu, 2010). Stress can be further classified as acute or chronic where acute stress is a combination of stress or stressors experienced for a short duration of time, typically less than 24 h and is considered immunoprepatory. Chronic stress results from a stressful event that is continually experienced for an extended duration of time, typically for more than 24 h and can result in immune dysfunction (Martin, 2009).

During an inflammatory response, the compliment (C) system becomes active and compliment proteins, C3a and C5a, in combination with cytokines, such as TNFα, help increase leukocyte migration to a site of infection (Baumann and Gauldie, 1994). Compliment proteins also aid in vasodilation, allowing for increased vasculature and leukocyte migration. Endothelial cells contract to express integrin and selectin to aid in leukocyte translocation (Mayadas et al., 2014). For a leukocyte to leave the peripheral blood and enter tissue, it first attaches with low affinity to endothelial surface receptors and then rolls along the endothelial cells slowing it down (Nourshargh and Alon, 2014). Next, it binds and attaches with a high affinity to the endothelial surface in preparation for translocation. Once the leukocyte advances into the tissue, it migrates towards the site of infection via chemotaxis (Mayadas et al., 2014; Selders et al., 2017). After the neutrophil recognizes the organism, it engulfs it in a process referred to as phagocytosis and destroys the organism via O2 dependent or O2 independent processes (Hampton et al., 1998).

The HPA axis is a major component of physiological stress. Activation of the HPA axis occurs in response to stress stimuli, causing stimulation of leukocytes and the production of pro-inflammatory cytokines. The pro-inflammatory cytokines then cause

glucocorticoid and catecholamine receptor expression and, in turn, alters trafficking, proliferation, and differentiation of T-cells (Dragoş and Tănăsescu, 2010). In response to stressful stimuli, corticotropin-releasing hormone is synthesized in the anterior pituitary in conjunction with vasopressin from the posterior pituitary. They work synergistically on the adrenal gland to release ACTH (Gillies et al., 1982). Then ACTH stimulates the adrenal gland to secrete catecholamines, such as dopamine and epinephrine from the adrenal medulla and glucocorticoids, such as cortisol, from the adrenal cortex. The HPA axis uses a negative feedback mechanism where the secretion of cortisol can down-regulate the secretion of ACTH from the anterior pituitary (Keller-Wood and Dallman, 1984; Gómez et al., 1998).

Chronic stress can occur during the auction market process causing short endocrine responses, alteration of protein and energy metabolism because glucose is broken down for energy. The extended release of cortisol can cause anorexia and reduced growth, altered rumen and digestion function, and immune dysfunction (Fluharty and Loerch, 1995). Acute stress causes stimulation of leukocytes that leads to increased pro-inflammatory cytokines, which orchestrate a homeorhetic response that can reduce growth by redistributing nutrients for events that are more significant for survival, such as immunity (Baumann and Gauldie, 1994). A homeostatic state is necessary for livestock to obtain optimal growth and stress, as well as inflammation, trigger a cascade of biological events that tax the animal body and causes anorectic effects. There is an increased demand for energy required for the immune system to function, and therefore, lipolysis occurs (Spurlock, 1997). Throughout an immune challenge, IGF-1 is lowered, followed by growth hormone that lessens the anabolic activities in an animal (Elsasser et al.,

2008). Driven by TNFα, glucose uptake by peripheral tissue is decreased and redirected to immune tissue to ensure adequate nutrient availability to combat infection. Amino acids are the building blocks of proteins, and during an inflammatory response, the liver becomes the primary organ for amino acid uptake to synthesize acute-phase proteins (DeRosa et al., 2000; Paulina and Tadeusz, 2011).

Metaphylactic Antimicrobial for the Control of BRD

Draxxin, Tulathromycin

Tulathromycin is an antimicrobial in the triamilide class labeled for the control of BRD in high-risk cattle associated with *MH, PM, HS,* and *MB* as a single dose therapy. An antimicrobial that is administered as a single dose therapy aids in reducing animal handling. Tulathromycin extensively penetrates the lung tissue with a prolonged duration of time making it highly efficacious in the clinical use for the control of BRD (Gáler et al., 2004; Hibbard et al., 2002) with a slaughter withdrawal period of 18 d. The recommended dosage for the control of BRD is 2.5 mg/kg of BW injected subcutaneously in the neck. The Draxxin (NADA 141-244) freedom of information studies depicts the pharmacokinetics of tulathromycin in plasma and lungs using 42 beef cattle that were randomized to either a tulathromycin-treated group or a control group. Following subcutaneous injection (2.5 mg/kg of BW), the relative bioavailability of tulathromycin for the lungs and plasma was approximately 94% indicating the superior capability of tulathromycin to penetration lung tissue. The total drug concentration was greater for the lungs in the calves that were administered tulathromycin than control

calves, and the $T_{1/2}$ life was 8.75 d and 2.75 d for lungs and plasma respectively displaying the affinity tulathromycin has for lung tissue. The MIC_{90} for the bacteria related to BRD are as follows: *MH* 2.0 µg/mL, *PM* 1.0 µg/mL, *HS* 4.0 µg/mL, and *MB* 1.0 µg/mL. Tulathromycin is a relatively safe antimicrobial to use, but at the recommended dose. It has caused temporary local tissue response that resulted in swelling and trim loss at harvest. When tulathromycin was administered at a one-time dose of 25 mg/kg of BW, 10 times the labeled dose, some local swelling occurred at the injection site, along with head-shaking and decreased feed intake, but did not result in any mortalities (FDA-FIS, 2005). Godinho et al. (2005) determined the efficacy of tulathromycin for the prevention of BRD in high-risk feedlot calves. After a 14-d arrival period, 1,251 calves were randomly assigned to receive either florfenicol, tulathromycin, or saline. Calves that were metaphylactically administered tulathromycin upon feedlot arrival weighed more than florfenicol treated calves and control calves (76.10, 71.40, 66.0 kg, respectively), and had less retreats (14.6%) when compared to florfenicol calves (24.9%) and control calves (43.8%). Rooney et al. (2005) conducted a similar study comparing the efficacy of tulathromycin, tilmicosin, and florfenicol for the control of BRD in high-risk cattle. At three different feedlots, 250 calves were randomly assigned to 1 of 3 treatments on arrival: tulathromycin (2.5 mg/kg of BW), tilmicosin (10mg/kg of BW) or florfenicol (40mg/kg of BW). Calves treated with tulathromycin had less BRD incidences when compared to florfenicol and tilmicosin. Furthermore, there were less second and third treatments in calves that received tulathromycin. Similarly, 399 high-risk calves were administered tulathromycin upon feedlot arrival and 402 control calves

were administered saline. After a 14-d receiving period, the metaphylactically treated calves had a 10.6% morbidity rate while the control calves had 59.4% (FDA-FIS, 2005).

Inflammation/acute phase response

Cytokines are polypeptides that mediate and regulate inflammation by initiating their actions as they bind to specific membrane receptors on target cells where they can generate a local or systemic response (Ackermann et al., 2010). A small splinter engorged in the finger is an example of a local reaction because cytokines are produced by leukocytes in a specific spot in the body, where bronchopneumonia is an example of how BRD can induce a systemic reaction. Microbial agents, such as viruses and bacterial pathogens, produce PAMPS (Srikumaran et al., 2007). Once pathogens are in the lung, resident alveolar macrophages activate the inflammatory response (McGill and Sacco, 2020). A series of systemic physiological reactions are coordinated by the innate immune system in response to infection, trauma, injury, or endotoxin injection. Soluble factors released by injured/dying cells signal leukocytes (tissue macrophages or blood monocytes) to the site of infection beginning the APR cascade. Cytokines, such as IL-1 and TNFα, stimulate the cells in connective tissue that can further initiate the cascade of events for APR activation (Hughes et al., 2013). Compliment proteins, C3a and C5a, encourage vasodilation of capillaries to increase blood flow to the area of infection, allowing more effective leukocyte migration. Once leukocytes translocate to the site of infection, when eliminating bacteria, tissue destruction can occur causing further inflammation, and a febrile response (Baumann and Gauldie, 1994; Williams et al., 2011).

Virus Vaccination in Beef Production

Vaccine strategy

The intent of vaccine administration is to provide immunization against disease through the activation of the adaptive immune response (Plotkin et al., 2008). A modified-live virus (MLV) vaccine contains viral antigens that the innate immune system identifies as a foreign body, thus giving rise to a cascade of events to provide immunity (Arthington et al., 2013). There are various (MLV) vaccines, killed virus (KV) vaccines, bacterins, and leukotoxins available against the commonly known BRD causative agents. A MLV vaccine contains a suspension of an attenuated or killed organism, while an inactive or KV vaccine consisting of virus antigen particles that have lost their ability to replicate or cause disease (Baumann, 2004). There is a plethora of commercially available MLV and KV vaccines for BHV-1, BVDV type 1 and 2, BRSV and PI3 along with bacterins for *MH, PM* and *HS* (Richeson, 2019). Vaccination at the cow-calf sector or ranch origin has resulted in aiding in the prevention of BRD (Schumaher et al., 2018). Pre-conditioning occurs at the ranch of origin and was first developed in the 1960's (Cole, 1985), and has consistently resulted in improved health and performance. Pre-conditioning is not a unanimously adopted practice because of the lack of cow-calf producer incentives and the need for planning and adequate facilities. Preconditioned calves should be weaned, receive a series of vaccinations, dewormed, castrated, dehorned, and bunk-broke before selling. Step et al. (2008) compared calves from different sources (single source or auction market) and weaning protocols. Calves from a single-sourced ranch (RANCH) were either weaned and shipped to a feedlot on the same

day (WEAN), weaned and remained on the ranch for 45 d without vaccination (WEAN45), or weaned, vaccinated and stayed on the ranch for 45 d before shipping (WEANVAC45). Auction market calves (MARKET) were purchased and a portion of the cattle from each RANCH group (WEAN, WEAN45, and WEANVAC45) were commingled with the MARKET calves (COMM). Throughout the 42-d trial, WEAN calves had the lowest DMI when compared to MARKET, WEAN45, and WEANVAC45 (6.85, 7.17, 7.54, 7.48 kg, respectively) calves. The rate of BRD morbidity was least for the WEAN45, followed by WEANVAC45, then WEAN and MARKET (5.9, 9.5, 33.51, and 41.0%, respectively). The percent of first BRD treatment was less for WEAN45 (5.0%) and WEANVAC45 (7.7%) compared to the MARKET (31.9%) and WEAN (22.2%) calves. The total cost per steer was greatest for MARKET calves ($61.03) and least for WEAN45 calves ($57.81). The MARKET, WEAN45, and WEANVAC45 consumed more feed than the WEAN cattle. This study indicates that weaning calves 45 d before transporting reduces morbidity and improves performance during the feedlot receiving period. Other studies have demonstrated that auction market calves have greater morbidity compared to preconditioned calves (70.4 vs 6.7%; Richeson et al., 2012), less death loss (4.44 vs 1.3%), and reduced BRD treatment (62.0 vs 19.0%; Lalman and Mourer, 2014). Additionally, pre-conditioned cattle had a lower cost of gain and heavier overall BW when compared to auction derived cattle (Lalman and Mourer, 2014). Veterinarians often recommend vaccinating at the cow-calf sector at branding, before weaning, and after weaning because calves are more likely to encounter acute stress situations that can be immunopriming as opposed to chronic stress that results in immune dysfunction (Fike et al., 2017; Roth and Perino, 1998; Roth and Kaeberle, 1982; Tarrant,

1990). Furthermore, vaccination at the cow-calf sector allows appropriate time for the vaccines to stimulate immunity and provide humoral protection (Confer et al., 2009) before commingling and chronic stress occurs (Stephenson et al., 2002). At branding, 96% of veterinarians recommended vaccination with at least one antigen, 99% recommended at least one vaccine with one antigen before weaning, 97% recommended at least one vaccine with one antigen after weaning and 61% suggested vaccine administration 7 to 21 d before shipment (Fike et al., 2017).

Vaccination of high-risk calves upon feedlot arrival

Despite the positive research that pre-conditioning calves has exhibited, only 34.7% of cattle entering a feedlot have pre-arrival processing information (USDA-APHIS, 2011). This could be because the small average U.S. beef herd size which is 43.5 cows per operation (USDA-APHIS, 2011), and many "hobby" ranchers do not have the knowledge, adequate facilities, or desire to pre-condition their cattle. There is also a lack of incentive because of the increased cost, risk, and time required for pre-conditioning (Smith, 2009). Groups of cattle are normally processed within 72 h of feedlot arrival (93.1%) with 96% of cattle receiving a respiratory vaccination at that time (USDA-APHIS, 2011). A safe and effective vaccine should build immunity in the host without causing disease or adverse effects. Dr. Joachim Frey, the head of research and director of bacteriology at the Institute of Veterinary Bacteriology of Berne specifies 8 principal requirements for animal vaccines to be successful: 1) contain the necessary antigenic determinants to induce protective immunity, 2) possess a high immunogenic potential, 3) be safe for administration without risk of clinical infection in the vaccine, 4) be safe for

humans, 5) induce a serological response that allows differentiation of vaccinated from infected animals, 6) be stable for long-term storage, 7) not be contraindicated for release in the environment, and 8) to be traceable in the animal population and the environment (Frey, 2007).

Several factors that can result in vaccine failure: improper storage or handling, incorrect injection site or technique, unsuitable timing of administration because of acute infections, or manufacturing errors that make the vaccine ineffective or unsafe (Rashid et al., 2009). Common management practice in newly arrived feedlot cattle is the administration of an MLV vaccine containing attenuated viral antigens that are commonly isolated from BRD-affected cattle (Terrell et al., 2011). The vaccine label for Titanium 5, a commercially available MLV product, reads "This vaccine is safe and efficacious; however, individual animals may be unable to develop an adequate immune response following vaccination due to concurrent disease, malnutrition, parasitism, or stress due to shipment or environmental conditions." As described previously in this review, acute and chronic stress causes physiological changes in the immune system that can be either immunopriming or immunosuppressive. When high-risk cattle arrive at a feedlot, they are typically in an immunosuppressive state because of chronic stress. It has been the long-time belief that administering a vaccine to immunocompromised cattle negatively impacts the ability to mount an immune response. On the contrary, a compromised immune system permits enhanced antigenicity via greater replication of an MLV vaccine in the host. Regarding KV, a compromised immune system can potentially reduce the immune response because there is not live replicating antigen (Richeson et al., 2009), which is the opposite outcome of MLV administration in the immunosuppressed

host. Poe et al. (2013) allocated 192 high-risk calves to either receive a pentavalent MLV vaccine upon arrival or a delayed (14 d) MLV vaccine. Blood samples were collected on d 0, 14, 28, and 42. Upon arrival, the average red blood cell concentration was elevated (10,500 no./µL), indicating a dehydrated state and negative energy balance. Furthermore, the calves that received an MLV vaccine upon arrival had the greatest antibody titers throughout the 42 d study for BVDV type 1a. This suggests that administration of an MLV vaccine allows for a pronounced vaccine response in high-risk calves because of a compromised immune system and greater antigenicity of the vaccine. Throughout the 42-d study, there were no differences in morbidity and performance (Poe et al., 2013). Richeson et al. (2009) used 263 high-risk auction derived calves to investigate the effects of on arrival and 14 d delayed vaccination. There were four treatment groups, arrival clostridial vaccine and respiratory vaccine (ACAR), arrival clostridial and delayed respiratory vaccine (ACDR), delayed clostridial and on-arrival respiratory vaccine (DCAR), and delayed clostridial and respiratory vaccine (DCDR). There were no statistical differences in BRD morbidity, but there was a numerical difference in the percent of calves treated a second time for ACAR and DCDR (38.5 and 25.5%, respectively). On d 0, calves arrived with elevated cortisol levels, indicating activation of the HPA axis caused by stress. Hematocrit levels were higher, indicating that dehydration and neutrophil concentration was also elevated which can occur in response to infection, injury, or stress. The elevated levels of cortisol, hematocrit, and neutrophils upon arrival suggest a period of physiological and physical stress and a negative energy balance (Fontenot and Richeson, 2017; Mostle and Palme, 2002). The calves that received an MLV respiratory vaccine upon arrival (ACAR and DCAR) had more antibody titers for

BVDV type 1a than the calves that received a delayed respiratory vaccine (ACDR and DCDR), suggesting a compromised immune system allows for greater MLV vaccine replication. Like Poe et al. (2013) there were no reported differences in performance. In another study by Richeson et al. (2015b), 370 calves were allocated to 1 of 3 treatments, on arrival MLV vaccine (AMLV), 14 d delayed MLV vaccine (DMLV), and no MLV vaccination (NMLV). From d 14 to 28, ADG was greater for DMLV treated calves followed by NMLV and then AMLV (0.65, 0.51, 0.47, kg/d). There was also a numerical difference in ADG for AMLV compared to DMLV on d 0 to 14 (0.34 vs 0.93 kg). There were no differences in BRD associated morbidity between treatments, but the calves that did not receive an MLV vaccine upon arrival tended to have a greater probability of being treated a second time compared to the calves that received a vaccination. Richeson et al. (2008) conducted a study with 528 beef bull and steer calves that were randomly assigned to 1 of 2 treatment groups, administration of an MLV vaccination upon arrival processing, or delayed MLV vaccination until d 14. Although there was not a negative control, calves that were administered a delayed MLV vaccination resulted in improved ADG on d 42 (0.65 vs 0.75 kg/d). Additionally, the BRD morbidity rate was numerically greater for calves that received an on-arrival MLV vaccination (71.5 vs 63.5%; Richeson et al., 2008). Furthermore, the calves that received an on-arrival MLV vaccine had greater IBR antibody titers on d 14, 28, 42, and overall when compared to the delayed vaccine calves. Rogers et al. (2016) conducted a large pen study to determine if delayed vaccination would alter the health or performance of 5,179 high-risk auction-derived heifers. There were not any differences amongst arrival MLV and delayed MLV vaccination administration for the number of calves diagnosed for BRD at least once.

However, there was an increased risk for BRD related treatment failures (calves treated more than once for BRD) for the calves receiving a MLV on arrival (8.36 vs 9.39%). Also, the BRD retreatment risk was greater for calves that received MLV vaccination upon arrival when compared to delayed vaccination (37.05 vs. 43.97%; Rogers et al., 2016). Hagenmaier et al. (2018) enrolled 2,575 high-risk beef heifers in a study to evaluate various vaccine programs. There were 3 treatments, pentavalent MLV vaccine and *MH* supernatant leukotoxoid vaccine up feedlot arrival (PRE), pentavalent MLV vaccine, and recombinant *MH* upon arrival (TNA), and pentavalent MLV vaccine and recombinant *MH* delayed for 28 d (TND). Endotoxins are located within the bacterial cell and released when ruptured, inducing an inflammatory response. A leukotoxoid vaccine is produced from the supernatant of the entire cell culture including endotoxin, while a recombinant vaccine is produced using only certain pieces. Hagenmaier et al. (2018) demonstrated that the leukotoxoid vaccine possessed more endotoxin when compared to the recombinant MH leukotoxin vaccine (56,120 vs 1,588 EU/mL). At closeout, there were no differences in BRD related morbidity outcomes or performance differences observed by delaying vaccination. However, the BRD case fatality risk was determined to be greater for both PRE (18.67%) and TNA (21.91%) than TND (13.61%).

Dexamethasone is a synthetic glucocorticoid that when intravenously administered to cattle for 3 consecutive days, can serve as a chronic stress model and when administered once, simulates an acute stress situation. Ceruloplasmin (Cp) and Hp are APP that are increased during periods of stress. Richeson et al. (2016) used dexamethasone as a stress challenge to illustrate how acute and chronic stress may generate different immunological effects when MLV or inactive vaccines are administered. Thirty-two steers were

randomly allocated to 1 of 3 treatments, acute immunosuppression (dexamethasone 0.5mg/kg of BW on d 0), chronic immunosuppression (dexamethasone 0.5 mg/kg of BW on d-3 to d 0), and control (no dexamethasone). On d 0, all calves were administered a combination respiratory vaccine that contained a pentavalent MLV fraction and a nonreplicating *MH* leukotoxoid portion. Blood was collected on d 0 and then once every 7 d until d 56 to determine antibody titers and on d -2, 0, 1, 3, 7, 14 to determine Hp evaluation and Cp activity. The steers receiving the chronic treatment had greater antibody titers on d 14 and 21 for IBRV and on d 14, 21, 28, and 56 for BVDV when compared to control. The leukotoxoid in the vaccine was inactivated, and when administered to the chronically stressed cattle, the antigenicity of the toxoid was reduced on d 14 when compared to the acute and the chronic treatments. Control steers had the greatest concentration of Cp and Hp followed by acutely treated cattle and then chronic treatment indicating that stress can give rise to the downregulation of the immune system.

Most of the studies above depicted that MLV vaccination administration upon feedlot arrival did not improve health and performance outcomes, and in some cases, delaying MLV vaccine improved performance and reduced the amount of BRD retreatment and/or mortality. Therefore, the efficacy of MLV vaccination upon arrival is questionable because of the timing of vaccination relative to the natural viral challenge (Richeson et al., 2009), stress-induced immunosuppression that can lead to enhanced antigenicity of the vaccine (Poe et al., 2013; Richeson et al., 2009) and safety concerns. Furthermore, it may simply be too late to vaccinate upon feedlot arrival because of the natural viral exposure and BRD outbreak that typically occurs shortly after arrival (Richeson, 2019). Delayed vaccination allows time for the immune system to return to a

homeostatic state and avoid increased antigen replication or endotoxin stacking (Ellis and Yong, 1997).

Conclusion

Respiratory vaccination is probably most effective in preventing BRD when administered at the ranch of origin, and vaccination upon feedlot arrival is not clearly shown to be beneficial from the existing literature. Auction derived calves are typically categorized as high-risk because of commingling, lack of preconditioning management, and prolonged stressors that can result in immune dysfunction. It can take 14 d or longer for a vaccine to protect against a pathogen, and with the majority of BRD cases occurring within the first 14 d of feedlot arrival, the efficacy of the vaccine is questionable due to the time it takes to mount a protective immune response. Furthermore, research has shown that high-risk calves are experiencing prolonged stress and dehydration upon feedlot arrival which can lead to immune dysfunction, allowing for increased MLV replication and concerns with vaccine safety if administered at this time. Conversely, the efficacy of antimicrobial metphylaxis in high-risk cattle is clearly defined in the literature and has repeatedly resulted in improved morbidity, mortality, and in many cases greater performance. Administration of antimicrobial metaphylaxis at feedlot arrival, relative to the pathogenesis of BRD is intuitive because the majority of BRD cases occur within the first 14 d of arrival. Visual diagnosis of BRD is a subjective measure that can present difficulties such as observer inexperience, or the prey instinct of cattle to disguise clinical signs of illness in the presence of an observer. Administering antimicrobial metaphylaxis at feedlot arrival provides time for animals to adapt to their environment before the

subjective decision to pull cattle for treatment and reduces the amount of animal handling. Therefore, when used judiciously, metaphylaxis is a critical tool for controlling BRD in high-risk feedlot calves.

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Chapter II: Comparative efficacy of metaphylaxis and respiratory vaccination in high-risk, newly received feedlot cattle

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ABSTRACT

Our objective was to compare metaphylaxis with tulathromycin (META) and vaccination with a pentavalent modified-live virus respiratory vaccine (MLV) in high-risk feedlot calves. Beef bulls (n = 372) and steers (n = 106) were blocked by truck load, stratified by initial BW (234 ± 1.32 kg), health status and sex, and randomly assigned to treatments arranged in a 2 × 2 factorial: 1) no META or MLV; 2) META administration on d 0 (**META**), 3) MLV administration on d 0 with revaccination on d 14 (**MLV**), and 4) META and MLV administration (**META+MLV**). Interactions and main effects were analyzed within a generalized complete block design using a mixed statistical model with 10 pen replicates/treatment. Body weight and feed refusals were recorded on d -1, 0, 14, 28, 55 and 56 to determine interim and overall (d 0 to 56) gain performance, dry matter intake, and gain to feed ratio. A subset (n = 256) was affixed with a 3-axis accelerometer ear-tag to quantify activity and rumination time. A 7-d post-metaphylactic interval was implemented for META and BRD cases were determined by treatment-blinded, trained investigators. Interactions were tested first, followed by the main effects of META and VAC if the interaction for a given dependent variable was non-significant ($P > 0.05$). The META groups had greater ADG from d 0 to 14, 14 to 28, and overall ($P \leq 0.01$). Body weight on d 14, 28 56 was increased ($P < 0.01$) for calves in the META group with a 13.52 kg increase on d 56. For each interim period and overall, DMI was greater ($P < 0.01$) for META, but not MLV ($P \geq 0.11$). There were no interactions between META and MLV for BRD morbidity. Therefore, we will be reporting the main effects of META and VAC. The BRD morbidity rate was less for META (18.5 vs. 51.2%; $P < 0.01$); however, it was not improved for MLV ($P = 0.37$). Increased daily rumination time was observed for META ($P < 0.05$). A META × day interaction existed ($P = 0.01$) for daily

rumination time and greater rumination minutes occurred for META groups from d 9 to 20 and on d 22, 24, 26, 27, and 29 ($P < 0.05$). The health and performance of high-risk feedlot cattle was improved by META, but not MLV.

Key words: bovine respiratory disease, health, metaphylaxis, modified-live virus vaccination

INTRODUCTION

Bovine respiratory disease (BRD), also known as "shipping fever", is the most costly disease to impact feedlot cattle in North America (Griffin, 1997; Miles, 2009) and despite advances in prevention and control, it remains the leading cause of feedlot morbidity and mortality in the stocker and feedlot sectors (Woolums et al., 2005). The percentage of cattle placed in feedlots that died of BRD was the same in 2007 as it was in 1991 (Miles, 2009). A major factor that may contribute to the lack of health improvement is the antiquated beef marketing system (Smith, 2009) where cattle, with a naïve immune system because of age and/or lack of vaccination, are sold at auction markets where they are highly commingled. In addition to the marketing system, cow-calf producers are compensated based on weaning weight, therefore, a recent industry-wide focus has been on genetic selection for rapid growth as opposed to disease resistance (Snowder, 2009). Bovine respiratory disease is responsible for 87.5% of morbidity (USDA-APHIS, 2011) in U.S. feedlots with 57.1% of feedlot related deaths attributed to respiratory tract disorders (Loneragan et al., 2001). The U.S. beef production system is segmented; thus, it begins at the cow-calf sector where the average beef herd size is 47.4 bovine animals (USDA-APHIS, 2011). In small herds, the death of a single calf could nullify the

marketing premium received from preconditioning (Smith, 2009). Therefore, a lack of economic incentive exists for smaller producers to precondition giving rise to predisposing factors of BRD including weaning, lack of vaccination, castration, dehorning, transportation stress, commingling, and nutritional stress. These factors can give rise to a compromised immune status of animals (Duff and Galyean, 2007). Metaphylaxis is the timely mass treatment of a group of high-risk animals with a Food and Drug Administration (FDA) approved antimicrobial to control an expected disease outbreak (Ives and Richeson, 2015) and 39% of all cattle placed in feedlots receive antimicrobial metaphylaxis (USDA-APHIS, 2011). There is an abundance of research-based evidence to support the efficacy of antimicrobial metaphylaxis in high-risk calves because this practice consistently results in improved morbidity and performance (Kilgore et al., 2005; Wellman and O'Connor, 2007; Ives and Richeson, 2015). Therefore, the objective of this study is to compare the efficacy of metaphylaxis with tulathromycin and pentavalent modified-live virus vaccination in high-risk, newly received beef calves. There is also a secondary objective to determine if health outcomes differed between calves that arrived with a pre-existing ear-tag vs. those that did not.

MATERIALS AND METHODS

All procedures were approved by the West Texas A&M University Institutional Animal Care and Use Committee before study initiation (IACUC # 12-10-18). The experiment was conducted from January 2019 to April 2019 at the West Texas A&M University Research Feedlot (WTRF), located 11.7 km east of Canyon, TX.

Arrival procedures

A total of 478 crossbreed beef bulls (n=372) and steers (n=106) were sourced from regional auction markets in east Texas and shipped approximately 744 kilometers (11 h) to the WTRF on January 23, 2019 (Block 1), February 5, 2019 (Block 2), February 22, 2019 (Block 3), March 12, 2019 (Block 4), and April 3, 2019 (Block 5). The day the calves arrived to WTRF (d -1) individual BW and the presence of a pre-existing ear-tag were recorded. Calves were also administered a clostridial-tetanus toxoid (Calvary 9, Merck Animal Health, Madison, NJ), *Mannheimia haemolytica* bacterin (Nuplura, Elanco Animal Health, Greenfield, IN), and a uniquely numbered ear-tag. Ear notch tissue samples were collected to test for Bovine Viral Diarrhea Virus persistent infection at a commercial laboratory (Cattle Stats, Oklahoma City, OK). A jugular venipuncture blood sample was collected to determine blood leukocyte differential (QScout BLD, Advanced Animal Diagnostics, Morrisville, NC) and each animal was predicted to be normal or abnormal health status according to a proprietary, leukocyte-based algorithm. Calves were penned together overnight and allowed ad libitum access to water, and a starter diet of 0.5% their arrival BW and coastal Bermuda grass hay at 0.5% arrival BW.

Calves were stratified within block according to their d -1 BW, arrival sex, and arrival health status and sorted into treatment pens. On d 0, an individual BW was recorded again and averaged with the d -1 BW to determine initial BW. Bulls were castrated via banding (Callicrate Pro, No-Bull Enterprises, St. Francis, KS) and administered an oral analgesic, meloxicam (Unichem Pharmaceuticals, Hasbrouck Heights, NJ) at 1mg/kg of BW. Parenteral anthelmintic (Normectin, Norbrook Labs, Overland Park, KS) and a growth-promoting implant (Component E-S with Tylan,

Elanco Animal Health), that contained 200 mg progesterone, 20 mg estradiol benzoate, and 29 mg tylosin tartrate, were also administered. Whole blood was collected via jugular venipuncture to determine leukocyte count and health status again on d 0. A subset of 256 bulls were affixed with a 3-axis accelerometer ear-tag (Allflex Livestock Intelligence, Madison, WI) to quantify circadian and daily rumination time. Calves were sorted into their treatment pens and provided a starter diet at 1.5% of initial BW starting on d 0.

Treatments

Experimental treatments consisted of: 1) negative control (**CON**), 2) s.c. administration of tulathromycin (Draxxin, Zoetis) at 2.5 mg/kg BW on d 0 **(META)**, 3) s.c. administration of 2 mL pentavalent MLV respiratory vaccine (Titanium 5, Elanco Animal Health) on d 0 with revaccination on d 14 **(MLV)**, 4) s.c. administration of tulathromycin at 2.5 mg/kg BW and 2 mL pentavalent MLV respiratory vaccination on d 0 with revaccination on d 14 **(META+MLV)**. A 7- d post-metaphylactic interval was implemented for cattle that received tulathromycin on d 0 (META and META+MLV). Calves that did not receive tulathromycin on d 0 were eligible for initial BRD treatment on d 1.

BRD Case definition

Steers were observed daily by trained morbidity investigators and assigned a clinical illness score (CIS; 0 to 4 severity scale) as described by Pillen et al., 2016. Steers morbidity investigators were blinded to the experimental treatment pen assignment. The eligibility of BRD candidates was determined via record retrieval of ear-tag number by a

separate, non-blinded investigator. Steers were considered a clinical BRD case if: 1) at least 2 clinical signs consistent with BRD (depression, nasal or ocular discharge, cough, abnormal respiration, gaunt appearance, inappetence) and a rectal temperature of ≥ 40.0°C existed for an animal, 2) CIS ≥ 2 and a rectal temperature of ≥ 39.7°C, 3) CIS ≥ 3, regardless of rectal temperature. To determine rectal temperature, steers were removed from the pen and restrained in a chute where a digital thermometer was used (GLA Agricultural Electronics, San Luis Obispo, CA). Steers treated at least once for BRD were considered BRD 1, steers treated at least twice for BRD, were considered BRD 2, steers treated at least 3 times for BRD were included in BRD 3 and steers treated at least four times for BRD are considered BRD 4. Steers considered a primary BRD case were treated with 40 mg/kg BW of florfenicol (Nuflor, Merck Animal Health), and assigned a 3-d post treatment interval (Baptiste and Kyvsgaard, 2017). After the expiration of the 3-d PTI, steers were considered a secondary BRD case using the same protocol as the primary BRD case definition and treated with 11 mg/kg BW enrofloxacin (Baytril, Bayer Animal Health, Shawnee Mission, KS) and assigned a 3-d PTI. Upon expiration of the second PTI, calves meeting the previously described BRD case definition were considered a tertiary BRD case and treated with 6.6 mg/kg BW ceftiofur crystalline free acid (Excede, Zoetis, Parsippany, NJ) and assigned a 7-d PTI. A final treatment was administered when the above BRD case definition was met. These steers were treated with 20 mg/kg BW of tilmicosin (Micotil, Elanco Animal Health). Steers that did not respond to treatment or resume satisfactory performance were considered chronically ill and removed from the study, or euthanized, as determined by the principal investigator or attending veterinarian.

Housing and Management

Steers were housed in soil-surfaced pens with 20.8 meters, squared of space allowance, and 50.6 cm of linear bunk space per animal. All steers were fed the same starter diet throughout the 56-d study. Bunk observations were performed twice daily (1600 and 0700 h) to determine adjustments to feed offering. Feeding began at 0730 h and feed was delivered steers using a rotary mixer (274-12B Forage Express Feed Mixer, RotoMix, Dodge City, KS). Individual BW were collected on d -1, 0, 14, 28, 55, and 56. Before recording BW, orts were collected, weighed, and sampled for DM determination in a forced-air oven at 60°C for 48 h. Residual DM was subtracted from DM offered to calculate DMI for interim periods and overall.

Statistical Analysis

Health and performance data were analyzed using the MIXED procedure of SAS version 9.4 (SAS Institute Inc., Cary, NC) in a generalized complete block design with a 2×2 factorial arrangement of treatments. Interactions were tested first, followed by the main effects of META and MLV if the interaction for a given dependent variable was not statistically significant. Truckload was included as a random affect. Pen within block served as the experimental unit for treatment affects, while the individual animal was the experimental unit when evaluating the effect of pre-existing ear-tag. Fishers exact test in the FREQ procedure of SAS was used to determine the difference in morbidity rate of steers that arrived with and without a pre-existing ear-tag. Activity and rumination data were managed and analyzed according to the procedures described in Tomczak et al.,

(2019). Briefly, activity and rumination minutes were summarized into hourly and daily means and analyzed using the MIXED procedure in SAS. This model included experimental treatment, time, and their interaction as main effects, while pen, block, and pen × block interaction were random. Animal within pen (or pen) was the subject for repeated measures. For all variables, statistical significance was declared at $P \leq 0.05$ and tendencies were noted at $0.05 < P \leq 0.10$.

RESULTS & DISCUSSION

Clinical health outcomes

Health outcomes are presented in Table 1. An interaction ($P < 0.01$) existed for days to 2nd treatment, and there were no other significant interactions between META and MLV for health variables. The BRD1 morbidity rate was less ($P < 0.01$) for calves that received metaphylaxis (18.5 vs. 51.2%). Also, the main effect of META reduced ($P < 0.01$) the morbidity rate for BRD2, BRD3, and BRD4. There were no differences ($P = 0.37$) in morbidity in the MLV treated calves. These findings are consistent with the findings of Tennant et al. (2014), where auction-derived calves were allocated to 1 of 3 metaphylaxis treatments, tulathromycin, tilmicosin, or control, within 24 to 48 h after feedlot arrival. In that study, steers that received tulathromycin had the lowest morbidity rate compared to calves that received tilmicosin or control. The days to primary BRD treatment were increased ($P < 0.01$) for META steers (19.8 vs. 8.5 d). A pharmacokinetic study where 2 mg/kg BW of tulathromycin was administered s.c. reported tulathromycin has an average half-life of 8 d (Nowakowski et al., 2004). Therefore, the pronounced distribution and absorption of tulathromycin could have influenced the days to primary

BRD diagnosis. There were no differences in rectal temperature ($P \geq 0.24$). Although rectal temperature is the most frequently used objective measure to identify morbid steers, it can be influenced by many factors such as ambient temperature (Rhynes and Ewing, 1973), handling stress (Galyean et al., 1995), and technique such as thermometer probe penetration depth into the rectum (Burfeind et al., 2010). The main effect of META resulted in less ($P < 0.01$) antimicrobial treatment cost but greater ($P < 0.01$) total antimicrobial cost ($31.50 vs. $16.58/animal). The percentage of steers deemed chronically ill was reduced for META (1.7 vs. 8.4%; $P < 0.01$) which is consistent with other trials evaluating the efficacy of antimicrobial metaphylaxis (Kilgore et al., 2005; Wellman and O'Connor, 2007; Ives and Richeson, 2015). Although there were no statistical differences, numerically the META+MLV treatment had the lowest morbidity rates for BRD 1 (16 %), BRD 2 (2.7%), BRD 3 (0.9%), and BRD 4 (0.9%).

The effect of arrival ear-tag status on performance of high-risk, newly received feedlot cattle is presented in Table 2. Steers that arrived with a pre-existing ear-tag were treated for BRD less often ($P = 0.02$; 25.2 vs. 37.6%). The presence of an ear-tag is easy to identify and record, provides evidence that the animal has been handled at least once before purchase, and could be used as a proxy for previous health management at the ranch of origin. Therefore, the arrival ear-tag status of high-risk calves may improve decision making for targeted metaphylaxis.

The results of this study indicate metaphylaxis with tulathromycin improved health outcomes in high-risk calves during the receiving period while pentavalent MLV respiratory vaccination with revaccination on d 14 did not. The safety and timing of MLV vaccination relative to the natural viral challenge and stress-induced immunosuppression

is questionable because of the enhanced antigenicity and replication of MLV vaccination. It has been reported that acute stress in steers, generally considered less than 24 h in duration, can be immuno-priming (Dragoș and Tănăsescu, 2010), but chronic stress, greater than 24 h, can result in immune dysfunction (Burton et al., 1995). Therefore, MLV vaccination of high-risk, chronically stressed calves at feedlot arrival probably does not improve health outcomes and may have negative impacts on health (Griffin et al., 2018; Richeson and Falkner, 2020). The META+MLV treatment had the lowest BRD morbidity rate but there were few statistically significant interactions observed.

Feedlot performance

Performance results are displayed in Table 3. There were no interactions observed for any of the performance variables ($P \geq 0.20$); therefore, only the main effect means are reported and discussed. The META groups had greater ($P < 0.01$) BW on d 14, 28, and 56. Calves that received antimicrobial metaphylaxis with tulathromycin were 13.4 kg heavier on d 56 compared to those that did not receive metaphylaxis (313.2 vs. 299.8 kg). In a study conducted by Tennant et al. (2014), metaphylactically treated calves were 8 kg heavier compared to calves that did not receive metaphylaxis. Additionally, META resulted in greater ($P < 0.01$) ADG from d 0 to 14 (1.12 vs. 0.40 kg), 0 to 28 (1.16 vs. 0.71 kg), and 0 to 56 (1.42 vs. 1.17 kg) and tended ($P = 0.06$) to increase ADG on 14 to 28 d (1.21 vs. 1.01 kg). The main effect of META increased ($P < 0.01$) DMI for every interim period and overall. From d 0 to 56, calves that received metaphylaxis consumed 6.63 kg/d DM compared to 5.84 kg/d DM for those that did not receive metaphylaxis. The G:F was improved ($P < 0.01$) from d 0 to 14 and overall for META.

The main effect of MLV improved ADG ($P = 0.04$) and G:F ($P = 0.02$) from d 28 to 56 and this result is likely influenced by compensatory gain from the numerically reduced growth for MLV steers between d 0 and 14. Compensatory gain occurs when cattle have been nutritionally deprived for an extended period of time and subsequently provided with adequate feed, such that growth occurs at a rate greater than expected (Sainz et al., 1995). High-risk cattle typically arrive at a feedlot with a nutrient deficiency because of the marketing process (Galyean, 2006). Furthermore, MLV vaccines contain antigen(s) that induce an inflammatory response (Arthington et al., 2013) and cytokines promote anorexia and tissue catabolism thus affecting DMI and ADG (Hughes et al., 2013). Because the inflammatory effects of the MLV vaccine administered on d 0 and 14 had likely subsided by d 28, the steers in this study began to consume more feed, allowing for compensatory gain and a greater ADG and G:F from d 28 to 56 than their non-vaccinated counterparts. Although no interactions were detected, the calves in the META+MLV treatment had numerically heavier d 56 BW (315.7 kg), overall ADG (1.46 kg), DMI (6.65), and G:F ratio (0.10 kg). This suggests that the beneficial effect of META could overcome any deleterious effects of MLV in high-risk, newly received beef cattle. The MLV treatment had the numerically least ADG and DMI from d 0 to 14 and 14 to 28, but there was no interaction observed ($P \geq 0.37$).

Of the 372 bulls and 106 steers used in the current study, 19 and 35%, respectively, arrived from the order buying facility with a pre-existing ear-tag. For all interim periods and overall, calves that arrived with a pre-existing ear-tag were heavier ($P \leq 0.03$) compared to their cohorts that did not arrive with a pre-existing ear-tag. On d 56, calves that arrived with a pre-existing ear-tag weighed 9.53 kg more than calves that did

not have an ear-tag, (304 kg vs. 314 kg; $P = 0.01$). The ADG was improved ($P \leq 0.03$) for calves that arrived with a pre-existing ear-tag from d 0 to 14, 14 to 28, 0 to 28, and overall. The overall ADG for calves that arrived with a pre-existing ear-tag was 1.40, compared to 1.27 kg/d for calves that did not arrive with a pre-existing ear-tag. An ear-tag present at feedlot arrival is an objective measure that indicates an animal has been handled at least once before sale and our data suggest it serves as a useful proxy for previous health management at the ranch origin and improved health and performance during the feedlot receiving period.

Activity and rumination behavior

The main effects of daily rumination minutes are displayed in Figures 1 (META) and 2 (MLV). In previous research, a 3-axis accelerometer ear tag was found to be a means of quantifying rumination time accurately (Wolfger et al., 2015) and calves that were treated for BRD had reduced step count 4 d before treatment (Pillen et al., 2016). There was no META × MLV × day interactions; therefore, effects on daily rumination minutes are reported relative to META or MLV × day only. A META × day interaction existed ($P = 0.01$) for daily rumination time. Greater rumination minutes occurred for META groups from d 9 to 20 and on d 22, 24, 26, 27, and 29 ($P < 0.05$). This is consistent with performance results where META had greater ADG and DMI. Rumination minutes did not begin to differ for the main effects of metaphylaxis until day 9 and this can possibly be attributed to the feeding protocol where all calves were provided a diet of 1.5% of initial BW regardless of treatment. If the cattle consume the entire daily ration, they are provided an additional 0.45 kg of DM/animal in the pen.

There was no difference ($P = 0.26$) for daily rumination time due to MLV. There was a META × day interaction ($P < 0.01$) for daily activity but no MLV × day interaction (data not shown; $P = 0.30$). In Tomczak et al. (2019), rumination time was reduced for BRD cases compared to clinically healthy controls which corroborates data in the current study and supports the positive health and performance impact of metaphylaxis that was observed.

APPLICATIONS

High-risk, newly received feedlot calves that were administered metaphylaxis with tulathromycin had improved health and performance. Pentavalent MLV respiratory vaccination administered on d 0 and 14 did not improve health and performance outcomes in high-risk calves during the receiving period. Calves that arrived with a pre-existing ear-tag had less morbidity and greater performance than cohorts that did not arrive with a pre-existing ear-tag. It is likely that calves arriving from auction markets with a pre-existing ear-tag had better health and nutritional management at the ranch origin, and this may be an easily identified proxy to better predict the health risk of individuals. Further research with larger sample size is needed to fully elucidate the safety and efficacy of MLV vaccination in high-risk beef cattle; however, the additional cost and potential negative interactions of excessive MLV replication in stressed cattle upon feedlot arrival may not warrant the use of this procedure.

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Table 1. Effect of metaphylaxis with tulathromycin and/or pentavalent modified-live virus respiratory vaccination on health outcomes of high-risk, newly received feedlot cattle.

	Treatment[1]					*P*-value		
Item	CON	META	MLV	META+MLV	SEM[2]	META	MLV	META×MLV
BRD1[3], %	53.3	21.0	49.2	16.0	-	<0.01	0.37	0.93
BRD2[4], %	23.6	6.7	25.8	2.7	-	<0.01	0.83	0.49
BRD3[5], %	11.8	4.1	16.7	0.9	-	<0.01	0.84	0.29
BRD4[6], %	7.6	2.5	8.3	0.9	-	<0.01	0.83	0.58
Chronic[7], %	9.3	2.5	9.2	0.9	-	<0.01	0.67	0.71
Respiratory mortality, %	2.5	0.0	0.8	0.8	-	0.19	0.64	0.19
Days to								
1st treatment	8.5	20.5	8.8	19.0	2.05	<0.01	0.65	0.63
2nd treatment	18.0[b]	20.3[b]	18.6[b]	42.6[a]	5.73	<0.01	<0.01	<0.01
3rd treatment	23.4	26.0	22.7	33.7	9.65	0.31	0.53	0.46
4th treatment	30.7	29.2	26.0	43.1	7.53	0.19	0.33	0.07
Rectal temperature, °C								
1st treatment	39.89	39.89	40.06	39.72	0.34	0.24	0.95	0.22
2nd treatment	39.06	39.30	39.56	40.00	0.88	0.58	0.20	0.44
3rd treatment	39.61	39.44	39.31	39.11	2.14	0.82	0.66	0.96
4th treatment	39.39	39.30	39.00	40.33	1.58	0.37	0.56	0.21
Antimicrobial cost[8], $/hd								
Draxxin	0.00	26.38	0.00	26.30	0.26	<0.01	0.87	0.87
Nuflor	9.61	4.13	8.97	3.06	0.95	<0.01	0.37	0.82
Baytril	3.07	0.94	3.34	0.42	0.62	<0.01	0.83	0.53
Excede	1.83	0.70	2.78	0.18	0.63	<0.01	0.74	0.25
Micotil	1.70	0.62	1.77	0.18	0.63	0.01	0.77	0.67
Total antimicrobial treatment cost[8]	16.21	6.39	16.85	3.92	2.34	<0.01	0.70	0.51
Total antimicrobial cost[8]	16.31	32.78	16.85	30.22	2.42	<0.01	0.69	0.51

[1]CON = no treatment; META = administered tulathromycin 2.5 mg/kg (Draxxin, Zoetis) on d 0; MLV = 2 mL of pentavalent modified-live virus respiratory vaccination (Titanium 5, Elanco Animal Health) on d 0 and 14; META+MLV = administered tulathromycin on d 0 and pentavalent modified-live virus respiratory vaccine on d 0 and 14.
[2]SEM= pooled standard error of the mean.
[3]Percentage of cattle treated for BRD at least once.
[4]Percentage of cattle treated for BRD at least twice.
[5]Percentage of cattle treated for BRD at least three times.
[6]Percentage of cattle treated for BRD four times.
[7]Cattle treated with an antimicrobial 4 times and/or removed from the study because of poor performance.
[8]Antimicrobial cost assumes the following: $4.13/mL for tulathromycin (Draxxin, Zoetis), $0.60/mL for florfenicol (Nuflor, Merck Animal Health), $0.53/mL for enrofloxacin (Baytril, Bayer Animal Health), $2.00/mL for ceftiofur crystalline free acid (Excede, Zoetis), $1.53/mL for tilmicosin (Micotil, Elanco Animal Health).

Table 2. Effect of arrival ear-tag status on performance of high-risk, newly received feedlot cattle.

	Pre-existing ear-tag[1]			
Item	No (n = 370)	Yes (n = 107)	SEM[2]	*P*-value
Steers, n	68	37	-	-
Bulls, n	302	70	-	-
Morbidity, %				
BRD1[3]	37.57	25.23	-	0.02
BRD2[4]	16.22	9.35	-	0.09
BRD3[5]	9.46	4.67	-	0.16
BRD4[6]	5.95	0.93	-	0.04
BW, kg				
Initial[7]	217	219	4.58	0.34
Day 14	230	235	5.18	0.03
Day 28	244	252	6.16	0.01
Final[8]	290	298	7.54	0.01
ADG, kg				
Initial to Day 14	0.81	1.06	0.26	0.01
Day 14 to 28	1.05	1.26	0.17	0.02
Initial to Day 28	1.02	1.20	0.20	0.02
Day 28 to 56	1.62	1.70	0.11	0.20
Initial to Day 56	1.27	1.40	0.10	0.02

[1]No = calves that did not arrive with pre-existing ear-tag;
Yes = calves that did arrive with a pre-existing ear-tag
[2]SEM = standard error of the mean
[3]Percentage of cattle treated for BRD at least once.
[4]Percentage of cattle treated for BRD at least twice.
[5]Percentage of cattle treated for BRD at least three times.
[6]Percentage of cattle treated for BRD at least four times
[7]Initial = average of d -1 and 0 BW
[8]Final = average of d 55 and 56 BW

Table 3. Effect of metaphylaxis with tulathromycin and/or pentavalent modified-live virus respiratory vaccination on performance of high-risk, newly received feedlot cattle.

	Treatment[1]					*P*-value		
Item	CON	META	MLV	META+MLV	SEM[2]	META	MLV	META×MLV
BW, kg								
Initial[3]	235	234	234	234	14.21	0.50	0.80	0.30
Day 14	240	249	239	250	12.34	<0.01	0.71	0.20
Day 28	256	266	253	267	12.45	<0.01	0.51	0.28
Day 56	299	311	300	316	14.68	<0.01	0.36	0.48
ADG, kg								
Initial to Day 14	0.44	1.12	0.36	1.11	0.23	<0.01	0.50	0.47
Day 14 to 28	1.07	1.19	0.95	1.22	0.23	0.06	0.68	0.47
Initial to 28	0.78	1.16	0.67	1.17	0.16	<0.01	0.43	0.37
Day 28 to 56	1.54	1.62	1.66	1.74	0.13	0.17	0.04	0.95
Initial to Day 56	1.17	1.39	1.17	1.46	0.10	<0.01	0.47	0.53
DMI, kg/d								
Day 0 to 14	3.94	4.54	3.73	4.49	0.54	<0.01	0.11	0.37
Day 14 to 28	5.32	6.22	5.14	6.12	0.39	<0.01	0.36	0.82
Day 28 to 56	7.18	7.91	7.26	8.06	0.51	<0.01	0.50	0.87
Day 0 to 56	5.86	6.61	5.82	6.64	0.41	<0.01	0.94	0.73
G:F, kg								
Day 0 to 14	0.0508	0.1119	0.0419	0.1139	0.2693	<0.01	0.61	0.43
Day 14 to 28	0.0886	0.0866	0.0835	0.0910	0.0177	0.71	0.95	0.52
Day 28 to 56	0.0974	0.0928	0.1040	0.0987	0.0063	0.06	0.02	0.89
Day 0 to 56	0.0902	0.0957	0.0919	0.0998	0.0075	<0.01	0.20	0.58

[1]CON = no treatment; META = administered tulathromycin 2.5 mg/kg (Draxxin, Zoetis) on d 0; MLV = 2 mL of pentavalent modified-live virus respiratory vaccination (Titanium 5, Elanco Animal Health) on d 0 and 14; META+MLV = administered tulathromycin on d 0 and pentavalent modified-live virus respiratory vaccine on d 0 and 14.
[2]SEM = standard error of the mean.
[3]Initial = average of d -1 and 0 BW.

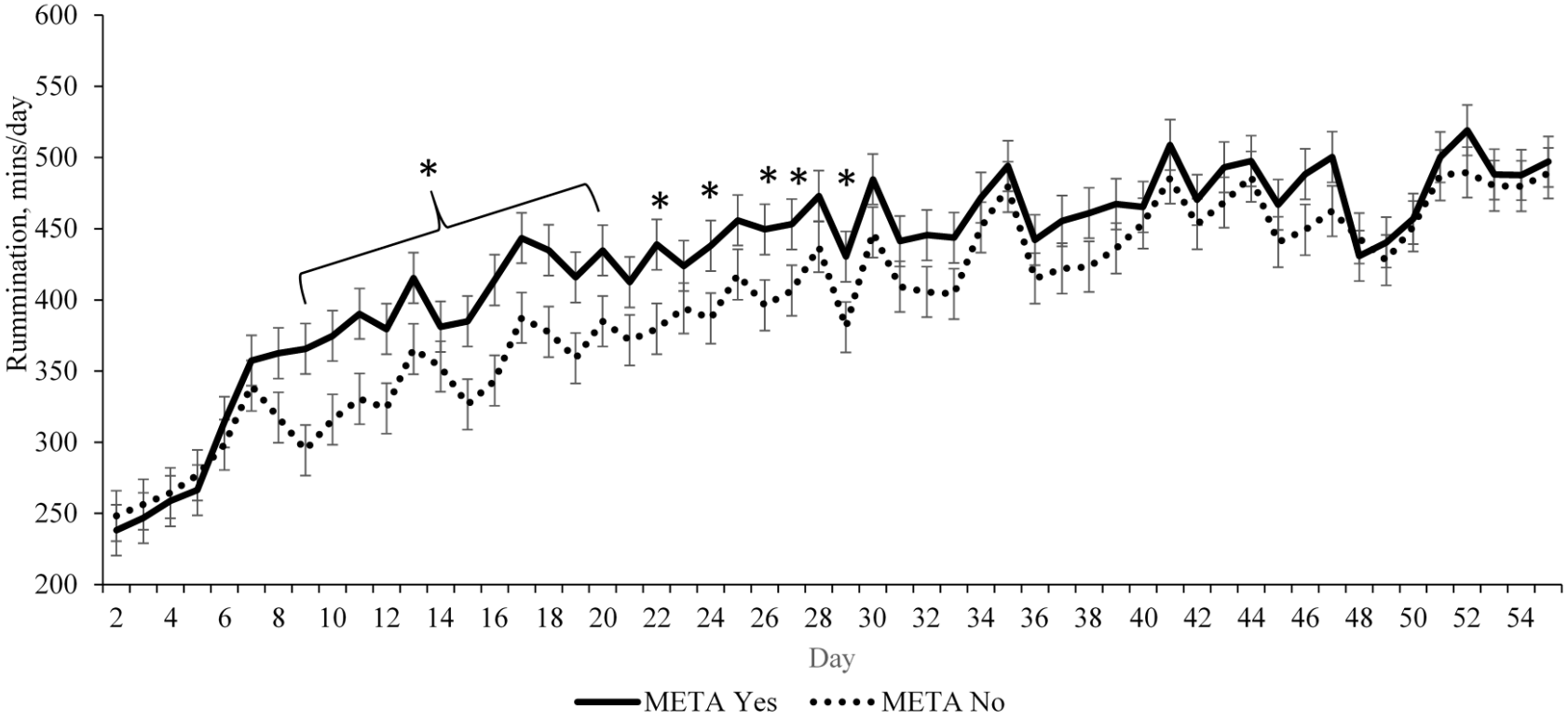

Figure 1. Rumination minutes was obtained from 3-axis accelerometer ear-tag (Allflex Livestock Intelligence, Madison, WI). A META × day interaction existed ($P = 0.01$) for daily rumination time. Greater rumination was observed in META groups from d 9 to 20 and d 22, 24, 26, 27 and 29 ($P < 0.05$).

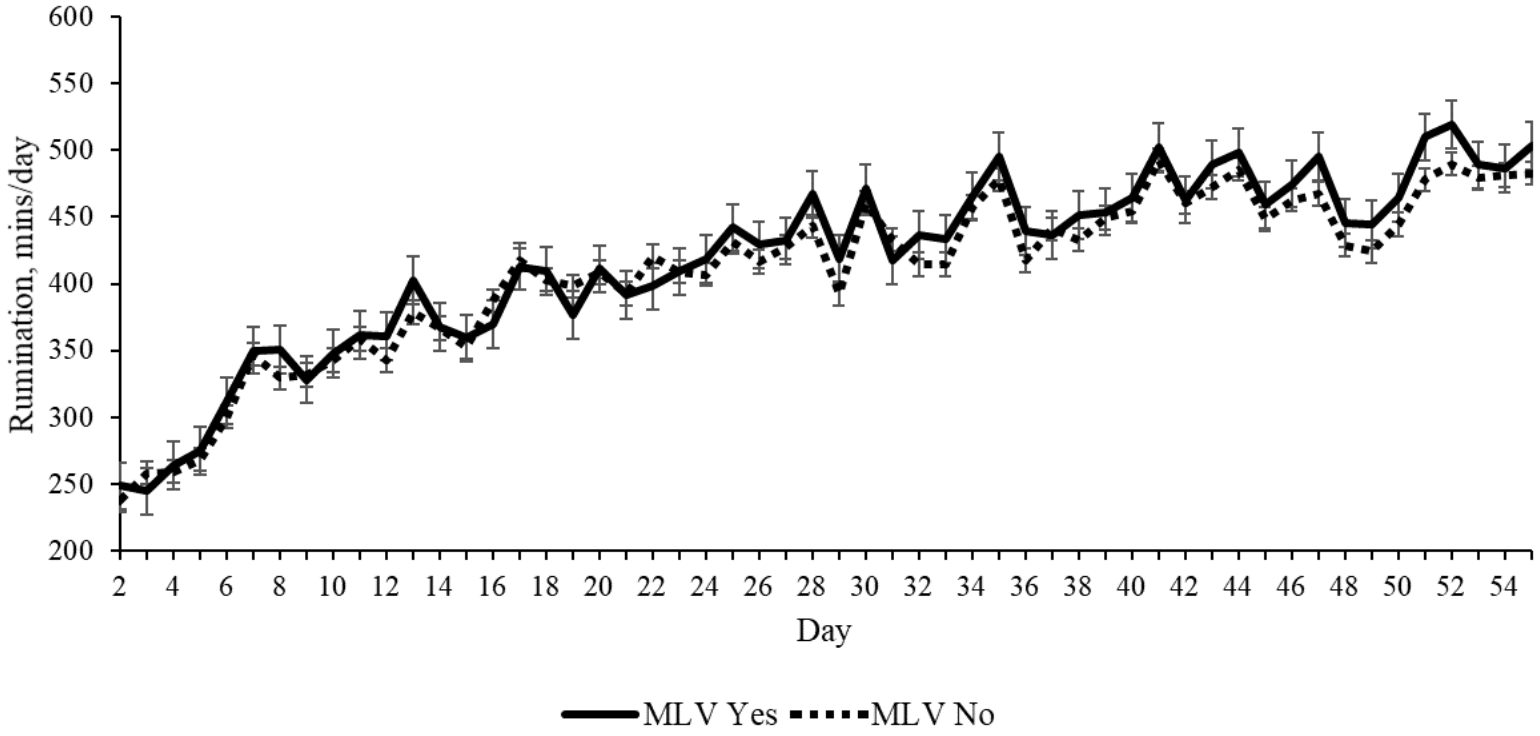

Figure 2. Rumination minutes was obtained from a 3-axis accelerometer ear-tag (Allflex Livestock Intelligence, Madison, WI). There was no difference (P = 0.26) for daily rumination time observed for calves that received a MLV vaccine (MLV Yes) and those that did not (MLV No).