VARIOUS FACTORS INVOLVED IN CONTROL, TREATMENT, AND INVESTIGATION OF BOVINE RESPIRATORY DISEASE IN HIGH RISK FEEDLOT CATTLE

by

SIDDARTHA TORRES

M.V.Z., Universidad Nacional Autonoma de Mexico, 1997
M.B.A., Instituto Tecnologico y de Estudios Superiores Monterrey, 2005
E.M.V., Universidad Nacional Autonoma de Mexico, 2008

AN ABSTRACT OF A DISSERTATION

submitted in partial fulfillment of the requirements for the degree

DOCTOR OF PHILOSOPHY

Department of Animal Science and Industry
College of Agriculture

KANSAS STATE UNIVERSITY
Manhattan, Kansas

2013

Abstract

Bovine Respiratory Disease Complex (BRDC) is the most common and costly disease in feedlot cattle in North America. Annual economic losses are estimated to be US$1 billion due to mortality, reduced performance, and treatment costs. The disease is a multifactorial syndrome caused by a combination of environmental factors, management practices, animal susceptibility, and viral and bacterial pathogens. The objectives of this dissertation were to evaluate two injectable antimicrobials for the treatment and control of BRDC in feedlot cattle, investigation of factors associated with BRDC mortality and morbidity, and to develop control charts based on statistical process control (SPC) principles to monitor cattle mortality rates.

Two multi-site prospective studies were conducted to evaluate the comparative efficacy of the administration of gamithromycin and tulathromycin for the treatment and control of BRDC. A total of 2,529 animals were enrolled at two commercial feedlot locations to evaluate the efficacy of the antimicrobials to control BRDC. Morbidity due to BRDC was higher ($P = 0.03$) among calves receiving gamithromycin compared with those receiving tulathromycin; however, treatments were considered bioequivalent ($P < 0.05$) for BRDC mortality, case fatality rate and re-treatment rate. Final BW, ADG, DMI and F:G, were similar ($P<0.05$) between the groups of calves receiving gamithromycin and tulathromycin. For the evaluation of treatment efficacy, a total of 1,049 calves were enrolled in the study. Re-treatment rate was higher among animals treated with gamithromycin compared with those treated with tulathromycin. Treatments were bioequivalent ($P < 0.05$) for case fatality rate, final BW, and ADG.

To evaluate factors associated with BRDC, a retrospective study was conducted to analyze BRDC mortality and morbidity associated with initial body weight, rectal temperature, and

castration and dehorning (tipping) at processing. Calves with lighter weights and fever at processing were at greater risk of mortality and morbidity due to BRDC. Also, bulls castrated at processing were at higher risk of developing BRDC. Finally, we developed control charts based on SPC principles to monitor and identify "normal" and special cases of variation of mortality rate. In feedlot cattle, monitoring lots of cattle through SPC principles can be used as a powerful tool for continuous improvement.

VARIOUS FACTORS INVOLVED IN CONTROL, TREATMENT, AND INVESTIGATION OF BOVINE RESPIRATORY DISEASE IN HIGH RISK FEEDLOT CATTLE

by

SIDDARTHA TORRES

M.V.Z., Universidad Nacional Autonoma de Mexico, 1997
M.B.A., Instituto Tecnologico y de Estudios Superiores Monterrey, 2005
E.M.V., Universidad Nacional Autonoma de Mexico, 2008

A DISSERTATION

submitted in partial fulfillment of the requirements for the degree

DOCTOR OF PHILOSOPHY

Department of Animal Science and Industry
College of Agriculture

KANSAS STATE UNIVERSITY
Manhattan, Kansas

2013

Approved by:

Co-Major Professor
Dr. Chris Reinhardt

Approved by:

Co-Major Professor
Dr. Dan Thomson

Copyright

Abstract

Bovine Respiratory Disease Complex (BRDC) is the most common and costly disease in feedlot cattle in North America. Annual economic losses are estimated to be US$1 billion due to mortality, reduced performance, and treatment costs. The disease is a multifactorial syndrome caused by a combination of environmental factors, management practices, animal susceptibility, and viral and bacterial pathogens. The objectives of this dissertation were to evaluate two injectable antimicrobials for the treatment and control of BRDC in feedlot cattle, investigation of factors associated with BRDC mortality and morbidity, and to develop control charts based on statistical process control (SPC) principles to monitor cattle mortality rates.

Two multi-site prospective studies were conducted to evaluate the comparative efficacy of the administration of gamithromycin and tulathromycin for the treatment and control of BRDC. A total of 2,529 animals were enrolled at two commercial feedlot locations to evaluate the efficacy of the antimicrobials to control BRDC. Morbidity due to BRDC was higher ($P = 0.03$) among calves receiving gamithromycin compared with those receiving tulathromycin; however, treatments were considered bioequivalent ($P < 0.05$) for BRDC mortality, case fatality rate and re-treatment rate. Final BW, ADG, DMI and F:G, were similar ($P < 0.05$) between the groups of calves receiving gamithromycin and tulathromycin. For the evaluation of treatment efficacy, a total of 1,049 calves were enrolled in the study. Re-treatment rate was higher among animals treated with gamithromycin compared with those treated with tulathromycin. Treatments were bioequivalent ($P < 0.05$) for case fatality rate, final BW, and ADG.

To evaluate factors associated with BRDC, a retrospective study was conducted to analyze BRDC mortality and morbidity associated with initial body weight, rectal temperature, and

castration and dehorning (tipping) at processing. Calves with lighter weights and fever at processing were at greater risk of mortality and morbidity due to BRDC. Also, bulls castrated at processing were at higher risk of developing BRDC. Finally, we developed control charts based on SPC principles to monitor and identify "normal" and special cases of variation of mortality rate. In feedlot cattle, monitoring lots of cattle through SPC principles can be used as a powerful tool for continuous improvement.

Table of Contents

List of Figures

List of Tables

Acknowledgements

I would like to thank to several people for all their support during this program. First and foremost, I would like to thank my family for all their support in the decision to come to Manhattan, for their love and patience during this life-time adventure, especially Lupita and my daughters: Mariana, Sofia and Maria that have been my great motivation.

Also, I would like to acknowledge Dr. Dan Thomson and Dr. Chris Reinhardt. They made possible this great opportunity. They are my advisors, mentors, but most of all, my friends. They provided me guidance and assisted me to complete this great project.

I would like to thank to my advisory committee. Dr. Nora Bello, Dr. KC Olson, and Dr. Mike Apley. They inspired me with their leadership and passion in their fields, and it was my honor to have been able to interact, learn, and be mentored by them.

I would like to thank Dr. Bruce Nosky and all the members from Production Animal Consultation (PAC). They supported me in conducting the research projects, and it was my honor to spend time and learn from these great individuals.

I would also like to acknowledge the Beef Cattle Institute staff and students. They supported me in the projects and spent such a great time discussing important and non-important things about the beef industry, academia, and life in general.

Dedication

This thesis is dedicated to my parents: Guille y Chato. Thanks mom and dad for everything that you have taught me, thanks for encouraging and inspiring me to make this dream come true.

Chapter 1 - Literature Review

Introduction

Bovine respiratory disease complex (BRDC) is the most common and costly disease in the beef cattle industry in North America[23,41,64]. According to the National Animal Health Monitoring System (NAHMS) from the United States Department of Agriculture (USDA), BRDC is the primary cause of illness and death in feedlot cattle[72]. It is estimated that BRDC accounts for approximately 50% of morbidity and over 75% of mortalities in the feedyards[4]. Economic losses are due to mortality, reduced performance, treatment costs, and decreased carcass quality [23,41,64]. BRDC is a multifactorial syndrome caused by a combination of environmental factors, management practices, animal susceptibility, and viral and bacterial pathogens[20,41,68]. Extensive research on BRDC pathogenesis, diagnosis, prevention, and control measures has been conducted; however, BRDC morbidity and mortality rates have been increasing in recent years[20]. Currently, the administration of single dose, injectable antimicrobials have shown to be the most efficacious tool for control and treatment of the disease[5,25,29,45,74]. The objective of this literature review on Bovine Respiratory Disease Complex BRDC is to review the epidemiology, economic impact, preventive methods to control, and treatment of BRDC in feedlot cattle. In addition, briefly discuss the potential benefit of Statistical Process Control (SPC) as a tool to monitor animal health in beef cattle.

The epidemiologic triad of bovine respiratory disease complex

Animal health status is determined by the balance between protective factors (animal resistance) and risk factors (challenge of disease)[30,68]. This balance depends on the interaction among the

susceptible host, etiologic pathogens, and the environment: the three components of the epidemiologic triad. The development of BRDC has been associated with environmental factors, management practices, animal susceptibility, and viral and bacterial pathogens[41,45]. Stressful management practices (e.g. weaning, castration, transportation, commingling, etc.) promote the transmission and proliferation of commensal, but potentially pathogenic, microbes located in the nasopharynx of healthy cattle[3,12,24]. Viral and bacterial agents proliferate, become pathogenic, and damage the respiratory tract during the progression of subsequent respiratory disease[3,24,46] .

The clinical expression of BRDC varies according to the animal, the level of stress that animal experiences, management practices prior to and after the marketing process, and level of pathogen challenge[56,62-64,66].

Pathogens involved in the development of bovine respiratory disease complex

Pathogens involved in the development of BRDC include viruses and bacteria that act in a synergistic manner which results in bacterial pneumonia[2,16,26]. Viruses play an important role in the development of bacterial pneumonia since they predispose the animal's lung to bacterial infection by causing direct damage to the respiratory mucosa and lung parenchyma and inhibit the animal's defense mechanisms against bacteria that are commensal in the upper respiratory tract[26,68]. The major viruses involved in precipitating BRDC are: Bovine herpesvirus-1 (BHV-1) (Infectious Bovine Rinotracheitis); Parainfluenza Virus-3 (PI_3); Bovine Respiratory Syncytial virus (BRSV), and Bovine Viral Diarrhea Virus (BVDV). The latter organism has been recognized as a major pathogenic partner associated in the development of BRDC[24,46]. In addition, Bovine respiratory coronavirus has also been identified as a viral pathogen involved in the development of BRDC; however, the importance as a major virus is still under investigation[46].

Even though viral agents can produce clinical signs consistent with BRDC without bacterial infection, naturally occurring BRDC generally is considered to involve concurrent infection with bacteria[26,68]. Indeed, one highly effective experimental model for development of BRDC involves the exposure to *Mannheimia haemolytica* after infection with bovine herpesvirus-1 (BHV-1)[28,68]. Bacterial pathogens involved in the development of BRDC include *Pasteurella multocida*, *Mannheimia haemolytica* (formerly *Pasteurella haemolytica*), *Histophilus somni* (formerly *Haemophillus somnus*), and *Mycoplasma bovis*[12,23,24,46]. Although all these bacteria have been implicated as primary pathogenic agents in BRDC, *Mannheimia haemolytica* has been considered the most important bacterial pathogen in precipitating the disease. These bacteria are considered commensals of the upper respiratory tract and nasopharynx; however, stress and viral infection are predisposing factors for the bacterial infection in the lower respiratory tract[3,12,24].

Bacterial virulence factors include adhesins, capsular polysaccharide, outer membrane proteins, iron-binding proteins, lipopolysaccharides and lipo-oligosaccharides, enzymes, and toxins[12,24].

These virulence factors are important in the pathogenesis of the disease because allow bacterial attachment and proliferation in the respiratory mucosa in the lower respiratory tract[12,24,46]. In addition, these factors cause severe inflammation, damage to the immune system, and destruction of the lung tissue[12,22,24,46].

Other bacterial pathogens associated with BRDC include *Arcanobacterium pyogenes*, *Birbistenia threalosi*, and other species of Pasteurella and Mycoplasma[24]; however, the importance of these pathogens has not been established.

Predisposing factors associated with environment

Environmental predisposing factors, other than viral and bacterial pathogens, are necessary to induce naturally occurring BRDC. Several predisposing factors, also referred as “stressors”, have

been postulated to be associated with the development of the disease[3,4,68]. These factors include: transportation, weaning practices, weather conditions (cold, cold combined with wet conditions, and sudden and extreme changes in ambient temperature), transportation, commingling with unfamiliar animals, handling, painful procedures such as castration and dehorning, malnutrition, and acute metabolic disorders[2,8,16,26,43,68].

Transportation

Transportation is the most well-recognized predisposing factor for BRDC, and it has been associated with the disease for decades; indeed, this environmental factor led to the common denomination of the disease as "shipping fever"[66,68].

Transportation has been associated with stress, and causes an increase in circulating glucocorticoids [2,66]. Glucocorticoids are linked to immunosuppression leading to an increase in infectious disease susceptibility [2,16,66]. Even though practically all the beef cattle in the United States are transported at least once in their entire life, not all transported cattle develop BRDC. One study, conducted under experimental circumstances, reported that animals transported for 12hr had higher morbidity rates compared with animals transported for 24hrs, and the study concluded that other factors such as sorting, loading, and early transit are most likely to be associated with the development of BRDC than hours of transit [53]. However, recent studies reported a significant association between body weight loss during transportation and BRDC morbidity and overall mortality in feeder cattle, and associations between transportation and increase of stress biomarkers related to episodes of BRDC morbidity and mortality[8,9]. These studies concluded that stress related to transportation is involved in the development of the disease[68].

Weather

Weather has been linked to the development of BRDC, and the highest incidence of BRDC is normally observed during the season of fall[34]. During this time of the year, cattle are typically weaned and marketed through auction markets for further shipment to the feedyards. This seasonality increases cattle traffic through auction markets which leads to an increase in time that cattle spend in stockyards, and potentially delays the loading and unloading processes. These changes in normal marketing logistics may contribute to increased stress, dehydration, and susceptibility to disease[66,68]. In addition, this situation increases cattle commingling and exposure to infected animals that are spreading viral and bacterial pathogens to the immunosuppressed population.

Even though it has been postulated that sudden and extreme changes in weather conditions predispose to BRDC, more research is needed to determine the effect of this extreme sudden change in weather conditions on BRDC[68].

Castration and dehorning

Castration of bulls is performed to reduce aggression and mounting behavior of males; in addition, castration has shown to improve beef quality[7, 11, 82]. Therefore, castration is a common practice in the US beef industry standards[11]. It is recommended to castrate bull at early life to reduce economic losses due to reduced performance, and improve animal welfare[7,42]. In the feedlot industry, castration of intact bulls is an intervention performed at processing upon arrival. It is a painful procedure that has shown to increase plasma cortisol and haptoglobin concentrations, and decrease gamma-interferon production resulting in animal immunosuppression[10,18], and animals may be at greater risk of developing infectious diseases[11]. Consequently, it is believed that intact bulls that are castrated at feedlot arrival are at greater risk

of developing BRDC[18,82]; nevertheless, evidence has been incostintent[68] . One study evaluating the effect of castration on health and performance (n=105 calves) reported that reported that morbidity (animals that were pulled) and treatments were significantly higher ($P \leq 0.03$) in calves that were castrated surgically compared with those that were purchased as steers. However, in another experiment (n=283 calves), no evidence of differences ($P \geq 0.22$) in first treatment or retreatment rates were found between calves that were purchased as steers, or bulls that were banded or surgically castrated[6]. Another study reported that castrated bulls had marginally greater overall morbidity rates and BRDC incidence rates compared with steers[10]. Dehorning is a management practice performed at processing after cattle arrives to the feedyard. Dehorned cattle are safer to handle and reduce hide damage and carcass bruises[65]. Like castration, dehorning is a painful procedure that increases plasma cortisol resulting in immunosuppression[65,69]. Dehorning has shown to have negative impact in cattle performance[6,16,35,82]. In addition, dehorning has shown to affect negatively cattle health; indeed, it has been reported that dehorning can increase morbidity rate by 30% compared with non-dehorned animals[39].

Individual animal susceptibility

It has been postulated that individual animal factors are associated with susceptibility or BRDC. These individual factors include gender, age or weight, genetics, and behavior.

Gender

Although it is believed that steers are at higher risk of developing BRDC compared to heifers, there is no conclusive evidence in the literature about the effect of gender on BRDC morbidity or mortality in feeder cattle. For instance, one study reported that from 1994 to 1996, steers and heifers had the same risk of mortality due to BRDC; however, mortality rates were higher in

heifers compared to steers from 1997 to 1999[34]. Other studies have reported that steers were at higher risk of developing BRDC compared to heifers; nonetheless, authors concluded that this finding can be confounded by management practices performed only in males (e.g. castration of intact bulls)[64,68].

Weight at arrival

Many studies have reported that calves which are lighter upon feedlot arrival are at higher risk of developing BRDC compared with heavier cattle[56,69]. One study reported that calves weighing less than the average weight were 1.4 times more likely to develop BRDC compared with those weighing more than the average weight. Likewise, a study analyzed BRDC incidence during 12 weeks in 122 pens of feedlot cattle, and reported that heavier arrival weights were associated with decreased morbidity risk[56]. Cattle weight at arrival can be a good predictor of BRDC mortality and morbidity in feedlot cattle, and can be used to categorize animals into risk groups; then, management and economic decisions based on risk assessment can be conducted[56].

Genetics

Even though heritability of BRDC susceptibility has been postulated, it has been reported to be very low. Instead, susceptibility to BRDC seems to varies among different cattle breeds[63,68]. The breeds *Bos taurus* are more susceptible to develop BRDC compared to *Bos indicus* breeds, and within *Bos taurus*, Hereford animals seems to be at higher risk of developing BRDC compared with other breeds[63].

Clinical signs associated with bovine respiratory disease complex

Severity of clinical signs of BRDC varies from unapparent to per-acute death [12,24]. When clinical signs are observed, they are usually evident between 7 to 10 days after the stressful situation; however, in newly received cattle, clinical signs can be present as late as 27 days after

arrival[24,81]. Typical clinical signs include depression and anorexia, nasal and ocular discharge, fever, increased respiratory rate, and moist cough. Depending on the severity of anorexia, animals can experience slight to severe weight loss[81]. At auscultation, lungs reveal vesicular and bronchial cranial-ventral sound that progress to laud bronchial tones indicating consolidation that are moist in early stages and become dry in advanced conditions. Finally, animals may stand with abducted elbows and extended neck to increase ventilation and pulmonary capacity; in some cases, animals can present diarrhea[81].

Diagnosis of morbid animals is commonly based on the DART system (Pharmacia Upjohn Animal Health, Kalamazoo, MI) or modifications[20]. The system consists of clinical evaluation and scoring of depression, appetite, respiration, and temperature. Diagnosis of BRDC under field conditions is difficult because beef cattle exhibit prey behavior and perceive care personnel (e.g. pen riders) as predators. Consequently, sick animals often mask clinical symptoms; thus, delaying early detection and treatment[24,50].

Typically, diagnosis of BRDC is based on a combination of objective (i.e. rectal temperature, body weight) and subjective (i.e. depression, abnormal appetite, and respiratory signs) assessments of morbid animals[67]; nevertheless, there is a high degree of diagnostic error. Indeed, previous studies have shown that diagnosis of BRDC based on DART attributes has sensitivity and specificity rates of 61.8 and 62.8% respectively[77]. One study conducted in South Africa reported that only 55.4% of animals treated once for BRDC had lung lesions at slaughter[71]. Similarly, another study found that only 78% of steers treated for respiratory disease (either before weaning or in the feedlot) had lung lesions at slaughter[79]. Consequently, large proportion of false-positives and false-negatives can bias assessments of morbidity rates. Hence, clinical scores and lung lesions at slaughter seems to be poor methods to accurately detect diseased

animals[77]. New technologies that increase the sensitivity and specificity of BRDC diagnosis are needed to increase accuracy in evaluating morbidity rates feeder cattle.

Economic impact of bovine respiratory disease complex

Bovine respiratory disease is the most costly and common disease in beef cattle in North America; it has been estimated that annual economic losses due to BRDC are US $1 billion due to due to morbidity, mortality, treatment cost, and reduction in performance and carcass value[22,23,41,45,58]. In addition, it is estimated that over US$3 billion are spent annually on preventive measures for BRDC in beef cattle[23]. One study reported that on an individual live-animal basis, the economic losses associated with lower body weight gain and treatment cost for BRDC infection was $13.90 per animal; this study evaluated 18,112 calves from 1987 to 2001[64]. Likewise, another study analyzed health records from 5,975 animals in combination with lung lesions at slaughter, and reported that BRDC incidence decreased ADG by 0.07 kg per animal per day, reduced hot carcass weight by 8.16 kg, and reduced marbling score. The economic loss due to reduced performance and negative impact on carcass traits was estimated at $23.23, $30.15, and 54.01 for animals that were treated once, twice or three times, respectively[58]. Another assessment of the economic impact of BRDC was conducted by the Ranch to Rail program conducted by Texas A&M[40]. Data from this program showed that BRDC was associated with higher production cost, lower feedlot performance, and lower USDA quality grade. According to these data, animals that had at least one treatment for BRDC returned $92.26 less than animals that remained healthy through the entire feeding period[40]. In another study conducted in 2007, feedlot animals were segregated according to the number of BRDC treatments received during the first 63 days of feed; subsequently, animals were grouped in pens according to the number of treatments received: 0, 1, 2, or 3 treatments for BRDC, or deemed as

chronic. Then, all calves were fed until they reached a similar ultrasound fat-content endpoint. The study reported no evidence of BRDC differences on carcass traits, beef tenderness, or palatability. Likewise, no evidence of differences in final body weight was found among animals that received 0, 1, 2 or 3 treatments for BRDC. The number of days on feed required to reach the same endpoint were different among treatment groups, so animals that received 0 or 1 treatment for BRDC were slaughtered on day estimated of 162, and calves that received 2 or 3 treatments had estimated days on feed of 182 and 189, respectively[27]. This study concluded that regardless of number of treatments for BRDC, animals appear to maintain the potential to produce carcasses with similar characteristics as healthy animals; however, additional days on feed are required to reach this endpoint[27]. From an economic standpoint, losses due to BRDC, based on this model, involve only treatment costs and approximately 18 additional days on feed, and no negative effect on carcass merit.

Preventive measures

In an effort to minimize the negative effects of BRDC, the beef industry has developed several pre-arrival and post-arrival interventions known as preventive measures. The most common interventions include preconditioning, vaccination, health protocols at processing (including metaphylaxis), and nutrition management[69].

Preconditioning

The concept of preconditioning was first described in 1965 by Dr. John Herrick, and it is considered a pre-arrival practice to reduce mortality and morbidity in the feedyard by strengthening animals' immunity, preventing stressors involved in the marketing process, and increasing animal resistance to pathogen[16,76]. Even though preconditioning protocols are not well-defined and include multiple variations of interventions, the common components of

preconditioning include castration and dehorning at early life, administration of respiratory and clostridial vaccinations, deworming, weaning approximately 30-45 days prior to shipping, and training to eat from a feed bunk and drink from water tanks[16,69,76].

The benefits of preconditioning were questionable two decades ago because of the lack of consistent results reported in the literature; however, in the last few years, large randomized control trials have shown that this practice is valuable, improving health and performance in feedlot cattle[69]. One study conducted in Canada with 12,313 calves reported that calves which were vaccinated and conditioned prior to shipment were less likely to receive treatment for BRDC in the feedlot during the first 28 days after arrival compared with calves acquired from conventional auction markets[36]. Another study including 273 calves originated from unknown sources or two different preconditioning programs reported that preconditioned animals had higher ADG, better feed conversion, and lower morbidity and mortality ratios in feeder cattle; this study reported that the added value of calves that were preconditioned compared with those with unknown origin was between $46.83 and $49.54 per animal[55].

Despite the evidence of preconditioning programs in improving health and performance in beef cattle, the adoption of this valuable tool is very low in cow-calf operations[76]. Furthermore, the lack of vertical coordination within the US beef industry makes it difficult to implement this type of program because of misunderstanding of the economic value for both cow-calf and feedlot operations[69]. It is important for the beef industry to increase the adoption of this practice to improve performance, health and well-being of beef cattle.

Processing protocols

Upon arrival to the feeding facility, beef cattle are subject to a series of procedures commonly known as processing. Processing typically includes weighing and giving an ear tag for animal

identification, administration of vaccines, parasiticides, antimicrobials, and anabolic implants, castration of intact bulls, dehorning, and administration of an abortificant to pregnant heifers; in some cases, administration of injectable vitamins and minerals and oral administration of direct fed microbials is also practiced[69]. Processing practices are aimed at improving health and performance, and minimizing morbidity and mortality of animals at risk of developing respiratory disease.

Time of processing

Effect of time of processing after arrival on animal health has been discussed for many years; however, there is not conclusive evidence about effects attributable to timing of processing[69]. In a feedlot consultant survey conducted to 23 veterinarians in north-America, the majority of veterinarians (91%) require that long-hauled (defined as greater than 8 hours) animals be allowed an extended period of rest (between 12 to 24 hours) before processing, and for those animals subjected to short hauls (defined as less than 8 hours), veterinarians (74.8%) require that animals rest less than a 6 hour period[70]. Since there are countless variations in processing protocols, no conclusive evidence is available pertaining to the effect of processing on BRDC morbidity and mortality. Further research with randomized control field trials and standardize processing protocols will help to determine the proper timing for processing high-risk and low-risk calves.

Vaccination at arrival

Respiratory vaccination at arrival against bacterial pathogens, viral pathogens, or both, is common among practically all feeding facilities[69,72]. According to the USDA, vaccination administered at processing includes antigens against BVD (94.4%), IBR (96.9%), PI_3 (86.3%), BRSV (87.4%), *Histophillus somni* (62.1%), and *Pasteurella spp* (55.3%)[72]. A feedlot consultant survey conducted to 23 veterinarians revealed that all consultants recommend vaccination for

high-risk calves at processing against IBR and BVD Types I and II; in addition, 65.2%, 60.9% , 21.7% and 73% of the veterinarians recommend vaccination against BRSV, PI_3, *Histophilus somni*, and *Mannheimia haemolytica*, respectively[70]. Surprisingly, there is little information in the literature that supports this practice in reducing BRDC morbidity and mortality[54]. Besides, it was hypothesized that vaccination at arrival may be a detrimental practice because animals are stressed, already exposed to pathogens, and perhaps experiencing immunosuppression [54]. In a study conducted in Ontario, vaccination at arrival increased morbidity and mortality in feedlot cattle[37]. Also, a review of respiratory vaccination at arrival concluded that most vaccines administered at processing are ineffective in preventing BRDC[38]. It can be argued that these conclusions are not valid because they were done in the 1980's, and vaccines currently available are different[20]. Unfortunately, no additional research has been conducted to evaluate the efficacy of vaccination in preventing BRDC. In recent years, research has focused on comparing different multivalent modified live vaccine protocols using different antigen strains, and these studies do not include negative control groups[19,20,61,69,78]. Therefore, it is not possible to determine the efficacy of vaccination at arrival in preventing BRDC. More research must be conducted in order to determine effective respiratory antigen immunization protocols for feedlot cattle.

Health monitoring parameters

In the modern feedlot industry, population based medicine is one approach that allow consultants to study interactions among health and productivity. A clear definition of health outcomes that can be monitored is critical for the success of the health program in the feeding operation[13].

From epidemiological perspective, incidence and prevalence are the most used health outcomes in the feedlot industry[13]. Incidence is the probability that an individual animal will develop the

disease in a defined period of time, and it refers to the number of new events, in a defined population within a specific period; prevalence is related to all the cases of disease existing at specific point in time in a population rather than new cases occurring over a period of time[15].

Incidence is normally calculated as the number of new cases of disease in a certain period of time divided by the total number of animals that were at risk at the beginning of the time period. The formula to calculate prevalence is the number of animals in the population with the disease at a certain point of time divided by the total number of animals in the population at that certain point of time[15]. In the cattle feeding industry, health outcomes commonly measured include: morbidity, mortality, case fatality, re-treatment, and chronic animals (non-responders). Usually, these outcomes are expressed in terms of incidence[13].

Mortality rate is obtained by dividing the number of calves that died during a time period by the number of calves in the group that was at risk (population at risk). In feeder cattle, the number of animals that arrived (per each lot of cattle or over the entire cattle population) is typically used as population at risk. The period of time can be determined by the veterinarian consultant, and it usually is conducted by month, year, season, or at close-out[13].

Case fatality rate, a measure of mortality, is referred to as the percentage of animals that died among those that were identified as having the specific disease. Case fatality rate is calculated by dividing the number of animals that died by the number of animals that were identified as diseased during a certain period of time[13].

Re-treatment rate refers to the proportion of calves that required a second treatment for the same disease for which they were previously treated[15]. It is calculated by dividing the number of animals that required a second treatment by the number of calves that received the initial treatment during a certain period of time. Further treatments rates can also be determined

following the same rationale for re-treatment rate. Percentage of chronic animals, also called non-responders, is calculated by dividing the number of calves that did not responded to therapy (also known as realizers) by the total number of calves that received the initial therapy during a certain period of time[13].

Metaphylaxis to control bovine respiratory disease complex

Metaphylaxis, also referred as control, consists of mass administration of an approved antimicrobial in an animal population that is at imminent risk of developing disease, before the onset of illness[16,45]. The goal of metaphylaxis is to address the bacterial infection in the respiratory tract of stressed animals which may have a compromised immune system[45]. In beef cattle, it was first reported in the early 1980's using the mass administration of injectable oxytetracycline on feedlot calves to reduce the incidence of BRDC[32,33]; later, several studies administering a single dose of injectable tilmicosin demonstrated to be efficacious in controlling BRDC in feeder cattle[21,44,59,60,73].

Studies have shown that metaphylaxis improves health and performance of high risk calves; it decreases BRDC morbidity and mortality; in addition, metaphylaxis has shown to increase average daily gain and feed efficiency compared with negative controls[45]. In the US, single dose injectable antimicrobials approved for metaphylaxis include oxytetracycline, tilmicosin, florfenicol, ceftiofur crystalline free acid, tulathromycin, and gamithromycin[5,21,29,31,33,47]. The selection of an antimicrobial in commercial settings is usually based on the characteristics of the drug, expected drug efficacy, and cost[45].

Comparative drug efficacy among drugs approved for BRDC control is normally determined by evaluating animal health and performance following metaphylaxis. Tulathromycin and tilmicosin have the greatest number of clinical trials for controlling BRDC reported in the

literature; comparisons against florfenicol, ceftiofur crystaline free acid (CCFA), and oxytetracycline have been conducted. Health outcome definitions vary among studies, so it is very difficult to establish a conclusive antimicrobial efficacy rate. For instance, 3 out of 12 studies didn't report mortality or morbidity rates, and the range for which health outcomes were evaluated was from 10 to 60 days on feed, so there is not a unique criteria established to evaluate health and performance. Finally, differences in health outcomes show that cattle enrolled in the studies were at different levels of risk, originated from different geographical locations, and were subjected to different processing protocols and management practices. The variability of risk factors for cattle makes difficult to conclude on absolute and relative efficacy of antimicrobials for metaphylaxis.

Treatment of bovine respiratory disease complex

A successful therapy program includes the following items: identification of disease challenges, case definition for sick animals, complete description of treatment protocol (dose, route/site of administration, frequency, volume, withhold, etc.), success/failure case definition, potential re-treatment protocols, and a system to monitor health outcomes.

Case definition for BRDC can vary among veterinary consultants; however, it usually includes a combination of clinical observations based on the DART system (Depression, Appetite, Respiration score, and Temperature). An example of case definition for BRDC includes calves showing respiratory clinical scores of 1 or 2 and having rectal temperature $\geq$ 104ºF, or animals showing clinical scores of 3 regardless rectal temperatures (Table-1). Animal health personnel should be well trained on case definitions for accurate diagnosis and early sick animal identification[17]. Cattle are prey animals that hide clinical signs as a means of self-preservation, which makes identification of sick animals difficult and imprecise.

Once animals are suspected to be suffering from BRDC in the home pen, it is recommended that further evaluations be done to confirm diagnosis. Confirmation should be done by experienced animal health personnel using diagnostic tools such as rectal thermometer and stethoscope for lung auscultation.

Written treatment protocols developed by a veterinarian should include the name(s) of the animal health product(s), dosage, route of administration, and withdrawal date. Animal health products have to be administered according to the label directions and following the Beef Quality Assurance guidelines from the National Cattlemen's Beef Association (NCBA). Antimicrobial use at a different dosage rate or different route is considered as "extra-label" use, and it is not approved by governmental agencies.

Antimicrobial consideration for initial therapy, including first and consecutive treatment regimen, involves potential interaction for sequential administration of antimicrobials[3]. Injectable antimicrobials labeled for treatment of animals diagnosed with BRDC include: tulathromycin, tildipirosin, CCFA, oxytetracycline, florfenicol, tilmicosin, enrofloxacin, danofloxacin, ceftiofur hydrochloride, ceftiofur sodium, spectinomycin sulfate, penicillin G, and ampicillin.

Post-treatment interval (PTI), or moratorium, is the period of time between last antibiotic treatment and further treatments. The suggested PTI varies according to each antimicrobial's pharmacokinetics[3]. Ancillary therapy for BRDC includes, but is not limited to: anti-inflammatories (steroidal and non-steroidal), vitamins, antihistamines, immuno-modulators, diuretics, and bronchodilators. These concurrent medications may substantially increase the cost of treatment, and there is no evidence in the literature supporting these practices in improving health outcomes or performance[3]. One study comparing antimicrobial treatment concurrent with

and without non-steroidal anti-inflammatory (e.g. flunixin meglumine, carprofen and ketoprofen) reported no evidence of differences among treatment groups in reference to clinical depression, illness scores, dyspnea, or coughing. Nevertheless, the authors reported reduced lung consolidation at necropsy among those animals that received flunixin meglumine.

After treatment protocol administration, animals may either be returned to their home pen for recovery or be assigned to a hospital pen. Animals have to be observed daily for clinical evaluation and determine recovery signs. Home pens should provide animal well-being and feed and water *ad libitum*. Animals that fail to respond to therapy have to be re-evaluated by qualified animal health personnel; if necessary, they will be deemed as non-responders and categorized as chronic.

Statistical process control

Statistical Process Control (SPC) is a powerful tool for monitoring, controlling, and improving processes and outcomes through statistical methods[51]. Even though this tool has been used for more than 80 years in the manufacturing and human health care industries, its application in food animal agriculture has not been extensively implemented[52]. Production systems in food animal agriculture are based on standardized operating procedures (SOP) and management practices than can be monitored using statistical methods[52]; therefore, SPC can be used for monitoring SOP outcomes, health outcomes and animal performance; hence, top management and animal care personnel can easily identify abnormal deviations and make early interventions to return animals to normal.

Statistical process control was developed during the 1920's by statistician Walter A. Shewarth; later, SPC was popularized by Edward W. Deming for use, first in military-industrial manufacturing in the U.S. war effort, and later by post-war Japanese industrial firms[51]

In livestock, the initial published information about the use of SPC was in the swine industry in 1977[80]. In the cattle industry, SPC has been implemented in dairies as a method to monitor and control mastitis, milk quality, bulk-tank milk somatic cell counts, and reproductive performance[14]. In beef cattle, SPC has been reported to monitor carcass quality[48], steer weight gain[57], and feeding behavior of newly received calves[49]. However, to our knowledge, no additional SPC reports on beef cattle health have been published.

Animal performance is critical to assure profitability and sustainability. Beef cattle operations measure productivity based on the efficiency on how capital, labor, energy, and commodities are transformed into the final product[14]. Feedlot profitability is affected by economic losses due to animal health conditions and/or animal performance deviations[14]. Developing an SPC system to monitor, evaluate and analyze health and performance otucomes in feedlot cattle will provide an easy-to-use tool to identify and differentiate between "normal" and "special" cases variation. Hence, veterinarians and other cattle care personnel can implement quick interventions to reduce the impact of potential losses, return animals to normal, and improve animal health and productivity.

Even though record keeping is a common practice in feedlot operations, it does not imply that actions will be, or should be, taken to improve health and performance. Experience has shown that SPC principles, in conjunction with other management practices, can be applied in feedlot production medicine and can become a very powerful tool for continuous improvement[52].

Control charts

Control charts are one of the most important SPC tools for monitoring and analysis. The foundation of control charts pertain to the theory of variation, understanding and defining what "normal" variation is, and identifying "special cases" of variation[1]. Control charts combine time

series methods with graphical representation of data, they have a center line and corresponding upper and lower control limits. The center line represents the overall mean (central tendency) of the observations, and the control limits are estimated using the standard deviation (sigma) technique[51]. The placing of control limits will depend on each individual observation and the level of type I and type II errors[51]. A robust control limit uses 3-sigma units from the mean[75]. Nevertheless, other considerations based on previous experience, feedlot targets, and statistical adjustments for binomial distributed data, can be used to properly define control limits. Statistical process control represents an invaluable opportunity to improve herd management and profitability[14]. In the feedlot industry, veterinarians and cattle care providers can take advantage of this easy-to-use and powerful tool to identify special cases of variation.

References

1. Adeoti O.A. On the applications of statistical process control in health care. *Nig J of Med*. 2009;18(1):25-28.

2. Aich P. Modern approaches to understanding stress and disease susceptibility: A review with special emphasis on respiratory disease. *Int J Gen Med*. 2009;2:19.

3. Apley M. Bovine respiratory disease: Pathogenesis, clinical signs, and treatment in lightweight calves. *Vet Clin North Am Food Anim Pract*. 2006;22(2):399-411.

4. Babcock AH, White BJ, Dritz SS, Thomson DU, Renter DG. Feedlot health and performance effects associated with the timing of respiratory disease treatment. *J Anim Sci*. 2009;87(1):314-327.

5. Baggott D, Casartelli A, Fraisse F, et al. Demonstration of the metaphylactic use of gamithromycin against bacterial pathogens associated with bovine respiratory disease in a multicentre farm trial. *Vet Rec*. 2011;168(9):241-241.

6. Berry BA, Choat WT, Gill DR, Krehbiel CR, Smith RA. Effect of castration on health and performance of newly received stressed feedlot calves. *Animal Science Research Report - Agricultural Experiment Station, Oklahoma State University*. 2001;3.

7. Bretschneider G. Effects of age and method of castration on performance and stress response of beef male cattle: A review. *Livest Prod Sci*. 2005;97(2-3):89.

8. Cernicchiaro N, White BJ, Renter DG, Babcock AH, Kelly L, Slattery R. Effects of body weight loss during transit from sale barns to commercial feedlots on health and performance in feeder cattle cohorts arriving to feedlots from 2000 to 2008. *J Anim Sci*. 2012;90(6):1940-1947.

9. Chirase NK. Effect of transport stress on respiratory disease, serum antioxidant status, and serum concentrations of lipid peroxidation biomarkers in beef cattle. *Am J Vet Res*. 2004;65(6):860.

10. Coetzee JF. Effect of oral meloxicam on health and performance of beef steers relative to bulls castrated on arrival at the feedlot. *J Anim Sci*. 2012;90(3):1026.

11. Coetzee JF. Erratum to "A review of pain assessment techniques and pharmacological approaches to pain relief after bovine castration: Practical implications for cattle production within the united states"[appl. anim. behav. sci. 135 (2011) 192–213]. *Appl Anim Behav Sci*. 2012;139(1-2):151.

12. Confer AW. Update on bacterial pathogenesis in BRD. *Animal Health Research Reviews*. 2009;10(02):145.

13. Corbin MJ. Assessing performance of feedlot operations using epidemiology. *Vet Clin North Am Food Anim Pract*. 2006;22(1):35.

14. De Vries A. Application of statistical process control charts to monitor changes in animal production systems. *J Anim Sci*. 2010;88(13 elect suppl):E11.

15. Dohoo I, Martin W, Stryhn H. *Veterinary epidemilogic research.* Charlottetown, Prince Edward Island, Canada: AVC Inc; 2003.

16. Duff GC, Galyean ML. BOARD-INVITED REVIEW: Recent advances in management of highly stressed, newly received feedlot cattle. *J Anim Sci*. 2007;85(3):823-840.

17. Edwards TA. Control methods for bovine respiratory disease for feedlot cattle. *Vet Clin North Am Food Anim Pract*. 2010;26(2):273-284.

18. FISHER A, KNIGHT T, COSGROVE G, et al. Effects of surgical or banding castration on stress responses and behaviour of bulls. *Aust Vet J*. 2001;79(4):279-284.

19. Frank GH. Effects of vaccination prior to transit and administration of florfenicol at time of arrival in a feedlot on the health of transported calves and detection of mannheimia haemolytica in nasal secretions. *Am J Vet Res*. 2002;63(2):251.

20. Fulton RW. Bovine respiratory disease research (1983–2009). *Animal health research reviews*. 2009;10(02):131.

21. Galyean ML. Effects of arrival medication with tilmicosin phosphate on health and performance of newly received beef cattle. *J Anim Sci*. 1995;73(5):1219.

22. Garcia MD. Effect of bovine respiratory disease and overall pathogenic disease incidence on carcass traits. *J Anim Sci*. 2010;88(2):491.

23. Griffin D. Economic impact associated with respiratory disease in beef cattle. *Vet Clin North Am Food Anim Pract*. 1997;13(3):367.

24. Griffin D, Chengappa MM, Kuszak J, McVey DS. Bacterial pathogens of the bovine respiratory disease complex. *Vet Clin North Am Food Anim Pract*. 2010;26(2):381-394.

25. Guthrie CA, Rogers KC, Christmas RA, Vogel GJ, Laudert SB. Efficacy of metaphylactic tilmicosin for controlling bovine respiratory disease in high-risk northern feeder calves. *The Bovine practitioner*. 2004;38(1):46-53.

26. Hodgson PD, Aich P, Manuja A, Hokamp K, Roche FM. Effect of stress on viral-bacterial synergy in bovine respiratory disease: Novel mechanisms to regulate inflammation. *Comp Funct Genomics*. 2005;6(4):244-250.

27. Holland BP, Burciaga-Robles LO, VanOverbeke DL, et al. Effect of bovine respiratory disease during preconditioning on subsequent feedlot performance, carcass characteristics, and beef attributes. *J Anim Sci*. 2010;88(7):2486-2499.

28. Jericho K, Langford E. Pneumonia in calves produced with aerosols of bovine herpesvirus 1 and pasteurella haemolytica. *Can J comp Med*. 1978;42(3):269-277.

29. Kilgore WR. Clinical effectiveness of tulathromycin, a novel triamalide antimicrobial, for the control of respiratory disease in cattle at high risk for developing bovine respiratory disease. *Vet ther*. 2005;6(2):136.

30. LeBlanc SJ. Major advances in disease prevention in dairy cattle. *J Dairy Sci*. 2006;89(4):1267.

31. Lechtenberg K, Daniels CS, Royer GC, Bechtol DT, Chester ST. Field efficacy study of gamithromycin for the control of bovine respiratory disease in cattle at high risk of developing the disease. *J Appl Res Vet*. 2011;9(2):184-192.

32. Lofgreen GP, Stinocher LH, Kiesling HE. Effects of dietary energy, free choice alfalfa hay and mass medication on calves subjected to marketing and shipping stresses. *J Anim Sci*. 1980;50:590.

33. Lofgreen GP. Mass medication in reducing shipping fever-bovine respiratory disease complex in highly stressed calves. *J Anim Sci*. 1983;56(3):529.

34. Loneragan GH, Dargatz DA, Morley PS, Smith MA. Trends in mortality ratios among cattle in US feedlots. *J Am Vet Med Assoc*. 2001;219(8):1122-1127.

35. Loxton IDL. The effect of dehorning brahman crossbred animals of four age groups on subsequent bodyweight gain. *Aust Vet J*. 1982;58(5):191.

36. Macartney JE. Health performance of feeder calves sold at conventional auctions versus special auctions of vaccinated or conditioned calves in ontario. *J Am Vet Med Assoc*. 2003;223(5):677.

37. Martin SW. The association between serological titers in infectious bovine rhinotracheitis virus, bovine virus diarrhea virus, parainfluenza-3 virus, respiratory syncytial virus and treatment for respiratory disease in ontario feedlot calves. *Canadian journal of veterinary research*. 1986;50(3):351.

38. Martin SW. Vaccination: Is it effective in preventing respiratory disease or influencing weight gains in feedlot calves? *Can Vet J*. 1983;24(1):10.

39. Martin SW. Factors associated with mortality and treatment costs in feedlot calves: The bruce county beef project, years 1978, 1979, 1980. *Can J comp Med*. 1982;46(4):341.

40. McNeill JW. 2000-2001 texas A&M ranch to reail - noth/south summary report. *Texas A&M*. 2001.

41. McVey DS. BRD research needs in the next 10–20 years. *Animal Health Res Rev*. 2009;10(02):165.

42. Micol D, Oury MP, Pcard B, Hocquette JF. Effect of age at castration on animal performance, muscle characteristics and meat quality traits in 26-month-old charolais steers. *Livestock Science*. 2009;120:116.

43. Mitchell GB, Clark ME, Siwicky M, Caswell JL. Stress alters the cellular and proteomic compartments of bovine bronchoalveolar lavage fluid. *Vet Immunol Immunopathol*. 2008;125(1–2):111-125.

44. Morck DW. Prophylactic efficacy of tilmicosin for bovine respiratory tract disease. *J Am Vet Med Assoc*. 1993;202(2):273.

45. Nickell JS, White BJ. Metaphylactic antimicrobial therapy for bovine respiratory disease in stocker and feedlot cattle. *Vet Clin North Am Food Anim Pract*. 2010;26(2):285-301.

46. Panciera RJ. Pathogenesis and pathology of bovine pneumonia. *Vet Clin North Am Food Anim Pract*. 2010;26(2):191.

47. Perrett T. A comparison of florfenicol and tulathromycin for the treatment of undifferentiated fever in feedlot calves. *Vet ther*. 2008;9(2):128.

48. Pleasants AB. Design and application of a cusum quality control chart suitable for monitoring effects on ultimate muscle pH. *N Z J Agric Res*. 1998;41(2):235.

49. Quimby WF. Application of feeding behaviour to predict morbidity of newly received calves in a commercial feedlot. *Can Vet J*. 2001;81(3):315.

50. Reinhardt CD. Relationship of various incoming cattle traits with feedlot performance and carcass traits. *J Anim Sci*. 2009;87(9):3030.

51. Reneau JK. Process control: Timely feedback for quaity milk production at the farm. *National Mastitis Council meeting Proceedings*. 2000.

52. Reneau JK. Using statistical process control methods to improve herd performance. *Am J Vet Res*. 2006;22(1):171.

53. Ribble CS, Meek AH, Shewen PE, Jim GK, Guichon PT. Effect of transportation on fatal fibrinous pneumonia and shrinkage in calves arriving at a large feedlot. *J Am Vet Med Assoc*. 1995;207(5):612-615.

54. Richeson JT. Effects of on-arrival versus delayed modified live virus vaccination on health, performance, and serum infectious bovine rhinotracheitis titers of newly received beef calves. *J Anim Sci*. 2008;86(4):999.

55. Roeber D, Umberger W. The value of preconditioning programs in beef production systems. *Selected paper presented at the 2002 Western Agricultural Economics Association Annual Meeting Long Beach, CA*. 2002.

56. Sanderson MW. Risk factors for initial respiratory disease in united states' feedlots based on producer-collected daily morbidity counts. *Can Vet J*. 2008;49(4):373.

57. Sard DM. Dealing with data: The practical use of numerical information--(14), monitoring changes. *Vet Rec*. 1979;105(14):323-328.

58. Schneider MJ, Tait RG, Busby WD, Reecy JM. An evaluation of bovine respiratory disease complex in feedlot cattle: Impact on performance and carcass traits using treatment records and lung lesion scores. *J Anim Sci*. 2009;87(5):1821-1827.

59. Schumann FJ. Prophylactic medication of feedlot calves with tilmicosin. *Vet Rec*. 1991;128(12):278.

60. Schumann FJ. Prophylactic tilmicosin medication of feedlot calves at arrival. *Can Vet J*. 1990;31(4):285.

61. Schunicht OC. Comparison of a multivalent viral vaccine program versus a univalent viral vaccine program on animal health, feedlot performance, and carcass characteristics of feedlot calves. *Canadian veterinary journal*. 2003;44(1):43.

62. Smith RA. North american cattle marketing and bovine respiratory disease (BRD). *Animal health research reviews*. 2009;10(02):105.

63. Snowder G. Genetics, environment and bovine respiratory disease. *Animal health research reviews*. 2009;10(02):117.

64. Snowder GD, Van Vleck LD, Cundiff LV, Bennett GL. Bovine respiratory disease in feedlot cattle: Environmental, genetic, and economic factors. *J Anim Sci*. 2006;84(8):1999-2008.

65. Stafford KJ. Dehorning and disbudding distress and its alleviation in calves. *The veterinary journal*. 2005;169(3):337.

66. Stanger KJ. The effect of transportation on the immune status of bos indicus steers. *J Anim Sci*. 2005;83(11):2632.

67. Step DL, Krehbiel CR, DePra HA, et al. Effects of commingling beef calves from different sources and weaning protocols during a forty-two-day receiving period on performance and bovine respiratory disease. *J Anim Sci*. 2008;86(11):3146-3158.

68. Taylor JD. The epidemiology of bovine respiratory disease: What is the evidence for predisposing factors? *Can Vet J*. 2010;51(10):1095.

69. Taylor JD. The epidemiology of bovine respiratory disease: What is the evidence for preventive measures? *Can Vet J*. 2010;51(12):1351.

70. Terrell SP, Thomson DU, Wileman, BW, et al. A survey to describe current feeder calf health and well-being program recommendations made by feedlot veterinary consultants in the United States and Canada. *The Bovine practitioner*, 2012 (45):2140-148.

71. Thompson PN, Stone A, Schultheiss WA. Use of treatment records and lung lesion scoring to estimate the effect of respiratory disease on growth during early and late finishing periods in south african feedlot cattle. *J Anim Sci*. 2006;84(2):488-498.

72. USDA. Health management and biosecurity in U.S. feedlots, 1999. in: USDA:APHIS:VS (ed.). *National Animal Health Monitoring Systems, Fort Collins, CO*. 2000.

73. Vogel GJ. Effects of tilmicosin on acute undifferentiated respiratory tract disease in newly arrived feedlot cattle. *J Am Vet Med Assoc*. 1998;212(12):1919.

74. Wellman NG, O'Connor AM. Meta-analysis of treatment of cattle with bovine respiratory disease with tulathromycin. *J Vet Pharmacol Ther*. 2007;30(3):234-241.

75. Wheeler DJ. *Understanding variation. the key to managing chaos.* Knoxville, TN: SPC Press; 1993.

76. White BJ, Larson RL. Preconditioned calves in the feedyard. In: Anderson DE, Ring DM, eds. *Food animal practice.* Saunders Elsevier; 2009:628-632.

77. White BJ. Bayesian estimation of the performance of using clinical observations and harvest lung lesions for diagnosing bovine respiratory disease in post-weaned beef calves. *J Vet Diagn Invest*. 2009;21(4):446.

78. Wildman BK, Perrett T, Abutarbush SM, et al. A comparison of 2 vaccination programs in feedlot calves at ultra-high risk of developing undifferentiated fever/bovine respiratory disease. *Can Vet J*. 2008;49(5):463-472.

79. Wittum TE. Relationships among treatment for respiratory tract disease, pulmonary lesions evident at slaughter, and rate of weight gain in feedlot cattle. *J Am Vet Med Assoc*. 1996;209(4):814.

80. Wrathall AE. Reproductive failure in the pig: Diagnosis and control. *Vet Rec*. 1977;100(12):230.

81. Zecchinon L, Fett T, Desmecht D. How mannheimia haemolytica defeats host defence through a kiss of death mechanism. *Vet Res*. 2005;36(2):133-156.

82. Zweiacher ER. Effects of method and time of castration of feeder calves. *J Anim Sci*. 1979;49(1):5.

Table 1-1 Clinical Score Scale for Bovine Respiratory Disease Complex

Score	Description
0	Normal: Nothing unusual in animal's attitude and no abnormal respiratory symptoms present.
1	Mild depression (somewhat slow coming to feed bunk, but did eat). Mild respiratory symptoms present; serous nasal or ocular discharge and/or cough.
2	Moderate depression (slight head/ears dropping, reluctant to move about, reluctant to come to the feed bunk). Moderate respiratory distress: Mucosus or mucopurulent nasal or ocular discharge and/or increase in respiratory rate or effort.
3	Severe depression (pronounced head/ear droop' very reluctant to move). Severe respiratory distress: marked increase in respiratory rate or effort including: open mouth breathing, abdominal breathing, or extended head)
4	Moribund

Chapter 2 - Comparative efficacy of gamithromycin and tulathromycin for the control of undifferentiated bovine respiratory disease complex in high risk calves under field conditions.

Siddartha Torres, MVZ; Dan U. Thomson, DVM, PhD; Nora M. Bello, DVM, PhD; Bruce Nosky, DVM; Chris D. Reinhardt, PhD

From the Department of Clinical Sciences (Torres, Thomson), College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506; the Department of Statistics (Bello), Kansas State University, Manhattan, KS 66506; Large Animal Veterinary Services (Nosky), Merial Limited, Duluth, GA 30096; and the Department of Animal Sciences and Industry (Reinhardt), College of Agriculture, Kansas State University, Manhattan, KS 66506.

Abstract

Objective – To evaluate the comparative efficacy of gamithromycin and tulathromycin for the control of undifferentiated bovine respiratory disease complex (BRDC) in high risk calves under field conditions.

Animals – 2,529 calves.

Procedures - The study was conducted in two feedlot operations (sites) located in Kansas and Nebraska. Within each site, calves at high risk of developing BRDC were randomly assigned to two treatment groups: (1) Gamithromycin (n = 1,263) at 6.0 mg/kg s.c. and (2) Tulathromycin (n = 1,266) at 2.5 mg/kg s.c. Health outcomes (percentage morbidity, mortality, case fatality, and re-treatment) and animal performance (average daily gain [ADG], dry mater intake [DMI], and feed-to-gain [F:G]) were evaluated to determine the comparative efficacy of the antimicrobials.

Results – Morbidity due to BRDC was higher ($P = 0.03$) among calves receiving gamithromycin (31.0 ±4.0%; mean estimate ± std err) compared with those receiving tulathromycin (22.9 ±3.9%); however, treatments were considered bioequivalent ($P < 0.05$) for BRDC mortality, case fatality rate and re-treatment rate within the limits of ±3.5%, ±10%, and ±16%, respectively. Final BW, ADG, DMI and F:G, were similar ($P<0.05$) between the groups of calves receiving gamithromycin and tulathromycin within the limits of ±37kg, ±0.1kg, ±0.3kg, and ±0.7, respectively.

Conclusions and clinical relevance – BRDC morbidity rate was lower ($P=0.03$) in calves treated with tulathromycin compared with those treated with gamithromycin; nonetheless, treatments were considered bioequivalent for mortality rate, case fatality rate, re-treatment rate, and animal performance.

Abbreviations

ADG	Average daily gain
BW	Body Weight
BRDC	Bovine respiratory disease complex
CI	Confidence Interval
DMI	Dry matter intake
F:G	Feed-to-gain ratio

Introduction

Bovine Respiratory Disease Complex (BRDC) is the most common and expensive disease in feedlot cattle in the United States[1,2,3]. It accounts for approximately 50% of morbidity and over 75% of mortality in feedyards[4]. It has been estimated that BRDC causes annual economic losses of US$1 billion due to mortality, reduced performance, and treatment costs[2,5]. The BRDC is a multifactorial syndrome caused by a combination of environmental factors, management practices, animal susceptibility, and viral and bacterial pathogens[5,6]. Preventive and control measures include management practices that enhance immune response, optimize nutrition, reduce animal stress, and minimize pathogen challenge[5,6]. Methaphylaxis is one of the most effective control strategies for reduction of the negative effect of BRDC on health and performance[6]. Metaphylaxis normally consists of mass administration of an approved antimicrobial product in a cattle population at high risk of developing BRDC[6]. Tulathromycin is a relatively new subclass of antimicrobial macrolide (triamilide) labeled for metaphylactic use in cattle to control BRDC[3,7,8]. Administration of tulathromycin at feedyard arrival to control BRDC in high risk calves has been shown to be effective to reduce morbidity and increase ADG when compared with saline control[6]. Likewise, gamithromycin is a new antimicrobial azalide similar to macrolides that is approved for treatment and control of BRDC[3, 9, 10]. Administration of

gamithromycin in a metaphylactic manner also reduces morbidity due to BRDC when compared with saline controls[10, 11]. Both macrolides and azalides inhibit bacterial protein synthesis by binding 50s prokaryotic ribosomes[3,9]. Macrolides are normally considered bacteriostatic; however, gamithromycin has been shown to have bactericidal activity against *Mannheimia haemolytica, Pasteurella multocida, and Histophilus somni*[3]. In field trials, tulathromycin has shown superior clinical efficacy vs. other macrolides, such as tilmicosin for the treatment of BRDC[7, 12.] However, to our knowledge, no studies have been conducted to evaluate health outcomes and performance comparing gamythromycin vs. tulathromycin for the control of BRDC. The objective of this study was to evaluate the comparative efficacy of gamithromycin and tulathromycin for the control of BRDC in high risk calves under field conditions.

Materials and methods

Animals

A total of 2,529 crossbred calves purchased from auction markets located in Mississippi and northeast Oklahoma were enrolled in the study between October 2 and December 30, 2010. All procedures were approved by the Kansas State University Institutional Animal Care and Use Committee. The study was conducted at two commercial feedlot operations that were willing to participate, and formal consent to conduct the research in the feedlot facilities was provided. Feedyards were located in Kansas (n = 1,002; mean body weight (BW), ±SD, 227 ±18kg) and Nebraska (n = 1,527; 235 ±41kg). Animals were considered to be at high risk of developing undifferentiated BRDC. Risk factors for developing BRDC in this cattle population included: light body weight (230 ±34 kg), stress and length of transportation (ranged from 10 to 16 hours), and level of commingling at the auction market, during the transportation process, and upon arrival.

Processing

Upon arrival, animals were placed into pens by date of arrival at the feedyard facility and processed within 24 hours of arrival. Processing included giving an ear tag for individual identification, and recording of BW and rectal temperature. Intact bulls were castrated surgically. Calves were treated for internal and external parasites with fenbendazole[a] and ivermectin[b], and were vaccinated against clostridial pathogens[c]. The location in Nebraska administered a viral respiratory vaccination against bovine herpesvirus-1, parainfluenza-3 and bovine respiratory syncytial virus[d]. The site in Kansas administered a multivalent vaccine containing viruses of bovine herpersvirus-1, parainfluenza-3, bovine respiratory syncytial virus, and bovine viral diarrhea (type I and type II)[e] and an anabolic implant containing zeranol[f].

Enrollment and treatment

Animals were enrolled in the study only if they demonstrated no clinical signs of disease or injury as determined by the trial investigator at the time of post-arrival processing. Exclusion criteria included injury, debilitation, any clinical signs of systemic diseases, or any known previous administration of antimicrobials prior to arrival.

Animals that met the inclusion criteria were grouped in pairs based on order of appearance through the handling facility. Based on a randomization schedule previously developed for each site, animals within each pair were randomly allocated to receive either (1) Gamithromycin[g] (6.0 mg/kg, 2mL/50 kg, SQ, single-dose), or (2) Tulathromycin[h] (2.5 mg/kg, 1.25mL/50 kg, SQ, single-dose). Animal BW obtained at processing was used for dose determination. Treatments were administered subcutaneously in the same side of the neck in front of the shoulder, with a maximum volume of 10 mL per injection site. Treatments were administered by the investigator

at the time of processing. Incidence of castrated bulls did not significantly differ ($P = 0.33$) between the calves receiving tulathromycin (3.6%) and those receiving gamithromycin (3.3%).

From day 0 to day 120 post-enrollment, general health evaluations were conducted in the pens through routine feedlot health procedures performed by qualified animal health care personnel who were not present during the treatment administration (blinded). Morbid animals were examined and diagnosed as having BRDC or other (gastrointestinal, musculoskeletal, etc.) infirmities. Animals which were categorized as morbid due to BRDC were defined as animals showing clinical scores of 1, 2 or 3 according to the clinical score scale (Appendix A) and having rectal temperature equal or greater than 40 ºC. Sick animals received concurrent medications according to the standard feedyard procedures and returned to their study pens. In both sites, animals diagnosed with BRDC received a single dose of florfenicol[i] (40mg/kg BW, 6mL/45 kg, SQ) as a first treatment, and a single dose of enrofloxacin[j] (7.5-12.5mg/kg BW, 3.75-6.25mL/50kg, SQ) as a second treatment (re-treatment). Animals that received a third treatment during the 120 day period received Ceftiofur[k] (6.6 mg/kg BW, 1.5mL/45 kg, SQ base-of-the-ear) in Kansas and Oxytetracycline[l] (20mg/kg BW, 1mL/10kg, IM) in Nebraska. Moribund animals were humanely euthanized according to the guidelines of the Animal Welfare Committee of the American Association of the Bovine Practitioners[13]. Necropsy was performed by qualified personnel for animals that either died or were euthanized. Mortality attributed to BRDC was confirmed by presence of bronchopneumonia. Mortalities not associated with BRDC were not included in the analysis of BRDC mortality or case fatality rate.

For the analysis of animal performance, dry matter intake (DMI) and days on feed (DOF) were obtained during the entire feeding period. Individual animal BW was obtained at time of processing (arrival), and final BW was calculated based on the pen weight at time of harvest.

For the calculations on a deads-in basis, pen ADG was calculated by subtracting initial BW from final BW and divided by days on feed (DOF), and feed to gain (F:G) was calculated by dividing DMI by ADG. For the analysis of performance on a deads-out basis, animals that died due to BRDC during the first 120 DOF were excluded from the calculations of final BW, ADG and F:G.

Housing

Animals were housed in open air group pens. Average number of animals per pen was 50 in Kansas and 110 in Nebraska. Animals were fed with a ration formulated to meet or exceed the requirements of the National Research Council for maintenance and expected growth[14]. All animals had *ad libitum* access to water.

Statistical Analysis

Continuous responses, namely initial BW, rectal temperature at enrollment, final BW, ADG, DMI, and F:G were modeled using general linear mixed models. For all responses, the linear predictor included the fixed effect of treatment at arrival (e.i. gamithromycin or tulathromycin). Random effect specification was fine-tuned to each response to accommodate the experimental design structure while including only random effects with non-zero estimates of variance components. In all cases, the random effect of the combination of treatment and site was assessed but dropped from the models based on a variance component converged to zero.

For initial BW and for animal performance outcomes (i.e. final BW, ADG, DMI, and F:G), the random effect of arrival date was modeled as a blocking factor. For rectal temperature, the random effects of arrival date and its crossproduct with treatment was specified. Initial weight and total days on feed were used as covariates in the statistical models for rectal temperature and animal performance outcomes, respectively.

Generalized linear mixed models were fitted to categorical binary responses using a logit link function and assuming a Bernoulli distribution. For mortality, morbidity, and re-treatment, the linear predictor in the model included the fixed effects of treatment and rectal temperature status at arrival (Normal: < 40 ºC, or Fever: ≥ 40 ºC) and initial weight at arrival as a covariate; in turn, the random effect for the combination of arrival date and treatment was used to recognize the experimental unit for treatment. For modeling re-treatment, the covariate initial weight at arrival was removed due to a non-significant ($P > 0.05$) contribution to the model. For case fatality rate, the linear predictor in the model included treatment as a fixed effect and the combination of arrival date × treatment as a random effect to recognize the appropriate experimental unit for treatment.

Parameter estimates from the statistical models described above were used to conduct both classical and bioequivalence hypothesis testing. On a classical testing framework, treatments were considered to yield significantly different outcomes based on P-values < 0.05 on the corresponding ANOVA Type III F-test statistics; marginal evidence for treatment differences were declared at $P < 0.10$. In turn, 90% confidence intervals (CL) on treatment differences were constructed for each response to assess evidence for equivalent treatment performance[16]. If a 90% CI on the treatment difference fell within appropriate upper and lower equivalence limits set for a given response, then average bioequivalence ($P < 0.05$) between treatments for that response can be concluded[16].

All statistical models were fitted using a statistical analysis software[m]. Kenward-Roger's approximation was used to estimate degrees of freedom and to make the corresponding adjustments in estimation of standard errors. Pairwise comparisons were conducted using either

Tukey-Kramer or Bonferroni's method to adjust for multiple comparisons and prevent inflation of Type I error.

Results

No clinical adverse reactions were observed after treatment administration, and no animals were removed from the study before day 120. As expected, no evidence of differences between treatments was found for initial BW ($P \geq 0.97$) or rectal temperature ($P \geq 0.72$) at enrollment (table 2.1). Likewise, the proportion of animals that had fever at arrival did not differ ($P = 0.87$) between treatment groups (19.3% for both: gamithromycin and tulathromycin); thus indicating no evidence for concerns with the randomization approach.

The estimated overall morbidity rate (BRDC incidence) during the first 120 DOF was 31.0±4.0% (mean estimate ± std err). Meanwhile, differences between treatments were apparent ($P = 0.03$); animals that received gamithromycin had higher morbidity rate (31.0±4%) compared with those that received tulathromycin (22.9± 4%; Table 2.1). Regardless treatment, and given an average initial BW of 230 kg, the estimated odds of being treated (first treatment) for BRDC during the first 120 DOF were 1.78 times greater (95% CI = [1.3, 2.45]) for animals that had fever at arrival compared with those that had normal rectal temperature at arrival. For the covariate initial BW at arrival, the estimated odds ratio for being treated for BRDC (first treatment during the first 120 DOF) for a 50kg decrease in initial BW relative to the average arrival weight of 230kg was 1.41 (95% CI = [1.22, 1.63]). This odds ratio estimate indicates that there is a greater risk of being treated for BRDC during the first 120 DOF in lighter animals at arrival.

During the first 120 DOF, the estimated overall mortality rate averaged 3.84±1.0% (mean estimate ± std err). Estimated mortality rate for tulathromycin was 3.5±1.3% and for gamithromycin was 4.2±1.7%. Bioequivalence between treatments was established for mortality

rate due to BRDC within the limits of ±3.5%. The estimated overall case fatality rate averaged 15.9±3.1%. Case fatality rate averaged 19.5±3.9% for animals that received tulathromycin, and averaged 14.8±3.8% for animals that received gamithromycin. Then, treatment bioequivalence ($P < 0.05$) was established between gamithromycin and tulathromycin for BRDC case fatality rate within the limits of ±16%. Overall re-treatment rate (second treatment) averaged 40.1±2.6% across treatment groups. Re-treatment rate for gamithromycin was 41.5±4.18%, and re-treatment rate for tulathromycin was 39.6±3.4%. Treatments bioequivalence ($P < 0.05$) was established between gamithromycin and tulathromycin for BRDC re-treatment rate within the limits of ±10% (Table 2.2).

Regardless of treatment and given an average arrival weight of 230kg, the odds of mortality due to BRDC during the first 120 DOF were estimated to be approximately 1.5 times greater (95% CI = [1.045, 2.130]) for animal that had fever at arrival compared with those that had normal temperature at arrival, yielding an odds ratio of 1.49. After adjusting for temperature at arrival and regardless of treatment, the estimated odds ratio for mortality due to BRDC during the first 120 days for a 50kg decrease in initial BW relative to the average arrival weight of 230kg was 1.29 (95% CI = [1.06, 1.43]). The odds ratio estimate indicates that there is a greater risk of mortality due to BRDC during the first 120 DOF in animals that are lighter at arrival.

For the analysis of animal performance on a deads-in basis, final BW at harvest was bioequivalent ($P < 0.05$) between gamithromycin and tulathromycin within the limits of ±37kg. Also, bioequivalence between treatments ($P < 0.05$) was established for ADG within the limits of ±0.01kg. For F:G, bioequivalence ($P<0.05$) was established between animals that received tulathromycin or those that received gamithromycin within the limits of ±0.7 (table 2.3).

For animal performance on a deads-out basis, final BW was considered bioequivalent ($P<0.05$) between animals that received tulathromycin and those that received gamithromycin within the limits of ±9.5kg. Also, bioequivalence ($P<0.05$) was established for ADG between tulathromycin and gamithromycin within the limits of ±0.1kg. Finally, bioequivalence ($P<0.05$) was established for F:G between animals that received tulathromycin and those that receive gamithromycin within the limits of ±0.6 (table 2.4).

Discussion

Gamithromycin and tulathromycin have shown to be efficacious antimicrobials for the control of bovine respiratory disease when they are used in high risk calves according to the label dose[7, 12]. To our knowledge, this is the first experiment that compares gamithromycin vs. tulathromycin to control BRDC in high risk feedlot cattle.

Previous studies conducted to evaluate antimicrobials for the control of BRDC used a period of 10 days[10], 14 days[7,11], or 28 days[16] after enrollment to evaluate health outcomes; however, in the present study, we were interested in evaluating health outcomes over a longer period of time; therefore, a total length of 120 DOF was used to evaluate health outcomes. It is important to mention that 95% of the total cumulative mortality, for both gamithromycin and tulathromycin, occurred during the first 42 DOF (table 2.5); and 95% of the total cumulative morbidity occurred during the first 70 DOF (table 2.6). An evaluation over a period of 70 DOF (e.g. 10 weeks) will provide enough information about health performance in in high risk calves after metaphylactic administration of injectable antimicrobials.

In the present study, rectal temperature status at processing was monitored to control for animals experiencing fever at arrival and evaluate the effect of the treatment in animals with fever and those with normal temperature. There was no evidence of differences in the proportion of

animals with fever at arrival between treatments groups (P=0. 87); the proportion of animals with fever in both groups averaged 19.3% ; also, the interaction of treatment × rectal temperature status was not significant ($P \geq 0.69$) in the statistical models for morbidity, mortality, case fatality rate, and re-treatment rate. Therefore, the effect of treatment was the same in all levels of rectal temperature status: fever and normal temperature.

In the present study, the statistical model for mortality and morbidity included the covariate of initial BW, so we were able to account for the effect of body weight at arrival. The interaction of IBW × treatment was also evaluated; however, it was not significant ($P \geq 0.69$) in fitting the models for mortality or morbidity. Interestingly, this finding showed that the main effect of metaphylactic treatment did not interact with initial BW. It is important to mention that initial BW, used as a covariate in the models for mortality and morbidity, contributed significantly ($P < 0.01$) to the fit of the models; therefore, the analysis of odds ratios for initial BW showed that lighter animals were at greater risk for treatment or death due to BRDC. This finding agrees with the data reported in previous studies that have showed that body weight is associated with the development of BRDC[15].

Even though classical hypothesis testing was conducted for all outcomes, the bioequivalence hypothesis test was used for those outcomes where no evidence of differences was found ($P > 0.05$). With the classical hypothesis testing, a null hypothesis of no treatment mean differences can either be rejected or failed to be rejected, but it cannot be accepted[19]. That is, one cannot conclude on "no treatment differences" using the classical hypothesis testing approach because failure to reject the classical null hypothesis can be attributable to either no actual differences between group means[19], or simply a lack of statistical power in the experimental design. Thus, failure to reject a null hypothesis provides only indecisive results on the comparison of treatment

means. In order to assess the anticipated similarity of treatment performance (as opposed to differential treatment effects), we conducted bioequivalence hypothesis testing[19]. Using this approach, veterinarians and animal health personnel can expect that both antimicrobials will yield a similar outcome ($P<0.05$) within a difference established with the 95% confidence limits. Consequently, we established bioequivalence ($P < 0.05$) between antimicrobials within the limits for mortality, case fatality rate and performance (final BW, ADG, DMI, and F:G).

For the analysis of animal performance, both antimicrobials were considered bioequivalent ($P < 0.05$) for final BW, ADG, DMI and F:G (deads-in and deads-out basis). In a previous study comparing two macrolides, namely tulathromycin and tilmicosin[n], no evidence of differences ($P > 0.05$) were found in ADG between those antimicrobials given at arrival for control of BRDC in high risk calves[16]. However, no bioequivalence tests were conducted in that study.

It should be noted that mortality rates in the present study were much higher (overall mortality rate averaged 3.8±1.0%, mean estimate, ± SEM) compared with those reported in previous studies (overall mortality rate = 0%)[10,11]. This suggests that calves enrolled in the current study may have been at higher risk to develop BRDC at arrival compared with calves in previous studies. Risk factors for BRDC in the present study included: stress due to transportation which ranged from 10 to 16 hours, and light body weight at arrival (230 ±18 kg). In addition, calves were acquired from auction markets, and were commingled with unfamiliar animals at the auction market, during transportation, and at arrival to the feedlot. Furthermore, enrollment occurred during the fall and early winter; this time of the year also has been proposed a predisposing factor for developing BRDC[20].

Since the study did not include a negative control group, we were unable to determine the efficacy of metaphylaxis compared with placebo in terms of mortality, morbidity, re-treatment rate, and case fatality rate.

In the present study, morbidity rates were higher ($P \leq 0.03$) for animals receiving gamithromycin compared with those receiving tulathromycin, 31.0% and 22.9% respectively. This health outcome was the only one that was different between treatments ($P < 0.05$); nonetheless, it could be argued that evaluation of morbid animals is based on clinical observations of BRDC symptoms that combine subjective and objective evaluations. According to White et al., sensitivity and specificity of clinical diagnosis of BRDC under field situations is very low (61.8 and 62.8% respectively)[21] due to a high degree of diagnostic error. Further investigation with high sensitivity and specificity diagnosis technologies will allow us to perform more accurate evaluations of morbidity rates in field trials.

Conclusion

Under commercial feedlot conditions, the comparative efficacy of the administration of gamithromycin or tulathromycin to control BRDC was similar in mortality rate, case fatality rate, re-treatment rate, and animal performance (DMI, F:G, ADG), so both antimicrobials were considered bioequivalent. Nevertheless, animals treated with gamithromycin had greater morbidity rates (BRDC incidence) compared with tulathromycin.

Footnotes

[a] SafeGuard, Intervet/Schering-Plough Animal Health, Millsboro, DE.

[b] Ivomec Plus, Merial LTD, Duluth, GA.

[c] Vision 7/Somnus, Intervet/Schering-Plough Animal Health, Millsboro, DE

[d] Bovishield Gold 5, Pfizer Animal Health, New York, NY.

[e] Inforce 3, Pfizer Animal Health, New York, NY

[f] Ralgro, Intervet/Schering-Plough Animal Health, Millsboro, DE.

[g] Zactran, Merial LTD, Duluth, GA.

[h] Draxxin, Pfizer Animal Health, New York, NY.

[i] Nuflor, Intervet/Schering-Plough Animal Health, Millsboro, DE

[j] Baytril, Bayer Animal Health, Shawnee Mission, KS

[k] Excede, Pfizer Animal Health, New York, NY.

[l] Bio-Mycin, Boehringer Ingelheim Vetmedica, St. Joseph, MO.

[m] PROC GLIMMIX, SAS, version 9.3, SAS Institute, Cary, NC

[n] Micotil, Eli Lilly and Company, Indianapolis, IN.

References

1. Snowder GD, Van Vleck LD, Cundiff LV, et al. Bovine respiratory disease in feedlot cattle: Environmental, genetic, and economic factors. J Anim Sci 2006;84:1999-2008.

2. Griffin D. Economic impact associated with respiratory disease in beef cattle. Vet Clin North Am Food Anim Pract 1997;13:367.

3. Giguere S, Huang R, Malinski TJ, et al. Disposition of gamithromycin in plasma, pulmonary epithelial lining fluid, bronchoalveolar cells, and lung tissue in cattle Am J Vet Res 2011;72:326-330.

4. Babcock AH, White BJ, Dritz SS, et al. Feedlot health and performance effects associated with the timing of respiratory disease treatment. J Anim Sci 2009;87:314-327.

5. McVey DS. BRD research needs in the next 10–20 years. Animal Health Res Rev 2009;10:165.

6. Nickell JS, White BJ. Metaphylactic Antimicrobial Therapy for Bovine Respiratory Disease in Stocker and Feedlot Cattle. Vet Clin North Am Food Anim Pract 2010;26:285-301.

7. Kilgore WR. Clinical Effectiveness of Tulathromycin, a Novel Triamalide Antimicrobial, for the Control of Respiratory Disease in Cattle at High Risk for Developing Bovine Respiratory Disease. Vet ther 2005;6:136.

8. Duff GC, Galyean ML. BOARD-INVITED REVIEW: Recent advances in management of highly stressed, newly received feedlot cattle. J Anim Sci 2007;85:823-840.

9. Forbes AB, Ramage C, Sales J, et al. Determination of the Duration of Antibacterial Efficacy following Administration of Gamithromycin Using a Bovine Mannheimia haemolytica Challenge Model. Antimicrobial Agents Chemother February 2011;55:831-835.

10. Lechtenberg K, Daniels CS, Royer GC, et al. Field efficacy study of gamithromycin for the control of bovine respiratory disease in cattle at high risk of developing the disease. J Appl Res Vet 2011;9:184-192.

11. Baggott D, Casartelli A, Fraisse F, et al. Demonstration of the metaphylactic use of gamithromycin against bacterial pathogens associated with bovine respiratory disease in a multicentre farm trial. Vet Rec 2011;168:241-241.

12. Skogerboe TL. Comparative efficacy of tulathromycin versus florfenicol and tilmicosin against undifferentiated bovine respiratory disease in feedlot cattle. Vet ther 2005;6:180.

13. Practical Euthanasia of Cattle: Considerations for the Producer, Livestock Market Operator, Livestock Transporter, and Veterinarian. Brochure prepared by the Animal Welfare Committee of the American Association of Bovine Practitioners. 1999.

14. National Research Council. Tables of nutrient requirements. In: Nutrient requirements of beef cattle: 7th ed. Washington, DC: National Academy Press, 1996;102-112

15 Reinhardt CD. Relationship of various incoming cattle traits with feedlot performance and carcass traits. J Anim Sci. 2009;87(9):3030.

16. Rooney KA. Efficacy of tulathromycin compared with tilmicosin and florfenicol for the control of respiratory disease in cattle at high risk of developing bovine respiratory disease. Vet ther 2005;6:154.

17. Galyean ML. Effects of arrival medication with tilmicosin phosphate on health and performance of newly received beef cattle. J Anim Sci. 1995;73(5):1219.

18. Montgomery SP. Plasma metabolites of receiving heifers and the relationship between apparent bovine respiratory disease, body weight gain, and carcass characteristics. J Anim Sci. 2009;87(1):328.

19. Tempelman RJ. Experimental design and statistical methods for classical and bioequivalence hypothesis testing with an application to dairy nutrition studies. J Anim Sci 2004;82:E162.

20. Taylor JD. The epidemiology of bovine respiratory disease: What is the evidence for predisposing factors? Can Vet J. 2010;51(10):1095.

21. White BJ. Bayesian estimation of the performance of using clinical observations and harvest lung lesions for diagnosing bovine respiratory disease in post-weaned beef calves. J Vet Diagn Invest 2009;21:446.

Tables

Table 2-1 Least square means estimates (and estimated standard errors of the means) for initial BW and rectal temperature at arrival, and morbidity rate due to BRDC during 120 days on feed for high risk calves receiving tulathromycin or gamithromycin at arrival

ITEM	Tulathromycin	SEM	Gamithromycin	SEM	*P*-value
Rectal temperature (°C)	39.3	0.1	39.3	0.1	0.72
Initial BW[1] (kg)	228.0	5.6	227.9	5.6	0.97
BRDC Morbidity[2] (%)	22.9	3.9	31.0	3.8	0.03

[1] Animal BW at time of processing (arrival)
[2] BRDC morbidity incidence (first treatment)

Table 2-2 Least square means estimates (and estimated standard errors of the means) and bioequivalence limits for mortality, re-treatment, and case fatality rate due to BRDC during 120 days on feed in calves receiving tulathromycin or gamithromycin at arrival

ITEM	Tulathromycin	SEM	Gamithromycin	SEM	Bioequivalence Limits[3]
BRDC Mortality (%)	3.5	1.3	4.2	1.7	3.5
Re-treatment[4] (%)	39.5	3.4	41.5	4.2	10.0
Case fatality rate (%)	19.5	3.9	14.8	3.8	16.0

[3] Average bioequivalence between treatments ($P<0.05$) established within the ±limits
[4] BRDC re-treatment rate (second treatment)

Table 2-3 Least square means estimates (and estimated standard errors of the means) and bioequivalence limits for final BW, ADG, DMI, and F:G (from the entire feeding period) for calves receiving tulathromycin or gamithromycin at arrival. Analysis on a deads-in basis

ITEM	Tulathromycin	SEM	Gamithromycin	SEM	Bioequivalence Limits[1]
Final BW, kg	495.0	11.7	486.0	11.5	37.0
ADG, kg/day	1.1	0.03	1.0	0.03	0.1
DMI, kg/day	7.4	0.08	7.3	0.08	0.3
F:G ratio	6.6	0.18	6.8	0.18	0.7

[1] Average bioequivalence between treatments ($P<0.05$) established within the ±limits

Table 2-4 Least square means estimates (and estimated standard errors of the means) and bioequivalence limits for final BW, ADG, DMI, and F:G (from the entire feeding period) for calves receiving tulathromycin or gamithromycin at arrival, analysis on a deads-out basis

ITEM	Tulathromycin	SEM	Gamithromycin	SEM	Bioequivalence Limits[1]
Final BW, kg	530.1	6.3	529.5	6.3	9.5
ADG, kg/day	1.2	0.01	1.2	0.01	0.1
F:G ratio	6.5	0.14	6.6	0.27	0.6

[1] Average bioequivalence between treatments ($P<0.05$) established within the ± limits

Table 2-5 Number of animals that died due to BRDC (Case fatality rate) within the first 120 days post-enrollment that were treated with tulathromycin or gamithromycin, across all sites

Days on Feed	Gamithromycin	Tulathromycin	Total	Cumulative %
7	15	3	18	10
14	28	29	57	43
21	12	8	20	55
28	20	14	34	74
35	15	14	29	91
42	2	6	8	95
49	1	1	2	97
56	0	1	1	97
63	1	1	2	98
77	1	1	2	99
98	0	1	1	100
120	0	0	0	100
TOTAL	95	79	174	100

Cumulative BRDC mortality rate (%) from total (gamithromycin and tulathromycin)

Table 2-6 Number of animals that were morbid (BRDC incidence) within the first 120 days post-enrollment, across all sites.

Days on Feed	Gamithromycin	Tulathromycin	Total	Cumulative %
7	68	39	107	16
14	139	99	238	51
21	62	43	105	67
28	39	37	76	78
35	24	25	49	85
42	15	15	30	89
49	8	5	13	91
56	4	5	9	93
63	2	6	8	94
70	3	1	4	95
77	1	2	3	95
84	4	3	7	96
91	0	4	4	97
98	2	3	5	97
105	2	2	4	98
112	4	3	7	99
120	1	6	7	100
TOTAL	378	298	676	100

Cumulative BRDC morbidity rate (%) from total (gamithromycin and tulathromycin)

Chapter 3 - Comparative efficacy of gamithromycin and tulathromycin for the treatment of undifferentiated bovine respiratory disease complex in high risk calves under field conditions

Siddartha Torres, MVZ; Dan U. Thomson, DVM, PhD; Nora M. Bello, DVM, PhD; Bruce Nosky, DVM; Chris D. Reinhardt, PhD

From the Department of Clinical Sciences (Torres, Thomson), College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506; the Department of Statistics (Bello), Kansas State University, Manhattan, KS 66506; Large Animal Veterinary Services (Nosky), Merial Limited, Duluth, GA 30096; and the Department of Animal Sciences and Industry (Reinhardt), College of Agriculture, Kansas State University, Manhattan, KS 66506.

Abstract

Objective – To evaluate the clinical efficacy of gamithromycin and tulathromycin for the treatment of undifferentiated bovine respiratory disease complex (BRDC) in feedlot calves under field conditions.

Animals – 1,049 calves allocated in six feedlot operations (sites).

Procedures –Newly arrived feedlot calves diagnosed with BRDC were randomly assigned to two treatment groups: (1) Gamithromycin (n = 523) and (2) Tulathromycin (n = 526). Fatality rate, re-treatment rate, average daily gain (ADG), and body weight during 120 days post-enrolment were evaluated to determine the comparative efficacy of the antimicrobials. In addition, two sites evaluated clinical scores during 10 days after treatment to determine comparative recovery rates.

Results – During the 120 days post-enrollment period, re-treatment rate was higher among animals treated with gamithromycin (estimated mean±SEM; 17.7± 7%) compared with those treated with tulathromycin (9.0±4%). Treatments were bioequivalent ($P < 0.05$) for case fatality rate, and performance (final BW and ADG). Clinical scores during 10 days post-treatment were not significantly different ($P = 0.97$) between treatments.

Conclusions and clinical relevance – In the present study, gamithromycin and tulathromycin yield similar BRDC case fatality rate, ADG and final BW during the first 120 days post-treatment. Nevertheless, tulathromycin had lower re-treatment rates compared with gamithromycin.

Abbreviations

ADG Average daily gain

BW Body Weight

BRDC Bovine respiratory disease complex

CI Confidence interval

SD Standard Deviation

SEM Standard Error of the Mean

Introduction

Bovine Respiratory Disease Complex is the most costly and common disease in feedlot cattle in North America[1-3]. Approximately 50% of total feedlot morbidity and 75% of death loss is considered to be due to BRDC[2]. Annual economic losses are estimated at US$1 billion due to mortality, treatment costs, and reduction in performance, and carcass value[4 5, 6]. Bovine respiratory disease complex is a multifactorial syndrome caused by environmental factors, management practices, animal susceptibility, and viral and bacterial pathogens[6]. Single dose injectable antimicrobials have shown efficacy to treat animals diagnosed with BRDC[7-12]. Among injectable antimicrobials, tulathromycin is a relatively new macrolide that has shown superior clinical efficacy vs. other single dose macrolides, such as tilmicosin for the treatment of the BRDC[7, 11, 12]. Gamithromycin is a new Azalide antimicrobial similar to macrolides that is labeled for the treatment of BRDC[10, 13]. Both antimicrobials, tulathomycin and gamithromycin, inhibit bacterial protein synthesis by binding 50s prokaryotic ribosomes[13]. Macrolides are normally considered bacteriostatic; however, Gamithromycin has shown to have bactericidal activity against *M. haemolytica*, *P. multocida,* and *H. somni* [13, 14]. To our knowledge, no

comparative studies have been conducted to evaluate the comparative clinical efficacy of these antimicrobials for the treatment of BRDC. The objective of this field study was to evaluate the comparative efficacy of gamithromycin and tulathromycin for the treatment of BRDC in beef calves under commercial feedlot conditions.

Materials and Methods

Animals

A total of 1,049 crossbred calves acquired from auction markets across the United States were enrolled in the study between October and Dec of 2010.

All procedures were approved by the Kansas State University Institutional Animal Care and use Committee. This multi-site field study was conducted in six different commercial feedlot facilities (sites) that were willing to participate, and owners provided a formal consent to conduct the research in the feedlot facilities. Feedlots were located in Colorado (n=100; mean body weight (BW) ± Standard Deviation (SD); 220 ± 22 kg), Idaho (n = 200; 244 ± 25 kg), Kansas (n = 216; 227 ± 21 kg), Nebraska (n = 196, 244 ± 28 kg), Oklahoma (n = 112; 236 ± 21 kg), and Texas (n = 225; 244 ± 18 kg). Enrollment occurred between December 10th and December 12th in Colorado, November 6th and November 17th in Idaho, October 25th and November 1st in Kansas, December 6th and December 30th in Oklahoma, and November 7th and November 18th in Texas.

Processing

Upon arrival, animals were placed into pens by date of arrival at the feedyard and processed within 24 hours of arrival. Processing included giving an ear tag for individual identification, recording of BW, and intact bulls were castrated surgically. Calves were dewormed with ivermectin[a] or doramectin[b] (Idaho) and vaccinated against clostridial pathogens in Kansas[c],

Idaho[d], Oklahoma[e], and Texas[f]. A multivalent vaccine containing antigens against bovine herpersvirus-1, parainfluenza-3, bovine respiratory syncytial virus, and bovine viral diarrhea type I and type II was administered in Kansas[g], Nebraska[h], Colorado[i], Idaho[i], and Oklahoma[j]. In Texas, viral vaccination included antigens against bovine herpesvirus-1 and bovine viral diarrhea type I and type II[k]. In addition, an anabolic implant containing trenbolone acetate and estradiol was administered in Kansas[l], Idaho[m], and Texas[n] at the time of processing. No antimicrobials were administered at arrival.

Enrollment and treatment

After processing, animals were placed in their home pens and observed daily by qualified animal health care personnel to determine health status. Animals enrolled in the study included calves showing respiratory clinical scores of 1 or 2 and having rectal temperature ≥ 40ºC, or animals showing clinical scores of 3 regardless rectal temperatures (Appendix A). Animals that were injured, debilitated, or suffering from systemic diseases (gastrointestinal, musculoskeletal, etc.) other than BRDC were not included in the study. Body weight was obtained at the time of enrollment for dose determination and measurements of performance.

Animals that met the inclusion criteria were grouped in pairs based on order of appearance through the handling facility. Within each pair group, animals were assigned to treatment by a previously determined randomization schedule unique for each site, receiving either (1) Gamithromycin[o] (6.0 mg/kg, 2mL/50 kg, S.C., single-dose), or (2) Tulathromycin[p] (2.5 mg/kg, 1.25 mL/50 kg, S.C., single-dose). Treatments were administered subcutaneously in the same side of the neck in front of the shoulder, with a maximum volume of 10 mL per injection site. Treatments were administered by the investigator. No evidence of differences in castrated bulls

incidence across treatments ($P = 0.61$). All animals were observed for adverse experiences after treatment.

Enrolled animals in Colorado and Oklahoma were housed in a single hospital pen (both treatments combined within each site) and were observed daily (during 10 days port-treatment) by trained animal health care professionals who were blinded to treatment. Individual animal observations, based on clinical score scale (Appendix A), were recorded for each calf for the day of treatment and for 10 days post-treatment for further analysis. From day 0 through day 120 post-enrollment, general health evaluations were conducted within the home pens through routine feedlot health procedures performed by qualified animal health care personnel who were not present during the treatment administration (blinded). Morbid animals were examined and diagnosed as having BRDC or other disorders (gastrointestinal, musculoskeletal, etc.), and received concurrent medications common to both experimental treatment groups within each site according to the standard feedyard procedures and returned to their study pens. Animal health records were kept in order to analyze data pertaining to the numbers of animals that were treated for BRDC or died due to BRDC within the first 120 days post-enrollment. Necropsy was performed by qualified personnel for animals that either died or were euthanized. If necessary, humane euthanasia was performed according to the guidelines of the Animal Welfare Committee of the American Association of the Bovine Practitioners[15]. Mortalities not associated with BRDC were not included in the analysis of BRDC fatality rates.

Housing

Animals were housed in open air group pens. Animals were fed with a ration typical of the feedlot region and formulated to meet or exceed the requirements of the National Research Council[16] for maintenance and expected growth. All animals had *ad libitum* access to water.

Individual BW was obtained at time of enrollment and at day 120 (Colorado, Idaho, Nebraska and Oklahoma), day 170 (Texas) and day 180 (Kansas) to obtain ADG for each animal. Nevertheless, health was monitored continuously through day 120 at all sites. Average daily gain was calculated by subtracting initial BW from final BW and divided by DOF. Case fatality rate represents the number of calves that died due to BRDC during the first 120 DOF divided by number of calves enrolled in each treatment group; mortalities attributed to BRDC was confirmed by presence of bronchopneumonia at necropsy. Re-treatment rate represents the number of calves that required a second treatment for BRDC during the first 120 DOF divided by the number of calves initially enrolled.

Statistical Analysis

General linear mixed models were fitted for continuous responses (i.e. initial body weight, rectal temperature at enrollment, final BW, and ADG). The linear predictor in the model for initial BW and rectal temperature at enrollment included treatment as a fixed effect; enrollment-date and site were included as random effects. The combination of treatment × site was assessed but dropped from the models based on a variance component estimated at zero boundary. For final BW and ADG, the linear predictor in the model included treatment as a fixed effect, and the random effects of site and the combination of site × treatment was used as a random effect to recognize the experimental unit for treatment. Initial BW at arrival and days-on-feed were included as covariates for the analysis of final BW and ADG; however, the covariate days-on-feed was removed from analysis of ADG due to non-significant ($P > 0.05$) contribution to the model.

Generalized linear mixed models were fitted to categorical binary responses (i.e. case fatality rate and re-treatment rate) using a logit link function. The linear predictor in the model included

treatment as a fixed effect, and site as a random effect; the combination of treatment × site was assessed but dropped from the models based on a variance component estimated at zero boundary. Rectal temperature at enrollment and initial BW were used as covariates; however, the covariate rectal temperature at enrollment was removed from the analysis of case fatality rate based due to non-significant ($P > 0.05$) contribution to the model.

Clinical scores were analyzed using generalized linear mixed model assuming a categorical multinomial distribution of the response modeled with a cumulative logit link function. The linear predictor for the statistical model included the fixed effects of antimicrobial treatment, time point of evaluation (0 and daily until 10 days after treatment), and their 2-way interaction. The random effect of site combined with arrival date was fitted in the linear predictor as a blocking factor for antimicrobial treatment. In addition, a random effect of animal nested within treatment in each site-by-arrival date combination was also incorporated into the model to recognize the experimental unit for treatment and repeated measures over time for each animal.

Parameter estimates from the statistical models described above were used to conduct both classical and bioequivalence hypothesis testing. On a classical testing framework, treatments were considered to yield significantly different outcomes based on P-values < 0.05 on the corresponding ANOVA Type III F-test statistics; marginal evidence for treatment differences were declared at $P < 0.10$. In turn, 90% confidence intervals (CI) on treatment differences were constructed for each response to assess evidence for equivalent treatment performance[18]. If a 90% CI on the treatment difference fell within appropriate upper and lower equivalence limits set for a given response, average bioequivalence between treatments for that response can be concluded with $P < 0.05$[18].

All statistical models were fitted using a statistical analysis software[q]. Kenward-Roger's approximation was used to estimate degrees of freedom and to make the corresponding adjustments in estimation of standard errors. Pairwise comparisons were conducted using either Tukey-Kramer or Bonferroni's method to adjust for multiple comparisons and prevent inflation of Type I error.

Results

No clinical adverse reactions were observed after treatment administration, and no animals were removed from the study before day 120 post-treatment. Within each site, animals arrived to the feedlot facility within a period of 1 day (Colorado and Kansas), 6 days (Nebraska), 8 days (Idaho and Oklahoma), and 10 days (Texas). At enrollment, no evidence of differences ($P = 0.38$) were found in initial body weight among calves receiving gamithromycin (235±1.6kg) and those receiving tulathromycin (236±1.6kg). Likewise, no evidence of differences for rectal temperature at enrollment ($P = 0.64$) were found comparing calves receiving gamithromycin (40.2±0.06ºC) and those receiving tulathromycin (40.2±0.06ºC). Moreover, the proportion of animals with fever (rectal temperature ≥ 40ºC) at enrolment was not significantly different ($P = 0.11$) between gamithromycin (64.5±5%) and tulatrhomycin (60.4±6%, Table 3.1). Across treatment groups, enrollment (initial treatment for BRDC) was administered at 3.6±0.7days after cattle arrived to the feedyard (for both treatment groups), and no evidence of differences were found in DOF for the first treatment (P=0.52) between treatment groups. Animals receiving gamithromycin were enrolled in average at 3.6±0.7 days after arrival, and those treated with tulathromycin were enrolled in average at 3.7±0.7 days after arrival (Table 3.1).

Overall re-treatment rate (second treatment) due to BRDC averaged 12.8±5% (estimated mean±SEM) across treatment groups. Re-treatment rate was greater ($P < 0.01$) in calves treated

with gamithromycin (17.7± 7%) compared with those treated with tulathromycin (9.0±4%, Table 3.1). Interestingly, the covariate initial BW at enrolment yield a significant contribution to fit the model for re-treatment rate ($P<0.04$); then, controlling for treatment, the estimated odds ratio for re-treatment for a 50kg reduction in initial BW relative to the average arrival weight of 233kg was 1.55 (95% CI = [1.01, 2.39]); hence, animals with lower initial BW had greater risk of re-treatment for BRDC during the first 120 DOF, same for both treatments. Likewise, the covariate rectal temperature yield a significant contribution to fit the model for re-treatment rate ($P\leq0.01$). The estimated odds ratios for re-treatment rate was 1.8 (95% CI = [1.4, 2.3]) times greater for an increment of 1°C relative to a 39.9°C; the same odds ratio both treatment groups. Therefore, animals with greater rectal temperature were at higher risk of being re-treated during the first 120 DOF. Overall estimated case fatality rate due to BRDC averaged 4.1±2.4% across treatment groups. For calves treated with tulathromycin, case fatality rate was 3.7±2%, and for calves treated with gamithromycin, case fatality rate averaged 4.2±2%; consequently, both treatment were considered bioequivalent at ±2.0% of case fatality rate ($P < 0.05$, Table 3.2). Tulathromycin was used as a reference category for estimation of the 90% CI on the mean treatment difference in the bioequivalence test. Interestingly, the covariate rectal temperature yield a significant contribution to fit the model of case fatality rate ($P<0.01$). Then, the estimated odds ratio for mortality due to BRDC for an increment of 1ºC in rectal temperature relative to a rectal temperature of 39.9ºC was 1.94 (95% CI = [1.51, 2.48]); therefore, the odds of died due to BRDC was 1.9 times greater in animals with fever (rectal temperature ≥ 40.0 ºC) compared with those with normal rectal temperature.

For the analysis of performance (i.e. final body weight and average daily gain), no evidences of differences was found between treatment groups. Therefore, bioequivalence tests were conducted

for performance outcomes. For final body eight, bioequivalence ($P < 0.05$) was established for final BW between gamithromycin (450, ±7.0kg) and tulathromycin (456, ±7.0kg) within the limits of ±7kg. Likewise, ADG was considered bioequivalent ($P<0.05$) between animals that received tulathromycin (1.57, ±0.06kg) and gamithromycin (1.52, ±0.06kg) within the limits of ±0.09kg (Table 3.2).

For the analysis of clinical scores during 10 days after treatment administration, only performed in the feedlots located in Cololado and Oklahoma, no evidence of treatment effect on clinical scores were found (P=0.97). In addition, regardless of antimicrobial treatment, clinical scores changed over time (P<0.01), whereby lower scores became more frequent during the 10 day long evaluation period.

Discussion

Both Gamithromycin and Tulathromycin have shown to be efficacious for treatment of animals diagnosed with bovine respiratory disease when they are used in accordance with the label[7-12]. To our knowledge, this is the first field study comparing gamithromycin vs. tulathromycin for treatment of BRDC in feedlot cattle. Due to animal welfare considerations, the present study did not include a negative control, so we were unable to compare the antimicrobial efficacy against placebo and thus formally assess treatment effect of the antimicrobials.

In the present study, cattle were considered to be at high risk of developing BRDC. Risk factors for BRDC included: initial body weight (233.8±24kg) at arrival, acquisition from auction markets, commingling, and stress of transportation. In addition, time of the year at arrival (October, November, and December) has been associated with higher risk of developing BRDC[19, 20]. Although information about cattle buyer was available, geographical location of the

auction markets was not provided; therefore, we were unable to estimate length and time of transportation.

As expected, no evidence of differences ($P \geq 0.39$) between treatment groups at enrollment was observed for initial body weight, rectal temperature, or the proportion of animals with fever (rectal temperature ≥ 40°C). Also, the average DOF at enrollment did not differ ($P=0.52$) between treatment groups. Therefore, no evidence of concerns with the randomization approach were found, so calves in both treatment groups were considered similar.

Previous studies comparing antimicrobial efficacy for the treatment of BRDC in cattle have evaluated health outcomes during 10, 14, or 28 days after treatment[7,8,9,10,11]. In order to obtain as much data as possible, health outcomes in the present study were evaluated over a period of 120 days. Interestingly, no re-treatment or fatality cases were observed after 105 days post-treatment. In addition, by day 35 post-treatment, cumulative re-treatment rate was 95% of the ultimate total number of animals receiving a second treatment (Table 3.3) and case fatality rate was 78% of the final number of case fatalities (Table 3.4).

In the present study, we found that cumulative re-treatment rate during the first 120 days post-treatment was higher ($P<0.01$) in animals treated with gamithromycin compared with those treated with tulathromycin (Table 3.1). This information agrees with the study conducted by Skogerboe who reported differences in cure rates (during 28 days after treatment) comparing two single dose injectable macrolides, tilmicosin[r] and tulathromycin, for the treatment of BRDC[11]; however, in that study, differences were found only in one of two sites and no statistical analysis were provided across both sites. Likewise, the study conducted by Kilgore reported that cure rate was greater ($P<0.01$) in animals receiving tulathromycin (78%) compared with those receiving tilmicosin (65%) across 4 sites (Texas, Idaho, Nebraska, and California), and within

each site[7]. It is important to mention that this study evaluated health outcomes only during 14 days after treatment.

In the present study, sites were modeled as random effects to allow for a broad scope of inference[18]; therefore, analyses within each site were not conducted. The random effect of site and the combination of site × treatment allows us to account for the variability between feedlots when performing treatment comparisons; as a result, we can infer across the greater U.S. feedlot population for which the participating feedlots might be considered a representative sample[18].

For the analysis of re-treatment rate, the interaction of initial BW × treatment, and fever × treatment were assessed, but they were dropped from the linear predictor due to non-significant contribution to fit the model ($P \geq 0.44$). Therefore, the main effect of treatment was the same for different levels of initial body weight and rectal temperature.

For those outcomes were no evidence of differences were detected ($P > 0.05$) with classical hypothesis testing (failing to reject the hypothesis null of no "treatment differences"), we conducted a bioequivalence test. Using this methodology, we concluded on similarities in treatment performance within a confidence limit (±mean treatment difference)[22]. Using the bioequivalence test, we established bioequivalence of ±2% for case fatality rate ($P < 0.05$) between gamithromycin and tulathromcyin, indicating that the estimated mean case fatality for tulathromycin (3.7±2%) minus the estimated mean of case fatality of gamithromycin (4.2±2%) will result in a mean treatment difference between the limits (bioequivalence limits) of ±2.0%.

Similarly, in the study conducted by Kilgore in 4 feedyards, no evidence of differences in mortality rates were found ($P > 0.1$) between tulathromycin (0.6%) and tilmicosin (1%), across sites and within sites[7]. In addition, in the study conducted by Skogerboe in two feedlots, one site (Colorado) reported greater mortality rate in animals treated with tilmicosin (6%) compared with

those treated with tulathromycin (0%); however, the other site (Texas) reported no evidence of differences in mortalities between animals treated with tulathromycin and those treated with tilmicosin[11].

Average daily gain during the subsequent 120 days after treatment was similar ($P < 0.05$) for animals receiving gamithromycin (1.52±0.06 kg) and those receiving tulathromycin (1.57±0.06 kg). Likewise, Skogerboe reported that ADG during the first 28 days after treatment was greater ($P < 0.05$) for the animals treated with tulathromycin compared with those treated with tilmicosin; however, no evidence of differences between treatments was found in ADG from day 0 through harvest[11]. Compensatory gain has been shown in previous studies for morbid animals after day 135 to 238[1]; this suggests that evaluation of ADG is only relevant if it is measured during short periods after treatment. Subsequently, a serial evaluation of ADG at different time periods will allow us to identify differences in performance and evaluate compensatory gain.

Diagnosis of morbid animals is commonly based on clinical signs that include a combination of objective (i.e. rectal temperature) and subjective (i.e. depression, abnormal appetite, and respiratory signs) animal attributes[20]. Previous studies have shown that BRDC diagnosis under field conditions based on these attributes has low sensitivity and specificity, 61.8 and 62.8% respectively[23]. Consequently, a high degree of diagnosis error is expected. Thompson found that only 55.4% of animals treated once for BRDC had lung lesion at slaughter[24]; similarly, Wittum (1996) found that only 78% of steers treated for respiratory disease (either before weaning or in the feedlot) had lung lesion at slaughter[25]. Consequently, a big proportion of false-positive and false-negative can bias the results for morbidity rates. Hence, clinical scores and lung lesions at slaughter are poor methods to truly detect diseased animals[23]. New technologies

that increase the sensitivity and specificity of BRDC diagnosis will increase accuracy in evaluating morbidity rates in field trials.

Conclusion

Under commercial feedlot conditions, both antimicrobials performed similarly and were considered bioequivalent for case fatality rate, average daily gain, and final body weight. Nevertheless, calves treated with tulathromycin had lower re-treatment rates compared to gamithromycin.

Footnotes

a. Ivomec Plus, Merial LTD, Duluth, GA.

b. Dectomax, Pfizer Animal Health, New York, NY.

c. Caliber 7, Boehringer Ingelheim Vetmedica Inc., St. Joseph, MO.

d. Vision 8, Intervet/Schering-Plough Animal Health, Millsboro, DE.

e. Vision 7, Intervet/Schering-Plough Animal Health, Millsboro, DE.

f. Essential 2, Colorado Serum Company, Denver, CO.

g. Bovishield Gold 5, Pfizer Animal Health, New York, NY.

h. Express 5, Boehringer Ingelheim Vetmedica Inc., St. Joseph, MO.

i. Pyramid 5, Boehringer Ingelheim Vetmedica Inc., St. Joseph, MO.

j. Titanium 5, Agri Laboratories LTD, St. Joseph, MO.

k. Vista 3 SC, Intervet/Schering-Plough Animal Health, Millsboro, DE.

l. Component TE- IH, Eli Lilly and Company, Indianapolis, IN.

m. Revalor G, Intervet/Schering-Plough Animal Health, Millsboro, DE.

n. Revalor-IH, Intervet/Schering-Plough Animal Health, Millsboro, DE.

o. Zactran, Merial LTD, Duluth, GA.

p. Draxxin, Pfizer Animal Health, New York, NY.

q. PROC GLIMMIX, SAS, version 9.3, SAS Institute, Cary, NC

r. Micotil, Eli Lilly and Company, Indianapolis, IN.

References

1. Snowder GD, Van Vleck LD, Cundiff LV, et al. Bovine respiratory disease in feedlot cattle: Environmental, genetic, and economic factors. *J Anim Sci* 2006;84:1999-2008.

2. Babcock AH, White BJ, Dritz SS, et al. Feedlot health and performance effects associated with the timing of respiratory disease treatment. *J Anim Sci* 2009;87:314-327.

3. Schneider MJ, Tait RG, Busby WD, et al. An evaluation of bovine respiratory disease complex in feedlot cattle: Impact on performance and carcass traits using treatment records and lung lesion scores. *J Anim Sci* 2009;87:1821-1827.

4. Garcia MD, Thallman RM, Wheeler TL, et al. Effect of bovine respiratory disease and overall pathogenic disease incidence on carcass traits. *J Anim Sci* 2010;88:491-496.

5. McVey DS. BRD research needs in the next 10–20 years. *Animal Health Res Rev* 2009;10:165.

6. Nickell JS, White BJ. Metaphylactic Antimicrobial Therapy for Bovine Respiratory Disease in Stocker and Feedlot Cattle. *Vet Clin North Am Food Anim Pract* 2010;26:285-301.

7. Kilgore WR. Therapeutic efficacy of tulathromycin, a novel triamilide antimicrobial, against bovine respiratory disease in feeder calves. *Vet ther* 2005;6:143.

8. Nutsch RG. Comparative efficacy of tulathromycin, tilmicosin, and florfenicol in the treatment of bovine respiratory disease in stocker cattle. *Vet ther* 2005;6:167.

9. Schunicht OC, Booker CW, Guichon PT, et al. An evaluation of the relative efficacy of tulathromycin for the treatment of undifferentiated fever in feedlot calves in Nebraska *Can Vet J* 2007;48:600-606.

10. Sifferman RL, Wolff WA, Holste JE, et al. Field efficacy evaluation of gamithromycin for treatment of bovine respiratory disease in cattle at feedlots. *J Appl Res Vet M* 2011;9:166-175.

11. Skogerboe TL. Comparative efficacy of tulathromycin versus florfenicol and tilmicosin against undifferentiated bovine respiratory disease in feedlot cattle. *Vet ther* 2005;6:180.

12. Wellman NG, O'Connor AM. Meta-analysis of treatment of cattle with bovine respiratory disease with tulathromycin. *J Vet Pharmacol Ther* 2007;30:234-241.

13. Giguere S, Huang R, Malinski TJ, et al. Disposition of gamithromycin in plasma, pulmonary epithelial lining fluid, bronchoalveolar cells, and lung tissue in cattle. *Am J Vet Res* 2011;72:326-330.

14. Forbes AB, Ramage C, Sales J, et al. Determination of the Duration of Antibacterial Efficacy following Administration of Gamithromycin Using a Bovine Mannheimia haemolytica Challenge Model. *Antimicrobial Agents Chemother* February 2011;55:831-835.

15. Practical Euthanasia of Cattle: Considerations for the Producer, Livestock Market Operator, Livestock Transporter, and Veterinarian. Brochure prepared by the Animal Welfare Committee of the American Association of Bovine Practitioners. 1999.

16. National Research Council. Tables of nutrient requirements. In: *Nutrient requirements of beef cattle*: 7th ed. Washington, DC: National Academy Press, 1996;102-112

17. Huang RA, Letendre LT, Banav N, et al. Pharmacokinetics of gamithromycin in cattle with comparison of plasma and lung tissue concentrations and plasma antibacterial activity. *J Vet Pharmacol Ther* 2010;33:227-237.

18. Tempelman RJ. Invited review: Assessing experimental designs for research conducted on commercial dairies. *J Dairy Sci* 2009;92:1.

19. Taylor JD. The epidemiology of bovine respiratory disease: What is the evidence for predisposing factors? *Can Vet J*. 2010;51(10):1095.

20. Loneragan GH, Dargatz DA, Morley PS, Smith MA. Trends in mortality ratios among cattle in US feedlots. *J Am Vet Med Assoc*. 2001;219(8):1122-1127.

21. Tempelman RJ. Experimental design and statistical methods for classical and bioequivalence hypothesis testing with an application to dairy nutrition studies. *J Anim Sci* 2004; 82:E162.

22. Step DL, Krehbiel CR, DePra HA, et al. Effects of commingling beef calves from different sources and weaning protocols during a forty-two-day receiving period on performance and bovine respiratory disease. *J Anim Sci* 2008;86:3146-3158.

23. White BJ. Bayesian estimation of the performance of using clinical observations and harvest lung lesions for diagnosing bovine respiratory disease in post-weaned beef calves. *J Vet Diagn Invest* 2009;21:446.

24. Thompson PN, Stone A, Schultheiss WA. Use of treatment records and lung lesion scoring to estimate the effect of respiratory disease on growth during early and late finishing periods in South African feedlot cattle. *J Anim Sci* 2006;84:488-498.

25. Wittum TE. Relationships among treatment for respiratory tract disease, pulmonary lesions evident at slaughter and rate of weight gain in feedlot cattle. *J Am Vet Med Assoc* 1996;209:814.

Tables

Table 3-1 Least square mean estimates and estimated standard errors of the means for BW and rectal temperature (at enrollment), and re-treatment rate (from enrollment through day 120 post-treatment) of animals treated for BRDC with tulathromycin and gamithromycin

ITEM	Tulathromycin	SEM	Gamithromycin	SEM	*P*-value
Initial body weight (kg)	236	1.6	235	1.6	0.41
Rectal temperature (°C)	40.2	0.1	40.2	0.1	0.79
Days on feed at enrolment	3.7	0.7	3.6	0.7	0.52
Re-treatment (%)	9.0	3.9	17.7	6.7	< 0.01

Table 3-2 Least square means estimates (and estimated standard error of the mean) and bioequivalence limits for final BW, ADG, and Case fatality rate (from enrollment through day 120 day post-treatment) of animals treated for BRDC with tulathromycin and gamithromycin

ITEM	Tulathromycin	Gamithromycin	SEM	Bioequivalence Limits (±)[1]
Final BW (kg)	456	450	7.0	13.0
ADG, (kg/day)	1.57	1.52	0.06	0.1
Case fatality rate (%)	3.7	2.4	4.2	2.4

[1] Average bioequivalence between treatments ($P<0.05$) established within the ±limits

Table 3-3 Number of animals that were re-treated (second treatment) for BRDC within the first 120 days post-enrollment, across all sites.

Days post-enrolment	Number of calves re-treated			Cumulative re-treatment (%)
	Tulathromycin	Gamithromycin	Re-treatment by period	
7	5	5	10	5
14	35	51	86	49
21	12	43	55	77
28	14	12	26	90
35	5	9	14	97
42	0	1	1	98
49	0	2	2	99
63	0	1	1	99
84	0	1	1	100
TOTAL	71	125	196	100

Table 3-4 Number of animals that died due to BRDC (Case fatality rate) within the first 120 days post-enrollment that was treated with tulathromycin or gamithromycin, across all sites.

Days post-enrolment	Number of mortalities			Cumulative Mortality %
	Tulathromycin	Gamithromycin	Mortalities Total	
7	16	8	24	29
14	10	7	17	49
21	1	1	2	52
28	4	8	12	66
35	2	8	10	78
42	1	3	4	83
49	1	3	4	88
56	1	0	1	89
70	0	1	1	90
77	1	2	3	94
84	1	0	1	95
91	0	1	1	96
98	1	0	1	98
105	0	2	2	100
TOTAL	39	44	83	100

Chapter 4 - Mortality and morbidity due to bovine respiratory disease complex in feedlot cattle, associated with rectal temperature, castration, dehorning (tipping), and body weight at time of processing

Siddartha Torres[1], MVZ; Dan U. Thomson[2], PhD, DVM; and Chris D. Reinhardt[3], PhD

[1,2]Department of Clinical Sciences, College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506, USA

[3] Department of Animal Sciences and Industry, College of Agriculture, Kansas State University, Manhattan, KS 66506, USA

Abstract

This study was conducted to evaluate initial body weight (IBW), rectal temperature, castration, and dehorning (tipping) at processing, as factors associated with mortality and morbidity due to Bovine Respiratory Disease Complex (BRDC) during the 120 days after arrival. The analysis included a total of 3,365 individual animal records from three feedlots located in Kansas (n=1,002, BW 479 lb., SD ± 40 lb.), Nebraska (n=1,527, 519 lb., ± 91 lb.), and Texas (n=838, 572 lb., ± 41 lb.). Generalized linear mixed models were used to fit the categorical binary outcomes of mortality and morbidity. The estimated overall morbidity and mortality rates were 34.5% (SEM ± 4.8%) and 6.7% (SEM ± 1.9%), respectively. The estimated odds of morbidity was 1.85 (95% CI= [1.03, 3.32]) greater for castrated bulls compared with steers, given an average of 550lb at arrival and controlling for rectal temperature. The estimated odds of morbidity and mortality were 1.7 (95% CI = [1.35, 2.02]) times greater for calves with fever compared with those with normal temperature, same for steers and castrated bulls. For a 100 lb. reduction IBW relative to a baseline of 550 lb., the estimated odds of morbidity was 2.0 (95% CI = [1.56, 2.63]) times greater for febrile calves and 1.6 (95% CI = [1.37, 1.93]) times greater for calves with normal temperature. A reduction of 100 lb. in IBW relative to a baseline of 550 lb., the odds of mortality increased 1.4 (95% CI =[1.06, 1.87]) times, regardless of castration status and rectal temperature. These estimated odds ratios indicate that calves with lighter weights and those with fever at arrival are in a greater risk of death or of developing BRDC during the first 120 DOF. Also, animals that were castrated at arrival are at higher risk of developing BRDC. No evidence of association ($P \geq 0.22$) between dehorning and BRDC morbidity and mortality was observed. Monitoring rectal temperature and initial body weight can be beneficial tools to consider for early diagnosis, treatment, and care interventions of animals with BRDC.

Introduction

Bovine Respiratory Disease Complex (BRDC) is the primary cause of illness and death loss in feedlot cattle in the United States[28]. The disease accounts for approximately 50% of morbidity and 75% of mortalities in feedyards[3,14,27]. Annual economic losses are estimated in US $1 billion due to mortality, morbidity, treatment cost, and reduction in performance and carcass value [12-14]; in addition, it is estimated that the beef industry spends over US $3 billion annually on preventive measures[13]. BRDC is considered a multifactorial syndrome caused by environmental factors, individual animal susceptibility, and viral and bacterial pathogens[14,17]. Environmental factors, also referred as "stressors", are necessary to induce naturally occurring BRDC[19,27]. Stress increases glucocorticoids circulating in plasma which results in immunosuppression[1,9,26]. Consequently, virus and bacterial pathogens, acting in a synergistic manner, develop the bacterial pneumonia[19]. Weather conditions, transportation, weaning, and commingling are the most common stressors associated with BRDC mortality and morbidity[2,24,27]; moreover, it has been postulated that stress due to castration and dehorning can be associated with BRDC[27]; however, this association has not been consistently reported in the literature[10]. Likewise, animal weight at arrival has been reported as a risk factor for BRDC[20,21,23]. Like with castration and dehorning, the information is inconsistent and most studies do not report the magnitude of this association[27]. Besides, BRDC diagnosis is objectively supported by rectal temperature ≥ 104.0 ºF[22]; therefore, monitoring rectal temperature at processing is a potential tool for early diagnosis and treatment of sick animals[11]. However; this practice has potential limitations to identify sick cattle because body temperature increases with increasing ambient temperature and humidity and animal movement through the handling facility[11,15]. Controlling factors associated with the development of BRDC for early diagnosis and treatment is critical to reduce losses due to BRDC

and improve animal wellness. The objective of this study was to evaluate rectal temperature, castration, dehorning, and IBW at arrival, as factors associated with mortality and morbidity due to BRDC in feedlot cattle.

Material and methods

This study did not use animals; therefore, Animal Care and Use Committee approval from Kansas State University was not obtained.

Animals

A total of 3,365 individual animal health records from 3 feedyards located in Kansas (n=1,002, BW 479 lb., SD ± 40 lb.), Nebraska (n=1,527, 519 lb, ± 91 lb), and Texas (n=838, 572 lb, ± 41 lb), were used in the analysis. All calves were acquired from auction markets between October 2 and December 18, 2010. Animal records included: individual animal identification, date of arrival, pen identification, gender, initial body weight (IBW) at arrival, rectal temperature at processing, castration and dehorning procedures (only if performed), and mortality and morbidity due to BRDC during the first 120 days after arrival.

Processing and housing

Upon arrival, calves were processed within 24 hours. At processing, animals were given an ear tag for individual identification, vaccinated against clostidial (Kansas[a], Nebraska[a] , and Texas[b]) and viral pathogens (Kansas[c], Nebraska[d] and Texas[e]); in addition, animals were treated for internal and external parasites with fenbendazole[f] and ivermectin[g] respectively. Also, calves were mass treated with an injectable antimicrobial[h,i] to control BRDC. Animals received an anabolic implant in the feedlots located in Kansas[j] and Texas[k]. Intact bulls were castrated surgically practicing an open technique with the use of a "newberry" knife to cut the scrotum and application of an emasculator to crush and cut the testicular cords[5]; furthermore, the tip of the

horn (only the keratinized tissue of the horn) was removed using a guillotine shear in those animals with large horns[25] . After processing, animals were assigned to open air group pens according to weight and arrival date. Average number of animals per pen was 50 in Kansas, 110 in Nebraska, and 40 in Texas. Animals were fed with a ration formulated to meet or exceed the requirements of the National Research Council for maintenance and expected growth[18]. All animals had *ad libitum* access to water.

Health outcomes for BRDC.

General health observations were performed daily by pen riders from day 0 through day 120 after arrival. Morbidity due to BRDC included animals showing clinical scores of 1, 2 or 3 according to the clinical score scale (table 4.1) and having rectal temperature equal to or greater than 104ºF. Sick animals received antimicrobial medication according to the standard feedlot procedures and returned to their home pens. Moribund animals were euthanized following the guidelines of the Animal Welfare Committee of the American Association of the Bovine Practitioners. Mortality attributed to BRDC during the first 120 days on feed was confirmed by presence of bronchopneumonia at necropsy of those animals that either died or were humanely euthanized.

Statistical Model

Mortality and morbidity due to BRDC were fitted using generalized linear mixed models using a logit link function for binomial responses. For morbidity, the linear predictor in the model included the fixed effects of temperature status at arrival (Normal: < 104 °F, or Fever: ≥ 104 °F), castration and dehorning procedures (Castration:Yes/No, and Dehorning:Yes/No), and IBW at arrival was included in the model as a covariate. In addition, pen nested within feedlot was used as random effect. Also, gender (male or heifer) was evaluated as a fixed effect; however, it was

dropped due to non-substantial contribution (P=0.60) to fit the model. Finally, the interaction of rectal temperature × IBW was used to model fit due to its marginal contribution (P = 0.09).

For mortality, the linear predictor in the model included rectal temperature status at arrival, and castration and dehorning procedures as fixed effects; also, IBW was used as a covariate. Pen nested within feedlot was used as random effect. Two way interactions between fixed effects and covariate IBW were evaluated to fit the model; however, they were dropped due to non-significant (P≥0.57) contribution to fit the model. Parameter estimates from the statistical models described above were used to conduct classical hypothesis testing. Effects were considered significant based on P-values < 0.05 on the corresponding ANOVA Type III F-test statistics; marginal evidence of main effects was declared at P < 0.10.

All statistical models were fitted using the GLIMMIX[1] procedure of SAS (Version 9.3, SAS Institute, Cary, NC). Kenward-Roger's approximation was used to estimate degrees of freedom and to make the corresponding adjustments in estimation of standard errors.

Results

During the 120 days after arrival, the estimated morbidity and mortality rates were 34.5% (SEM ± 4.8%) and 6.7% (SEM ± 1.9%), respectively. At arrival, a total of 608 (18%) animals were identified with fever, and 2,757 (82%) animals had normal rectal temperature.

A total 113 calves (7.4%) were dehorned (tipped) and 51 calves (3.3%), purchased as bulls were surgically castrated. There was no evidence of a main effect (P≥ 0.22) of dehorning on BRDC mortality and morbidity. For morbidity rate, parameter estimates were significant for the main effects of castration (P= 0.04), rectal temperature status at processing (P=0.02), and the covariate IBW at arrival (P<0.01).

The estimated odds ratio of morbidity due to BRDC was 1.85 times greater (95% CI= [1.03, 3.32]) in castrated bulls compared with steers, controlling for fever status and a given average BW of 550 lb. at arrival. Likewise, the estimated odds ratio of morbidity was 1.7 greater (95% CI = [1.35, 2.02]) in calves with fever at processing compared with those with normal rectal temperature, same for castrated bulls and steers and given an average arrival BW of 550 lb.

The estimated odds of BRDC morbidity was 2.03 (95% CI = [1.56, 2.63]) greater for a reduction of 100 lb. of IBW, relative to a baseline of 550lb., and same for castrated bulls or steers and regardless rectal temperature at arrival.

These estimated odds ratios indicate that animals with lighter weights, animals that were castrated, and those with fever at arrival are at a greater risk of developing BRD during the first 120 days after arrival. Consequently, estimated morbidity rate estimates were greater for light weight calves compared with heavier animals.

For BRDC mortality, no evidence of effects of castration ($P = 0.24$) or dehorning ($P = 0.22$) were found. Nonetheless, IBW ($P < 0.02$) and fever status at arrival ($P < 0.01$) were associated with BRD mortality. Consequently, for a reduction of 100lb. in initial BW relative to a baseline of 550lb, the odds of mortality increased 1.4 (95% CI =[1.06, 1.87]) times, regardless rectal temperature status, castration, or dehorning procedures. Likewise, animals with fever at arrival had an estimated odds of mortality 1.6 (95% CI= [1.1, 2.2]) times greater than the odds of mortality in animals with normal temperature, regardless castration or dehorning procedures, and given an average of 550lb. of IBW.

The odds ratio estimate indicates that animals with lighter weights and fever at arrival are at greater risk of mortality due to BRD during the first 120 days after arrival. Also, the estimated morbidity rate was greater in lighter calves compared with heavier animals (Figure 4.2).

Discussion

At arrival, castration of intact bulls is performed to meet the beef industry standards[6]. Castration reduces aggression and mounting behavior of males and improves beef quality[8]; however, castration is a painful procedure that affects animal well-being and produces stress[6,9,10], and it can negatively impact health status[7,27] In the present study, the odds ratio estimate for castration indicates that bulls castrated at arrival were at higher risk of develop BRDC during the first 120 DOF compared with steers. This result agrees with the study conducted by Coetzee et al., (2012), who reported that castrated animals had greater BRDC incident compared with steers. Another study conducted two experiments to evaluate the effects of castration on health and performance[4]. In experiment one (n=105 calves) morbidity (animals that were pulled) and treatment (animals that were pulled and treated) rates were greater in calves that were castrated surgically compared with those that were purchased as steers; however, the second experiment (n=283 calves) reported no differences in first treatment or retreatment rates among bulls that were banded or surgically castrated and calves that were purchased as steers. In the present study, dehorning (tipping) was not associated with BRDC morbidity ($P = 0.61$) or mortality ($P = 0.22$). This finding disagrees with Martin et al., (1998) which reported that BRDC cases were 30% greater in calves that were dehorned compared with those not dehorned; however, the method of dehorning was not reported in that study. If it is performed accurately, tipping is less painful compared with horn amputation because tipping does not affect the pain-sensitive core of the horn[16,25]; this is the reason that we were not able to detect evidences of associations between tipping and BRDC. In addition, since there were no animals that were castrated and dehorned at the same time; the dehorning × castration interaction could not be tested.

In the present study, the odds ratio for initial BW estimate indicates that animals with lighter weights at arrival are at a greater risk of mortality due to BRD during the initial 120 DOF. This result agrees with one study that reported that calves weighing more than 318 kg were less likely to develop BRD (relative risk of 0.18), compared with calves weighing less than 218 kg[21,23]. Likewise, other authors have reported that animals categorized as yearlings have lower incidence of BRDC morbidity and mortality compared with calves[27]; however, animal age is difficult to monitor resulting in an arbitrary categorization of age. Body weight is an objective, easily-measured, animal characteristic that can be used as a factor to predict cattle health. Figures-1 and 2 show that IBW is not linearly correlated with BRDC morbidity and mortality. It has been postulated that monitoring rectal temperature has limited value in identifying morbid animals[15] because rectal temperature is affected by ambient temperature, humidity, and animal handling at processing[11]. In the present study, animals with fever at processing were at greater risk of death or to develop BRDC compared with those animals with normal temperature. This agrees with one study that evaluated metaphylactic antimicrobial administration compared with antimicrobial treatment given only to animals showing rectal temperature ≥ 39.7 °C (103.5°F). That study reported that monitoring rectal temperature was effective in reducing treatment cost, and reported no differences in performance or health outcomes between treatment groups[11]. Monitoring rectal temperature at arrival can be a potential tool for early diagnosis, treatment, and target management practices for animals with BRDC.

Conclusions

Calves with lighter weights and fever at arrival are at greater risk of mortality and morbidity due to BRD during the first 120 days after arrival. Also, castrated bulls are at higher risk of developing BRDC. These findings suggest that lighter calves require special attention and

veterinary interventions for early diagnosis and treatment of the disease. In addition, monitoring rectal temperature at arrival can be beneficial for treatment interventions of sick cattle. Then, minimize economic losses and animal welfare concerns due to BRDC in feeder cattle.

Footnotes

[a] Vision 7/Somnus, Intervet/Schering-Plough Animal Health, Millsboro, DE

[b] Essential 2, Colorado Serum Company, Denver, CO.

[c] Bovishield Gold 5, Pfizer Animal Health, New York, NY.

[d] Inforce 3, Pfizer Animal Health, New York, NY .

[e] Titanium 3, Agrilabs, St. Joseph, MO.

[f] SafeGuard, Intervet/Schering-Plough Animal Health, Millsboro, DE.

[g] Ivomec Plus, Merial LTD, Duluth, GA.

[h] Zactran, Merial LTD, Duluth, GA.

[i] Draxxin, Pfizer Animal Health, New York, NY.

[j] Ralgro, Intervet/Schering-Plough Animal Health, Millsboro, DE.

[k] Component TE-IH, Eli Lilly and Company, Indianapolis, IN.

[l] PROC GLIMMIX, SAS, version 9.3, SAS Institute, Cary, NC

References

1. Aich P. Modern approaches to understanding stress and disease susceptibility: A review with special emphasis on respiratory disease. *Int J Gen Med*. 2009;2:19.

2. Apley M. Bovine respiratory disease: Pathogenesis, clinical signs, and treatment in lightweight calves. *Vet Clin North Am Food Anim Pract*. 2006;22(2):399-411.

3. Babcock AH, White BJ, Dritz SS, Thomson DU, Renter DG. Feedlot health and performance effects associated with the timing of respiratory disease treatment. *J Anim Sci*. 2009;87(1):314-327.

4. Berry BA, Choat WT, Gill DR, Krehbiel CR, Smith RA. Effecto of castration on health and performance of newly received stressed feedlot calves. *Animal Science Research Report - Agricultural Experiment Station, Oklahoma State University*. 2001;3.

5. Bowman KF. The practice of large animal surgery. *Veterinary surgery*. 1985;14(2):166.

6. Bretschneider G. Effects of age and method of castration on performance and stress response of beef male cattle: A review. *Livest Prod Sci*. 2005;97(2-3):89.

7. Coetzee JF. Effect of oral meloxicam on health and performance of beef steers relative to bulls castrated on arrival at the feedlot. *J Anim Sci*. 2012;90(3):1026.

8. Coetzee JF. Erratum to "A review of pain assessment techniques and pharmacological approaches to pain relief after bovine castration: Practical implications for cattle production within the united states"[appl. anim. behav. sci. 135 (2011) 192–213]. *Appl Anim Behav Sci*. 2012;139(1-2):151.

9. Duff GC, Galyean ML. BOARD-INVITED REVIEW: Recent advances in management of highly stressed, newly received feedlot cattle. *J Anim Sci*. 2007;85(3):823-840.

10. Faulkner DB, Eurell T, Tranquilli WJ, et al. Performance and health of weanling bulls after butorphanol and xylazine administration at castration. *J Anim Sci*. 1992;70(10):2970-2974.

11. Galyean ML. Effects of arrival medication with tilmicosin phosphate on health and performance of newly received beef cattle. *J Anim Sci*. 1995;73(5):1219.

12. Garcia MD. Effect of bovine respiratory disease and overall pathogenic disease incidence on carcass traits. *J Anim Sci*. 2010;88(2):491.

13. Griffin D. Economic impact associated with respiratory disease in beef cattle. *Vet Clin North Am Food Anim Pract*. 1997;13(3):367.

14. McVey DS. BRD research needs in the next 10–20 years. *Animal Health Res Rev*. 2009;10(02):165.

15. Montgomery SP. Plasma metabolites of receiving heifers and the relationship between apparent bovine respiratory disease, body weight gain, and carcass characteristics. *J Anim Sci*. 2009;87(1):328.

16. Neely CD, Thomson DU, Kerr CA, Anderson DE, Reinhardt CD. Comparison of the effects of three different dehorning techniques on behavior and performance in feeder cattle in a western kansas feedlot. *Cattlemen's Day Beef Cattle Research*. 2012:15-18.

17. Nickell JS, White BJ. Metaphylactic antimicrobial therapy for bovine respiratory disease in stocker and feedlot cattle. *Vet Clin North Am Food Anim Pract*. 2010;26(2):285-301.

18. NRC. Nutrient requirements of beef cattle: Update 2000. *7th ed Natl Acad Press, Washington, DC*. 2000.

19. Panciera RJ. Pathogenesis and pathology of bovine pneumonia. *Vet Clin North Am Food Anim Pract*. 2010;26(2):191.

20. Reinhardt CD, Hands ML, Marston TT, Waggoner JW, Corah LR. Relationships between feedlot health, average daily gain, and carcass traits of angus steers. *Professional Animal Scientist*. 2012;28:11-19.

21. Reinhardt CD. Relationship of various incoming cattle traits with feedlot performance and carcass traits. *J Anim Sci*. 2009;87(9):3030.

22. Rose Dye TK. Rumen temperature change monitored with remote rumen temperature boluses after challenges with bovine viral diarrhea virus and mannheimia haemolytica. *J Anim Sci*. 2011;89(4):1193.

23. Sanderson MW. Risk factors for initial respiratory disease in united states' feedlots based on producer-collected daily morbidity counts. *Can Vet J*. 2008;49(4):373.

24. Snowder GD, Van Vleck LD, Cundiff LV, Bennett GL. Bovine respiratory disease in feedlot cattle: Environmental, genetic, and economic factors. *J Anim Sci*. 2006;84(8):1999-2008.

25. Stafford KJ. Dehorning and disbudding distress and its alleviation in calves. *The veterinary journal*. 2005;169(3):337.

26. Stanger KJ. The effect of transportation on the immune status of bos indicus steers. *J Anim Sci*. 2005;83(11):2632.

27. Taylor JD. The epidemiology of bovine respiratory disease: What is the evidence for predisposing factors? *Can Vet J*. 2010;51(10):1095.

28. USDA. Health management and biosecurity in U.S. feedlots, 1999. in: USDA:APHIS:VS (ed.). *National Animal Health Monitoring Systems, Fort Collins, CO*. 2000.

Tables

Table 4-1 Clinical Score Scale for animals with BRDC

Score	Description
0	Normal: Nothing unusual in animal's attitude and no abnormal respiratory symptoms present.
1	Mild depression (somewhat slow coming to feed bunk, but did eat). Mild respiratory symptoms present; serous nasal or ocular discharge and/or caugh.
2	Moderate depression (slight head/ears dropping, reluctant to move about, reluctant to come to the feed bunk). Moderate respiratory distress: Mucosus or mucopurulent nasal or ocular discharge and/or increase in respiratory rate or effort.
3	Severe depression (pronounced head/ear droop' very reluctant to move). Severe respiratory distress: marked increase in respiratory rate or effort including: open mouth breathing, abdominal breathing, or extended head)
4	Moribund

Figures

Figure 4-1 Estimated BRDC morbidity rate by IBW at arrival in steers and castrated bulls. Main effects of castration (*P*= 0.04) and initial body weight at arrival (P<0.01) were associated with BRDC morbidity. CASTRATED (animals that arrived at the feedyard as intact bulls and were surgically castrated), STEERS (animals that arrived at the feedyard as steers).

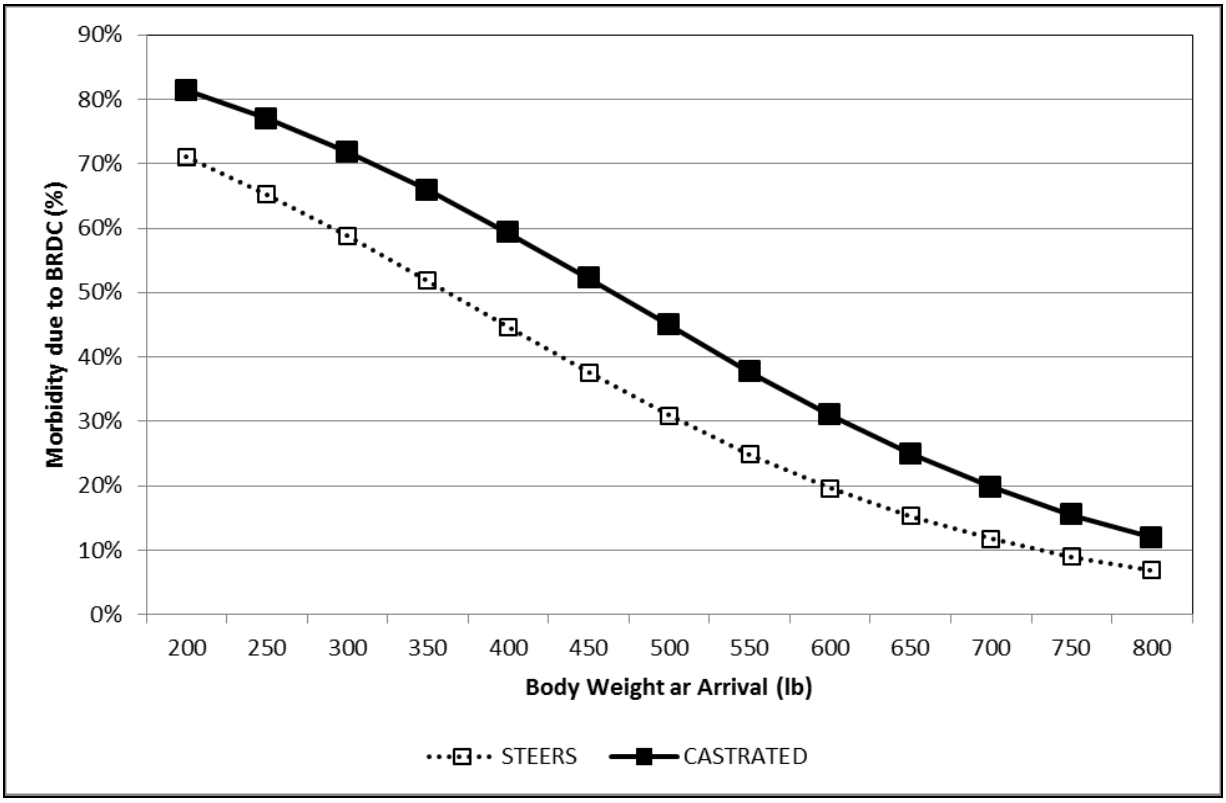


Figure 4-2 Estimated BRDC morbidity rate by IBW at arrival in animals with fever or normal temperature. Main effects of rectal temperature status at processing (P=0.02), and initial body weight at arrival (P<0.01) were associated with BRDC morbidity. Marginal interaction of IBW × rectal temperature (*P* = 0.09). NORMAL (animals that had rectal temperature <104°F at processing), FEVER (animals that had rectal temperature ≥104°F at processing).

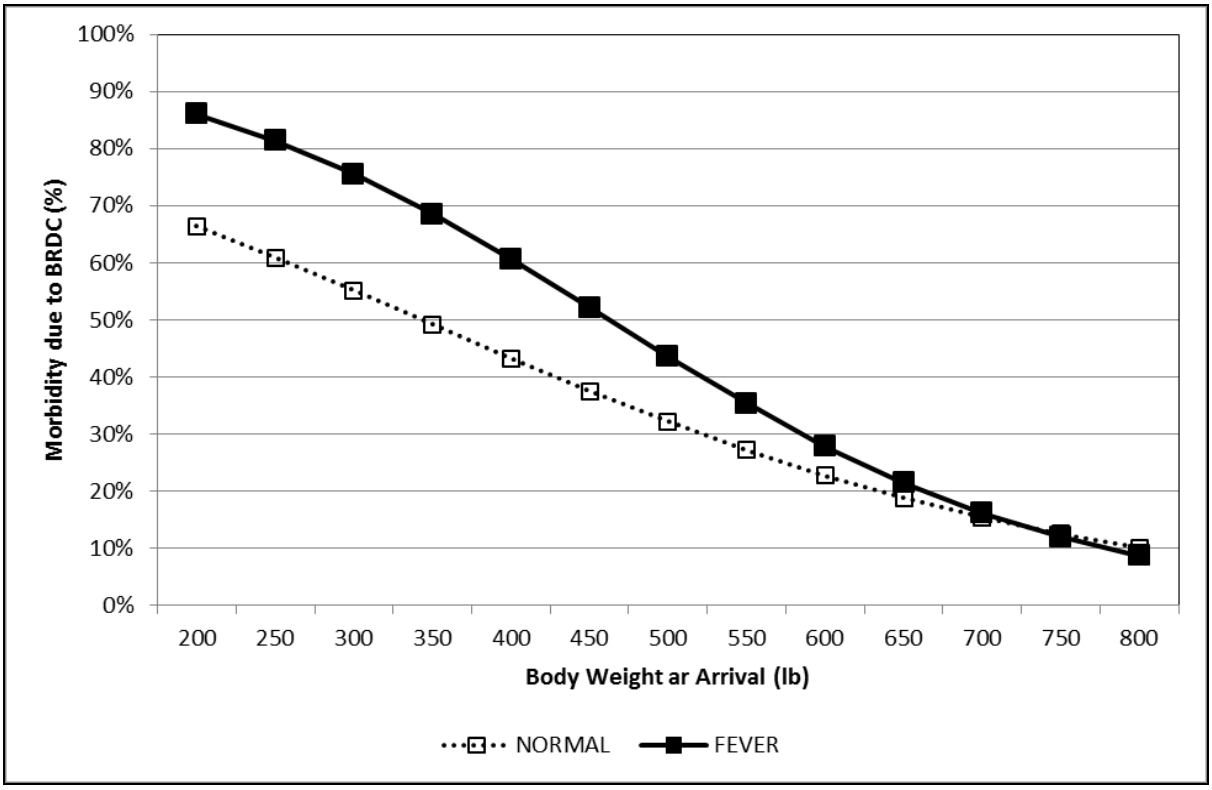
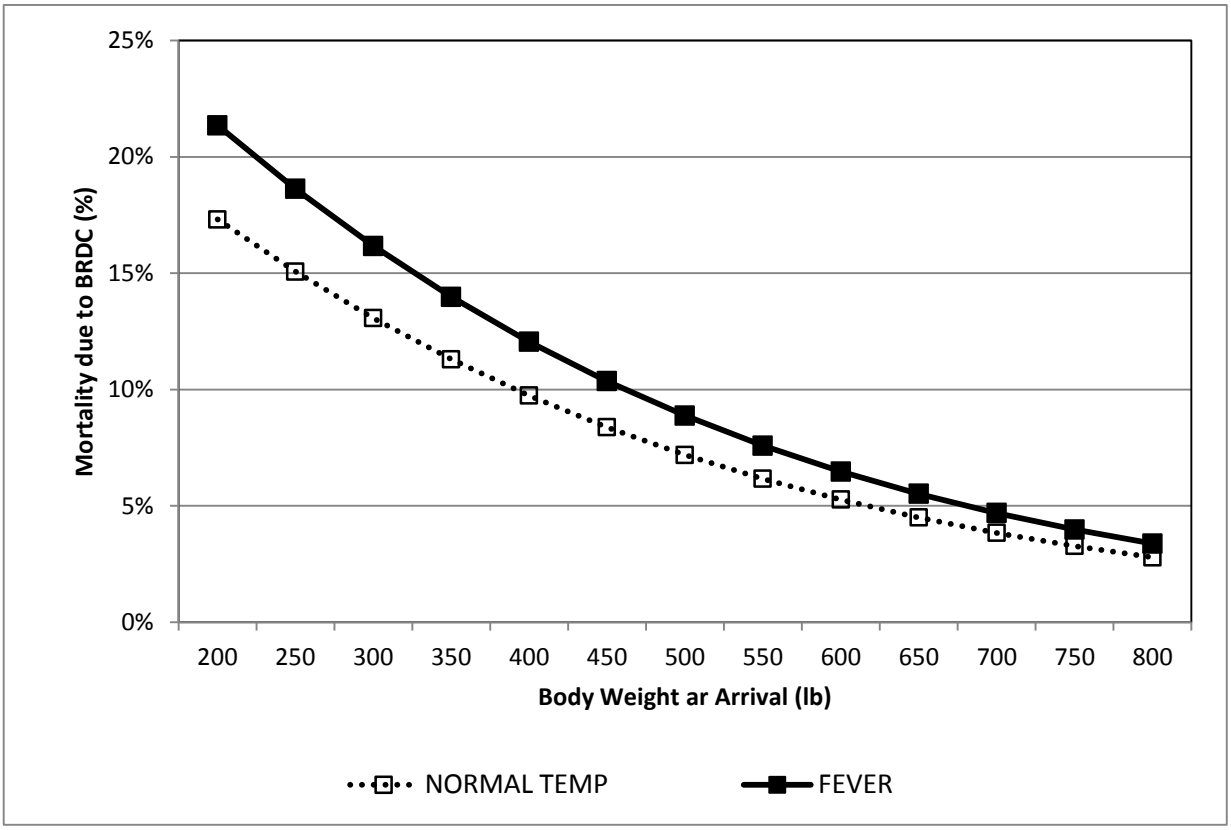


Figure 4-3 Estimated BRDC mortality rate by IBW at arrival. Rectal temperature status at arrival ($P < 0.01$) and IBW ($P < 0.02$) were associated with BRD mortality. Main effects of castration ($P = 0.04$), rectal temperature status at processing ($P=0.02$), and initial body weight at arrival ($P<0.01$) were associated with BRDC morbidity. NORMAL TEMP (Calves with rectal temperature <104°F) and FEVER (Calves with rectal temperature ≥104°F).



Chapter 5 - Statistical Process Control for monitoring mortality associated with Respiratory Disease Complex in feedlot cattl.

[1]Department of Clinical Sciences, College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506, USA

[3] Department of Animal Sciences and Industry, College of Agriculture, Kansas State University, Manhattan, KS 66506, USA

Introduction

Statistical Process Control (SPC) is a powerful tool for monitoring and controlling processes and outcomes through statistical methods[1]. It has been used for more than 80 years in the manufacturing and human health care industries[2]; however, its application in food animal agriculture has not been extensively implemented[2]. The production systems in the food animal industry are based on standardized operating procedures (SOP) and management practices; SOP outcomes can be easily measured and monitored[2]. Statistical process control can be used for monitoring SOP outcomes, health parameters, and animal performance which would benefit top management and animal care personnel in the feedlot industry to define normal variation, identify abnormal deviations, and make interventions to reduce the negative impact of special extreme cases of variation.

One of the most important SPC tools for monitoring and analysis is the control chart. The foundation of control charts is rooted in the theory of variation, understanding and defining what "normal" variation is, and identifying "special cases" of variation[3]. In livestock, the initial published information about the use of SPC was in the swine industry[4]. In the cattle industry, SPC has been implemented in dairies as a method to control mastitis, milk quality, bulk-tank milk somatic cell counts, and reproductive performance[5]. In beef cattle, SPC has been reported to monitor carcass quality[6], steer weight gain[7], and feeding behavior of newly received calves[8]. However, to our knowledge, no additional SPC reports on beef cattle have been published.

Profitability in cattle operations is affected by economic losses due to animal health conditions and/or animal performance deviations[5]. Developing an SPC system to monitor, evaluate, and analyze health and performance parameters in feedlot cattle will provide a tool to identify and differentiate between "normal" and "abnormal" cases of variation. Hence,

veterinarians and other cattle care personnel can implement interventions to reduce the impact of potential losses and improve animal health and productivity.

Record keeping in feedlot operations is a common practice. Nonetheless, record keeping by itself does not imply that actions will be, or should be, performed to improve health and performance. Experience has shown that SPC principles, in conjunction with other management practices, can be applied in cattle production medicine and can become a very powerful tool for continuous improvement[2]. The objective of this study is to develop control charts based on the SPC principles and other statistical tools to define "normal" variation for mortality due to BRDC in feedlot cattle, and identify, and describe abnormal "special cases of variation".

Material and methods

This study did not use animals; therefore, Animal Care and Use Committee Approval from Kansas State University was not obtained.

Database

This study is a retrospective study of commercial feedlot production data. A total of 359,344 individual animal records from 7 commercial feedlots, 4 located in Kansas (KAN1, KAN2, KAN3, KAN4) and 3 located in Nebraska [NEB1, NEB2, NEB3 [table 1]), were used in the analysis. Data were collected over a period of 32 months (Jan 2009 to Aug 2011). Individual animal records included animal identification, date of arrival, body weight (BW, lb) at arrival, and lot identification. Also, each lot contained information about the source (city & state of origin) and feedlot location. In addition, individual records contained information for mortality due to BRDC (over the entire feeding period). Animals that died due to Acute Interstitial Pneumonia were not included in the analysis. Lot consisted of an identified cohort of animals that arrived at the feedyard from a single source of origin on the same day; however, they may or

may not have been allocated to the same pen; consequently, information from each individual pen was not available.

A total of 96 lots (2,737 animals) were removed from analysis because each lot contained less than 40 animals within each lot. In addition, 23 lots (14,390 animals) were removed because they were considered too large for analysis (containing more than 500 animals per lot). After this consideration, a total of 342,217 animals were included in the analysis. Furthermore, animal gender categorized as "Holstein" or those with "unknown" gender or source were not included in the final dataset. In addition, animals that received metaphylaxis at arrival for control of BRDC were removed from the dataset. Finally, animals with initial BW greater than 1300 lb ("heiferettes") were excluded from the analysis.

Geographical region of origin was categorized as southeast (SE; Alabama, Arkansas, southeast Kansas, Florida, Georgia, Kentucky, Mississippi, Missouri, North Carolina, Tennessee, Virginia, and east-Texas), west (W; Arizona, California, Idaho, Montana, New Mexico, Utah, Washington, Wyoming, and western-Colorado), north east (NE; Illinois, Indiana, Iowa, Minnesota), south central (SC; eastern-Colorado, central and western Kansas, Oklahoma, and west-Texas), north central (NC; Nebraska, North Dakota, South Dakota), and Canada. Length of transportation (miles) was calculated using google maps (www.maps.google.com), and it consisted in the distance between the cities of origin to the feedlot location. In those source-locations where source only was specified as state or country, the city of origin was selected as a central point from the state of interest; as a result, length of transportation was categorized as short haul (SHORT; ≤ 250 mi), medium haul (MEDIUM; between 250 and 550 mi), and long haul (LONG; >550 mi). Furthermore, season of arrival was categorized as winter (WIN; December, January, and February), spring (SPR; March, April, and May), summer (SUM; June,

July, and August), and fall (FALL; September, October, and November). Finally, initial body weight (BW) was categorized as light weight calves (LIGHT; BW ≤ 550 lbs.), medium weight (MEDIUM; BW between 550 lbs. and 750 lbs.), and heavy (HEAVY; BW ≥ 750 lbs.).

Monitoring mortality rate across lots with control charts

Control charts based on time-series graphs were developed for each feedlot to monitor mortality rates across lots, establish control limits, and identify normal and special cases of variation. Typically, in a time-series chart, time (e.g. months, weeks, days, etc.) are marked off on the horizontal axis (x), and the values to monitor (e.g. morbidity and mortality rates) are marked in the vertical (*y*) axis. As a result, time passage in the time series graph is moving from left to right on the horizontal axis. The overall mean ($[\overline{X}]$; known as the central line in the time series chart) is computed using the average of the observations. Traditionally, the upper control limit (UCL) and lower control limit (LCL) are computed using a "three sigma limit" methodology. Consequently, the UCL is computed by multiplying the standard deviation (SD) by a fixed factor of 3.0 and adding the product to the overall mean ($UCL = \overline{X} + [3 \times SD]$); the LCL is obtained by multiplying the standard deviation (SD) by a fixed factor of 3.0 and subtracting the product to the overall ($LCL = \overline{X} - [3 \times SD]$)[9].

In the present study, lots were sequentially numbered by date of arrival to the feedyard and marked off in the horizontal (*x*) axis, like a time-series graph. The values for mortality rates (%) were marked in the vertical (*y*) axis. As a result, a time-series-type chart was used to identify normal variation and special cases of variation (SCV) for mortality rates. The overall mean in these control charts ($\overline{X}$) corresponded to the average mortality rate across all lots within each feedyard, during the entire period of analysis (Jan 2009 to Aug 2011). The upper control limit

(UCL) was computed using the "three sigma limit" methodology, and it was obtained by multiplying the standard deviation (SD) by 3.0 and adding the product to the overall mean [UCL= $\overline{X} + (3.0 \times \text{SD})$]. The overall mortality mean ($\overline{X}$) and standard deviation was computed using Microsoft Excel. The LCL was established at zero mortality rates since this is the lowest meaningful value that was considered normal variation.

Results

A total of 342,217 animals (2,286 lots) were included in the data set. Animals originating in the geographical regions of SE, SC, NC, CANADA, and WEST made up 44% (149,005 animals), 21% (72,298 animals), 14% (49,306 animals), 7% (24,944 animals), and 5% (17,774 animals) of the animals in the dataset (Table 5.1).

In the control charts for monitoring mortality rates across lots within each feedyard, mean mortality rate ($\overline{X}$), standard deviation (SD), and UCL was established for KAN01 ($\overline{X}$ =0.62%; SD=1.76%; UCL=5.59%), KAN02 ($\overline{X}$ =0.13%; SD=0.69%; UCL=2.23%), KAN03 ($\overline{X}$ =1.10%; SD=1.99%; UCL=7.08%), KAN04 ($\overline{X}$ =0.52%; SD=1.02%; UCL=3.60%), NEB01 ($\overline{X}$ =0.21%; SD=0.51%; UCL=1.75%), NEB02 ($\overline{X}$ =0.28%; SD=0.65%; UCL=2.23%), and NEB03 ($\overline{X}$ =0.41%; SD=0.94%; UCL=3.24%) Figures 5.1 – 5.7, table 5.2. Across all locations, special cases of variation (SCV) accounted for less than 2.2% of the total lots placed, thus indicating that at least 97.8% of the lots were considered within the "normal" variation for mortality rate.

For the analysis of geographical region of origin across all feedlot locations, the proportion of placements with lots considered within the limits of "normal" variation for mortality rate ($\overline{X}$)

originated in the SE (43%; $\overline{X}$=0.36%), SC (21%; $\overline{X}$ =0.47%), NC (14%; $\overline{X}$ =0.26%); EAST (9%, $\overline{X}$=0.32%), CANADA (7%; $\overline{X}$ =0.12%) and WEST (5%; $\overline{X}$=0.17%); the proportion of placements from lots considered as SCV originated in the SE (64%; $\overline{X}$=5.54%), SC (11%; $\overline{X}$=9.32%), NC (10%; $\overline{X}$=5.11%); EAST (5%, $\overline{X}$=4.16%), and WEST (11%; $\overline{X}$=4.41%) region; no SCV were identified in CANADA; Table 5.3). The region with the greatest mortality rates was SC ($\overline{X}$ =0.47% and $\overline{X}$ =9.32%, for "normal" and SCV, respectively).

From the analysis of season of arrival across all feedyards, the proportion of placements considered "normal" that arrived on WIN, SPR, SUM, and FALL was 21%, 28%, 28%, and 23%, respectively. For those lots considered SCV, animals arriving in WIN, SPR, SUM, and FALL made up 22%, 11%, 31%, and 36%, respectively. It is important to notice that the proportion of "normal" placements which arrived during the fall was 23%; however, fall placements constituted 36% of SCVs; conversely, "normal" placements arriving during the spring made up 28% of all "normal" placements, but spring placements made up only 11% of SCVs. The mean mortality rate for "normal" cattle was greater during the FALL ($\overline{X}$= 0.45%), than the rest of the seasons (SUM= 35%; WIN=0.34%; SPR = 0.27%), table 5.3.

Across all feedyards, the proportion of LIGHT, MEDIUM, and HEAVY placements which had "normal" mortality was 11%, 52%, and 37%. Lots which were categorized as LIGHT, MEDIUM, and HEAVY made up 31%, 62%, and 6% of lots considered SCV. There was a greater proportion of light weight animals that were considered SCV (31% of the placements) compared with those light weight animals considered "normal" (11% of the placements), and

although HEAVY animals made up 37% of "normal" placements, they only represented 6% of SCV (table 5.3).

For the analysis of distance of transportation (haul) across all feedyards, the proportion of "normal" placements with SHORT, MEDIUM, and LONG haul was 22%, 28%, and 51%, respectively. For the lots considered as SCV, the proportion of SHORT, MEDIUM, and LONG haul was 7%, 27%, and 66% (table 5.3).

Potential Applications

As an example of the application of SPC, 2 feedyard locations, one with the greatest mean mortality rate (KAN02) and another with the lowest mean mortality rate (KAN03), were selected for analysis. Mortality rate was plotted in a single control chart for comparison purposes (figure 5.8). Interestingly, overall mean mortality rate was 8 times greater for KAN03 ($\overline{X}$ =1.10%) than for KAN02 ($\overline{X}$ =0.13%). Likewise, the UCL was greater (3.2 times) for KAN03 (7.08%) compared with KAN02 (2.23%). Surprisingly, in both feedyards, 95% of the placements were originated from the same geographical regions (southeast and south-central) of the U.S. (Table 5.1).

Considering KAN02 as reference feedlot "benchmark", the UCL of 2.23% mortality rate was used in both feedyards to identify "normal" and special cases of variation. With this unique UCL (2.3%) for both feedlots, a new set of lots considered within the limit of "normal" variation and lots considered SCV in feedlot KAN03, whereas lots in the site KAN02 did not change.

With this new UCL in KAN03, a total of 195 lots were considered "normal", and 35 lots (26%) were considered SCV. For those lots considered "normal", the proportion of cattle originating in

EAST, SE, SC, and WEST, was 1%, 51%, 48% and 1%, respectively. In lots considered SCV, cattle originated in SE and SC and accounted for 43% and 53% of the lots.

The proportion of "normal" lots placed in WIN, SPR, SUM, and FALL were 17%, 35%, 29%, and 18%, respectively. For those lots considered SCV, placement during the FALL accounted for 43% of the placements. The proportion of "normal" lots that were considered LIGHT, MEDIUM, and HEAVY were 21%, 50% and 30%, respectively. For those lots classified as SCV, the proportion of LIGHT, MEDIUM, and HEAVY was 25%, 69%, and 6%, respectively. For lots considered "normal", cattle categorized al LIGHT had the greatest mortality rate ($\overline{X}$ =0.57%) and cattle categorized as HEAVY had the lowest mortality rate ($\overline{X}$ =0.26%). For the analysis of distance of transportation, the proportion of "normal" lots categorized as SHORT, MEDIUM, and LONG haul were 7%, 59%, and 33%, respectively. Only MEDIUM (51%) and LONG (49%) haul accounted for lots considered SVC, Table 5.4.

Conclusions

In the present study, the use of a UCL from KAN02 as a "benchmark feedlot" (based on an UCL from a feedyard with the lowest mean mortality rate with similar cattle demographics) was effective in identifying "alarm-signal" lots based on source of origin. One limitation of the present study is that we were unable to categorize death loss at different days on feed after arrival (e.g. 30 days, 60 days, 90 days).

A potential use of SPC in early detection of special cases of variation (extreme mortality and morbidity rates) is through establishing "normal" and UCL for mortality and morbidity rates at target days on feed after arrival. Then, estimation of mortality and morbidities in further stages

of the feeding period can be predicted; this information can be valuable for purchasing, economic, and financial decisions based on health and performance of the cattle.

Literature cited

1. Reneau JK. Process control: Timely feedback for quaity milk production at the farm. National Mastitis Council meeting Proceedings. 2000.

2. Reneau JK. Using statistical process control methods to improve herd performance. Am J Vet Res. 2006;22(1):171.

3. Adeoti OA. On the applications of statistical process control in health care. Nig J of Med. 2009;18(1):25-28.

4. Wrathall AE. Reproductive failure in the pig: Diagnosis and control. Vet Rec. 1977;100(12):230.

5. De Vries A. Application of statistical process control charts to monitor changes in animal production systems. J Anim Sci. 2010;88(13 elect suppl):E11.

6. Pleasants AB. Design and application of a cusum quality control chart suitable for monitoring effects on ultimate muscle pH. N Z J Agric Res. 1998;41(2):235.

7. Sard DM. Dealing with data: The practical use of numerical information--(14), monitoring changes. Vet Rec. 1979;105(14):323-328.

8. Quimby WF. Application of feeding behaviour to predict morbidity of newly received calves in a commercial feedlot. Can Vet J. 2001;81(3):315.

9. Wheeler DJ. Understanding variation. the key to managing chaos. Knoxville, TN: SPC Press; 1993.

Table 5-1 Total number of animals and proportion (%) of animals that were placed in 7 commercial feedyards (located in Kansas and Nebraska) that arrived between January 2009 through August 2011 from different geographical regions[1] of origin categorized as CANADA, EAST, NC (north-central), SC (south-central), SE (southeast), and WEST.

	Total number of animals placed at feedlot, according region of origin						
LOCATION	**CANADA**	**EAST**	**NC**	**SE**	**SC**	**WEST**	**Total**
KS01	----------	71	48	12,436	34,686	----------	47,241
KS02	----------	85	----------	15,941	7,390	1,179	24,595
KS03	----------	131	----------	12,060	16,373	189	28,753
KS04	----------	2,203	3,569	51,217	9,152	3,920	70,061
NEB1	22,837	5,173	29,670	448	717	1,139	59,984
NEB2	2,107	5,095	14,497	1,872	534	11,347	35,452
NEB3	----------	16,132	1,522	55,031	3,446	----------	76,131
Total (animals)	**24,944**	**28,890**	**49,306**	**149,005**	**72,298**	**17,774**	**342,217**

	Proportion (%) of animals placed at feedlot, according region of origin						
LOCATION	**CANADA**	**EAST**	**SC**	**SE**	**SC**	**WEST**	**Total (%)**
KS01	----------	0	0	26	73	----------	100
KS02	----------	0	----------	65	30	5	100
KS03	----------	0	----------	42	57	1	100
KS04	----------	3	5	73	13	6	100
NEB1	38	9	49	1	1	2	100
NEB2	6	14	41	5	2	32	100
NEB3	----------	21	2	72	5	----------	100
Total (%)	**7**	**8**	**14**	**44**	**21**	**5**	**100**

[1] Region of origin was categorized as southeast (SE; Alabama, Arkansas, Florida, Georgia, Kentucky, Mississippi, Missouri, North Carolina, Tennessee, Virginia, and east-Texas), west (WEST; Arizona, California, Idaho, Montana, New Mexico, Utah, Washington, Wyoming, and western-Colorado), north east (NE; Illinois, Indiana, Iowa, Minnesota), south central (SC; western-Colorado, Kansas, Oklahoma, and west-Texas), north central (NC; Nebraska, North Dakota, South Dakota), and Canada.

Table 5-2 Mean mortality rate (%) and corresponding standard deviation (SD, [%]), upper control limit (UCL, [%]), special cases of variation (SCV, [lots]), total number of lots placed and proportion of lots identified as SCV in 7 feedyards located in Kansas and Nebraska.

LOCATION	Mean[1]	SD[2]	UCL[3]	SCV[4]	Total lots	Proportion of lots SCV[5]
KS01	0.62	1.76	5.89	7	320	2.2
KS02	0.13	0.69	2.23	6	286	2.1
KS03	1.10	1.99	7.08	4	230	1.8
KS04	0.52	1.02	3.6	13	572	2.3
NEB1	0.21	0.51	1.75	2	315	0.6
NEB2	0.28	0.65	2.23	4	219	1.8
NEB3	0.41	0.94	3.24	21	942	2.2

[1] Mean = Average of mortality rate across all lots
[2] SCV = Special cases of variation (mean mortality rate > UCL)
[3] SD = Standard deviation
[4] UCL = Upper Control Limit (Mean + [SD × 3])
[5] Proportion of SCV (number of SCV [lots] divided be the total number of lots within each feedlot)

Table 5-3 Placements categorized as "normal" or special cases of variation (SCV) that arrived to 7 feedlots located in Kansas and Nebraska, categorized by region of origin[1] (Canada, east, north-central, south-central, and west) season of arrival[2] (WIN, SPR, SUM, and FALL), initial BW (LIGHT [BW ≤ 550 lb], MEDIUM [BW between 550 lb and 750 lb], or HEAVY [BW > 750lb]), and distance of transportation (SHORT, ≤ 250 mi; MEDIUM; between 250 and 550 mi, and LONG > 550 mi).

	Placements categorized as normal (mortality rate < UCL)				Placements categorized as SCV (mortality rate ≥ UCL)			
	Number of animals placed	Percent of normal lots placed	# of lots placed	Mean percent mortality (%)	Number of animals	Percent of SCV lots	# of lots	Mean percent mortality (%)
CANADA	24,944	7	134	0.12	------	------	--	------
EAST	28,629	9	267	0.32	261	5	3	4.16
NC	48,765	14	294	0.26	541	10	4	5.11
SE	145,473	43	1507	0.36	3,532	64	41	5.54
SC	71,698	21	521	0.47	600	11	5	9.32
WEST	17,183	5	105	0.17	591	11	5	4.41
TOTAL	336,692	100	2828	0.35	5,525	100	58	5.67
WIN	71,254	21	552	0.34	1,196	22	12	5.10
SPR	94,123	28	812	0.27	618	11	7	5.62
SUM	93,849	28	829	0.35	1,733	31	19	6.27
FALL	77,466	23	635	0.45	1,978	36	20	5.44
TOTAL	336,692	100	2828	0.35	5,525	100	58	5.67
LIGHT	37,797	11	390	0.42	1,736	31	18	5.15
MEDIUM	173,787	52	1478	0.40	3,447	62	35	5.97
HEAVY	125,108	37	960	0.23	342	6	5	5.42
Total	336,692	100	2828	0.35	5,525	100	58	5.67
SHORT	72,670	22	1597	0.32	395	7	41	5.69
MEDIUM	93,247	28	688	0.44	1,488	27	14	5.87
LONG	170,775	50	543	0.32	3,642	66	3	4.32
Total	336,692	100	2828	0.35	5,525	100	58	5.67

[1] Region of origin was categorized as southeast (SE; Alabama, Arkansas, Florida, Georgia, Kentucky, Mississippi, Missouri, North Carolina, Tennessee, Virginia, and east-Texas), west (WEST; Arizona, California, Idaho, Montana, New Mexico, Utah, Washington, Wyoming, and western-Colorado), north east (NE; Illinois, Indiana, Iowa, Minnesota), south central (SC; western-Colorado, Kansas, Oklahoma, and west-Texas), north central (NC; Nebraska, North Dakota, South Dakota), and Canada.

[2] Season was categorized as winter (WIN), spring (SPR), summer (SUM), and fall (FALL)

Table 5-4 Placements categorized as "normal" or special cases of variation (SCV) that arrived at 2 feedlots located in Kansas (KAN02 and KAN03) categorized by region of origin[1] (east, southeast, south-central, and west) season of arrival[2] (WIN, SPR, SUM, and FALL), initial BW (LIGHT [BW≤550 lb], MEDIUM [BW between 550 lb and 750 lb], or HEAVY [BW > 750lb]), and distance of transportation (SHORT, ≤250 mi; MEDIUM; between 250 and 550 mi, and LONG>550 mi).

	Placements categorized as normal in KAN03 (mortality rate < UCL)				Placements categorized as SCV in KAN03 (mortality rate ≥ UCL)			
	Number of animals placed	Percent of normal lots placed	# of lots placed	Mean percent mortality (%)	Number of animals placed	Percent of normal lots placed	# of lots placed	Mean percent mortality (%)
EAST	131	1	1	0.76		-		-
SE	10,405	51	99	0.41	1655	43	15	4.2
SC	13,041	48	93	0.61	3332	57	20	4.7
WEST	189	1	2	-		-		-
TOTAL	23,766	100	195	0.50	4,987	100	35	4.4
				-				-
WIN	4,064	17	34	0.40	929	17	6	3.4
SPR	8,104	35	69	0.46	593	14	5	5.1
SUM	6,522	29	57	0.67	2,388	43	15	4.2
FALL	5,076	18	35	0.41	1,077	26	9	5.2
TOTAL	23,766	100	195	0.50	4,987	100	35	4.4
				-				-
LIGHT	4,683	21	40	0.57	1,222	26	9	3.7
MEDIUM	12,258	50	97	0.61	3,589	69	24	4.8
HEAVY	6,825	30	58	0.26	176	6	2	3.0
Total	23,766	100	195	0.50	4,987	100	35	4.4
				-				-
SHORT	2,069	7	14	0.15	----	----	----	----
MEDIUM	14,387	59	116	0.54	2,579	51	18	3.9
LONG	7,310	33	65	0.50	2,408	49	17	5.0
Total	23,766	100	195	0.50	4,987	100	35	4.4

[1] Region of origin was categorized as southeast (SE; Alabama, Arkansas, Florida, Georgia, Kentucky, Mississippi, Missouri, North Carolina, Tennessee, Virginia, and east-Texas), west (WEST; Arizona, California, Idaho, Montana, New Mexico, Utah, Washington, Wyoming, and western-Colorado), north east (NE; Illinois, Indiana, Iowa, Minnesota), south central (SC; western-Colorado, Kansas, Oklahoma, and west-Texas), north central (NC; Nebraska, North Dakota, South Dakota), and Canada.

[2] Season was categorized as winter (WIN), spring (SPR), summer (SUM), and fall (FALL)

Figure 5-1 Control Chart for mortality rate (percent) by lot number (sequentially numbered by arrival date; n=320 lots [47,241 animals]) within a commercial feedlot located in Kansas (KAN1); placed from February 2010 through August 2011)). Mean mortality rate = 0.6%, SD=1.8%, and upper control limit (i.e. Mean + 3 SD) = 5.9%

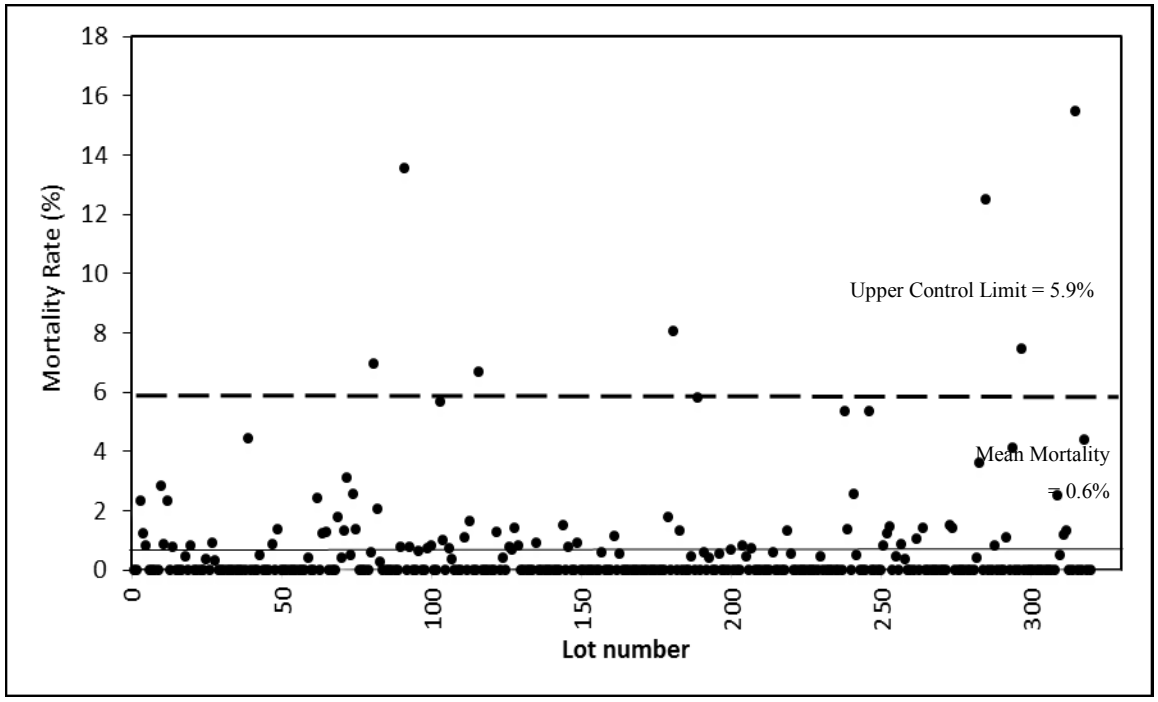


Figure 5-2 Control Chart for mortality rate (percent) by lot number (sequentially numbered by arrival date; n=286 lots [24,595 animals]) within a commercial feedlot located in Kansas (KAN2); placed from January 2009 through July 2011)). Mean mortality rate = 0.2%, SD=0.7, and upper control limit (i.e. Mean + 3 SD) = 2.2%

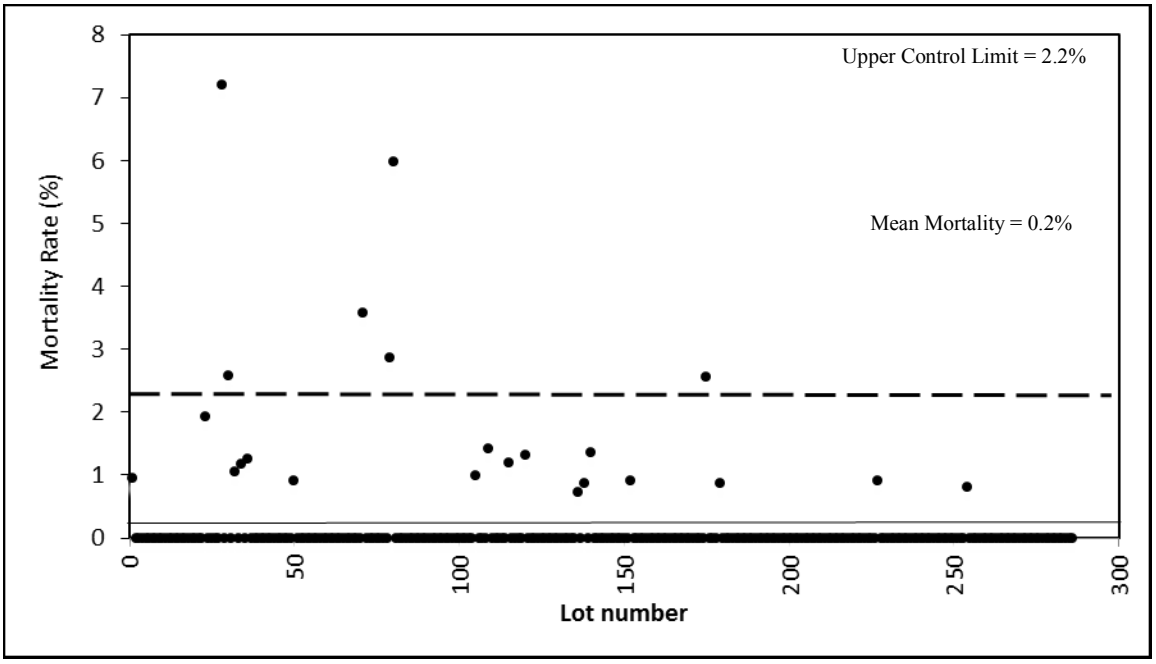


Figure 5-3 Control Chart for mortality rate (percent) by lot number (sequentially numbered by arrival date; n=219 lots [27,328 animals]) within a commercial feedlot located in Kansas (KAN3); placed from October 2009 through July 2011)). Mean mortality rate = 1.1%, SD=2.0, and upper control limit (i.e. Mean + 3 SD) = 7.1%

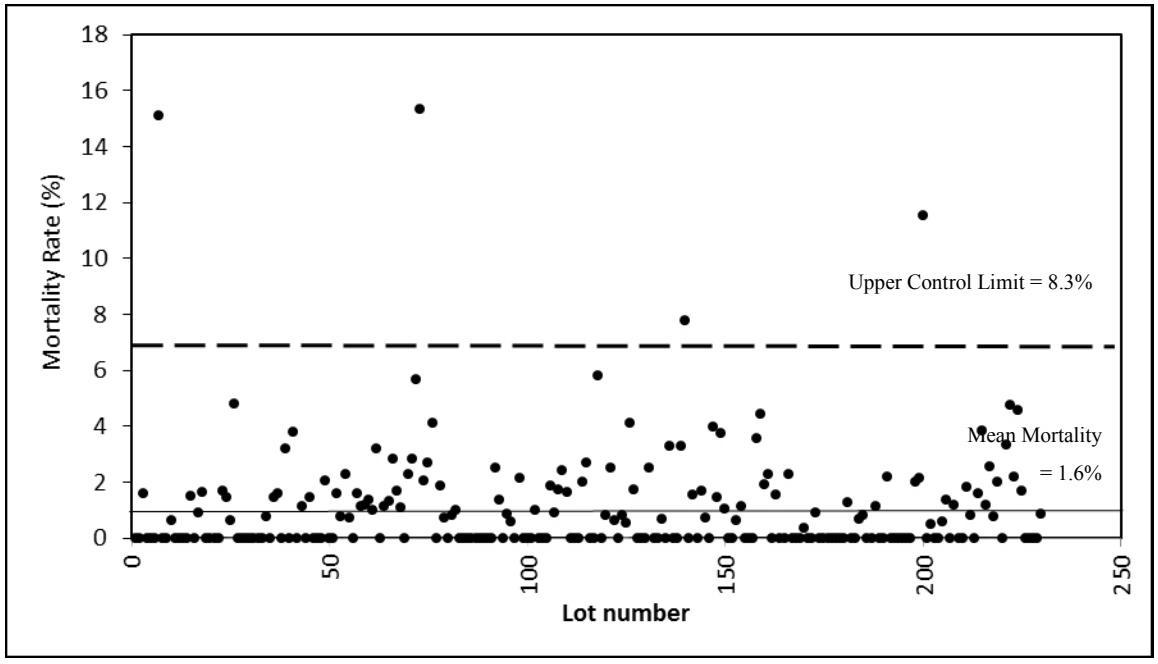


Figure 5-4 Control Chart for mortality rate (percent) by lot number (sequentially numbered by arrival date; n=572 lots [70,010 animals]) within a commercial feedlot located in Kansas (KAN4); placed from January 2009 through June 2011)). Mean mortality rate = 0.5%, SD=1.0, and upper control limit (i.e. Mean + 3 SD) = 3.6%

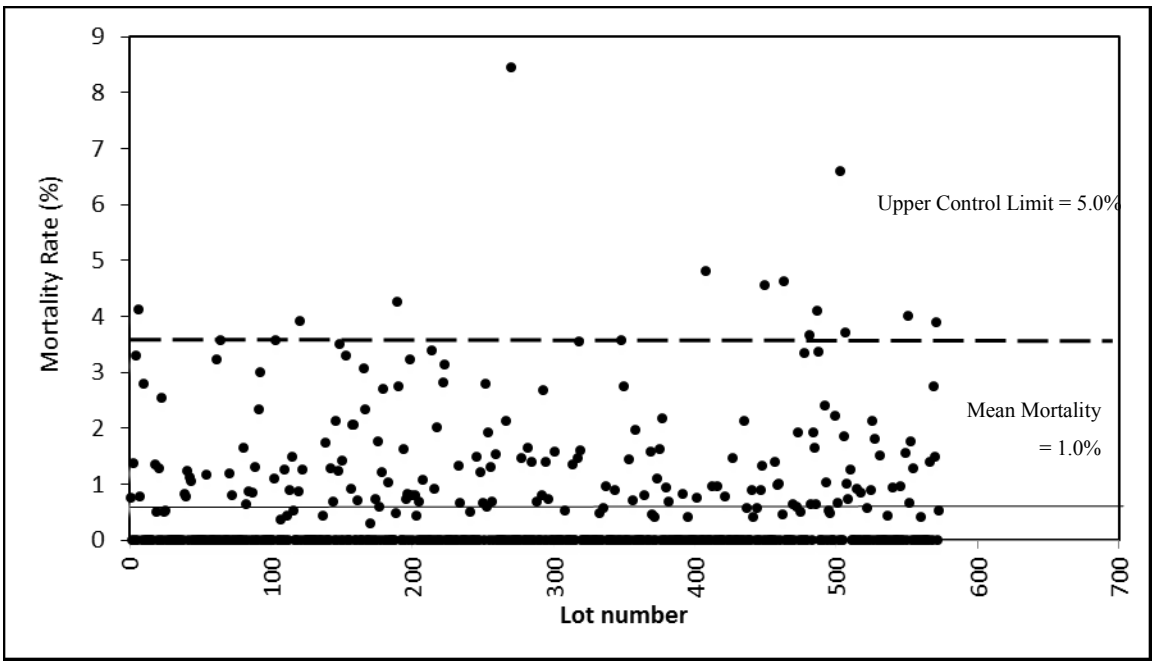


Figure 5-5 Control Chart for mortality rate (percent) by lot number (sequentially numbered by arrival date; n=315 lots [59,984 animals]) within a commercial feedlot located in Nebraska (NEB1); placed from January 2009 through May 2011)). Mean mortality rate = 0.2%, SD=0.5, and upper control limit (i.e. Mean + 3 SD) = 1.8%

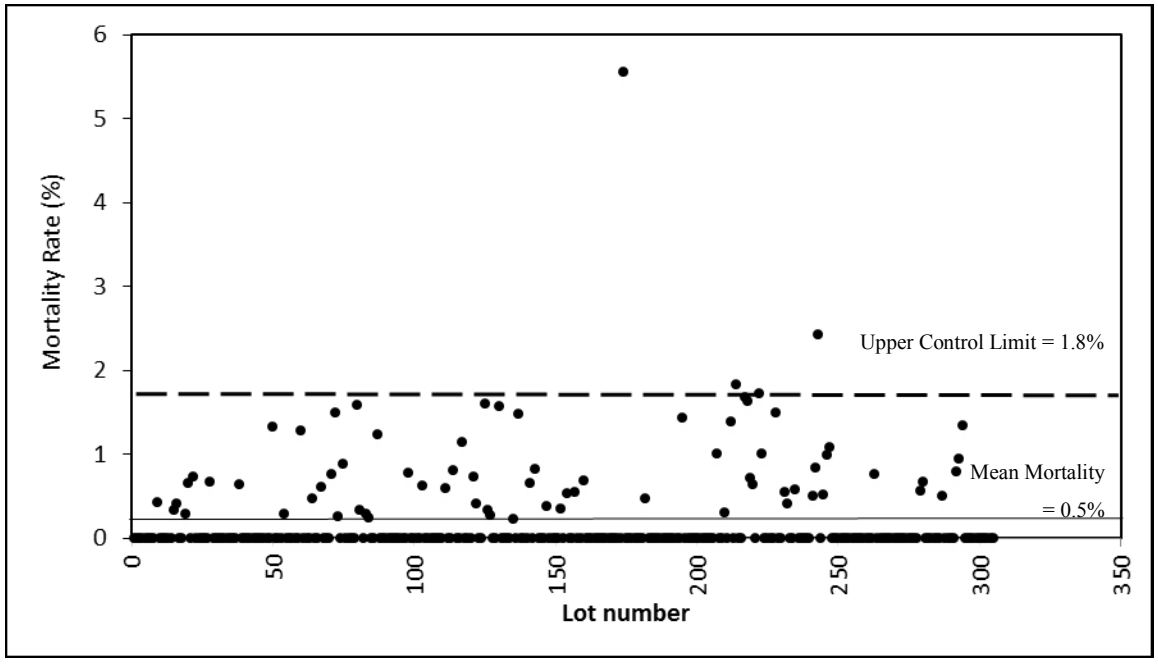


Figure 5-6 Control Chart for mortality rate (percent) by lot number (sequentially numbered by arrival date; n=219 lots [35,452 animals]) within a commercial feedlot located in Nebraska (NEB2); placed from January 2009 through June 2011)). Mean mortality rate = 0.4%, SD=0.9, and upper control limit (i.e. Mean + 3 SD) = 3.2%

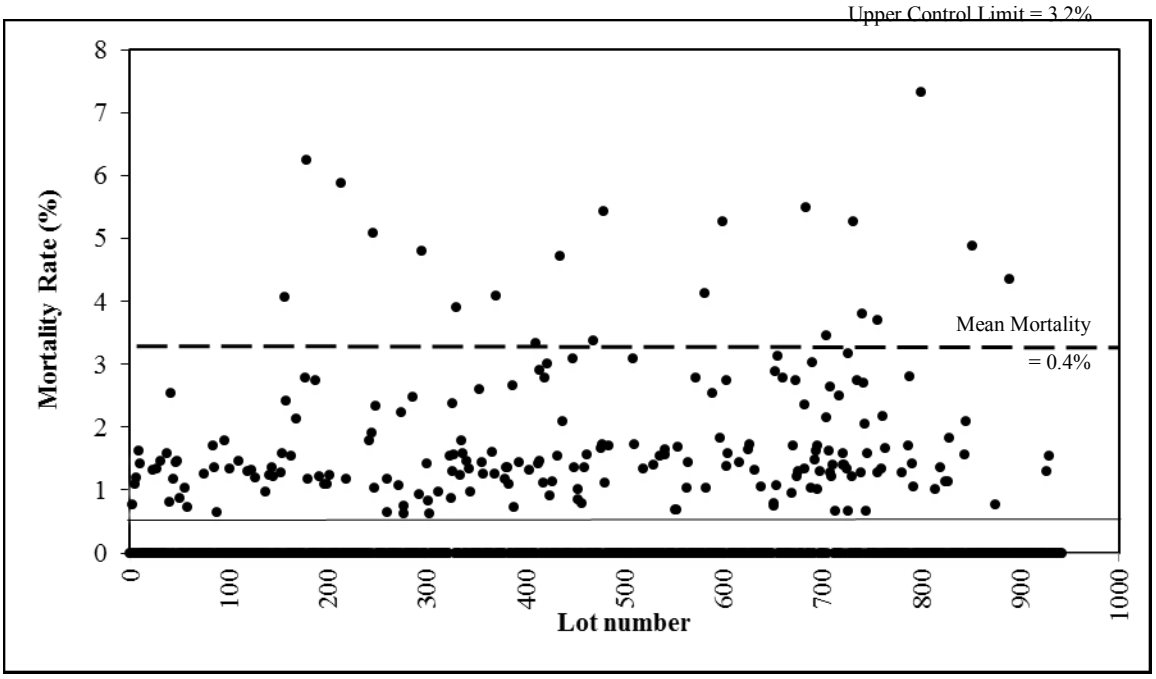


Figure 5-7 Control Chart for mortality rate (percent) by lot number (sequentially numbered by arrival date; n=943 lots [42,266 animals]) within a commercial feedlot located in Nebraska (NEB3); placed from January 2009 through July 2011)). Mean mortality rate = 0.4%, SD=0.9, and upper control limit (i.e. Mean + 3 SD) = 3.2%

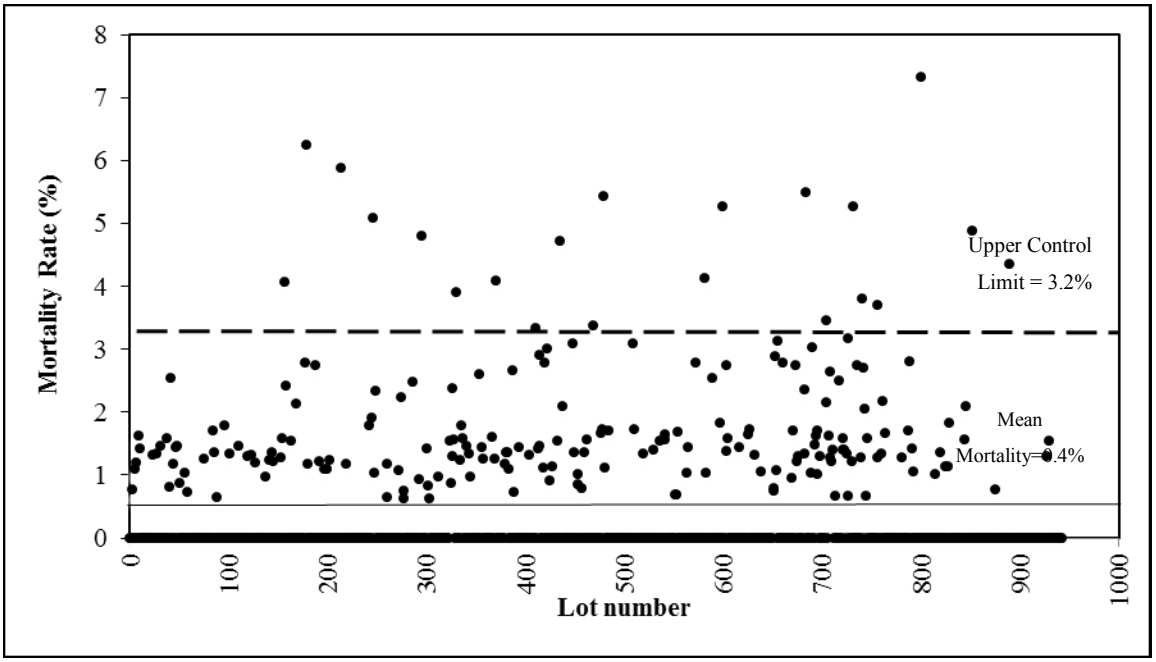
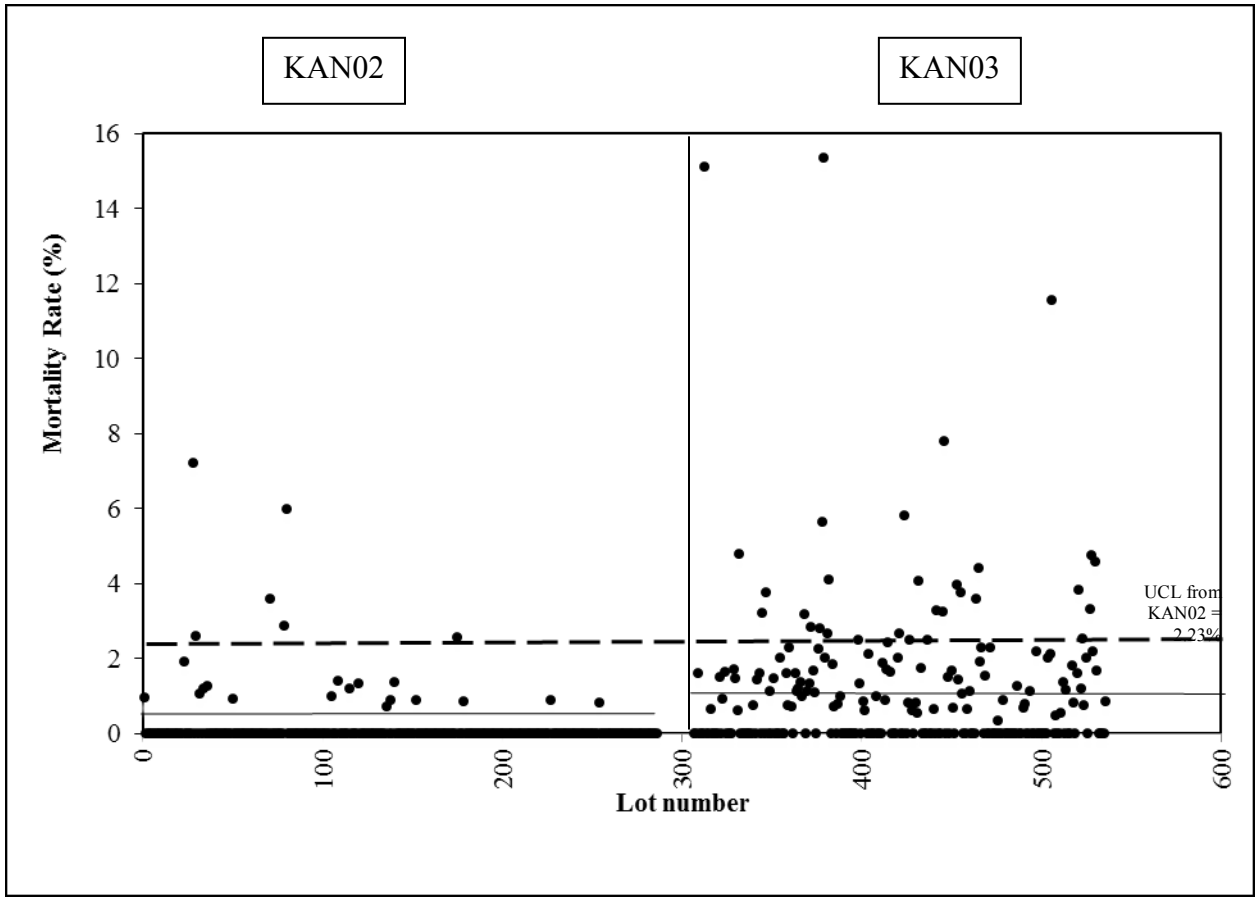


Figure 5-8 Control Chart for mortality rate (percent) by lot number (sequentially numbered by arrival date) within two commercial feedlots located in Kansas (KAN02 [n=286 lots (24,595 animals); and KAN03 [n=219 lots [27,328 animals]); placed from January 2009 through July 2011). Mean mortality rate was less in KAN02 ($\overline{X}$=0.13%; SD=0.69; UCL = 2.23%) compared with KAN03 ($\overline{X}$=1.10%; SD=1.99; UCL = 7.08%).



Appendix A - Clinical Score Scale for animals with BRDC

Score	Description
0	Normal: Nothing unusual in animal's attitude and no abnormal respiratory symptoms present.
1	Mild depression (somewhat slow coming to feed bunk, but did eat). Mild respiratory symptoms present; serous nasal or ocular discharge and/or cough.
2	Moderate depression (slight head/ears dropping, reluctant to move about, reluctant to come to the feed bunk). Moderate respiratory distress: Mucosus or mucopurulent nasal or ocular discharge and/or increase in respiratory rate or effort.
3	Severe depression (pronounced head/ear droop' very reluctant to move). Severe respiratory distress: marked increase in respiratory rate or effort including: open mouth breathing, abdominal breathing, or extended head)
4	Moribund