Predictive analytics and data management in beef cattle production medicine

by

Kaitlynn M. Abell

B.S., University of Florida, 2010
D.V.M., University of Florida, 2014

AN ABSTRACT OF A DISSERTATION

Submitted in partial fulfillment of the requirements for the degree

DOCTOR OF PHILOSOPHY

Department of Diagnostic Medicine and Pathobiology
College of Veterinary Medicine

KANSAS STATE UNIVERSITY
Manhattan, Kansas

2017

Abstract

Utilization of data analytics allows for rapid and real-time decision making in the food animal production industry. The objective of my research was to implement and utilize different data analytic strategies in multiple sectors of the beef cattle industry in order to determine management, health, and performance strategies.

A retrospective analysis using reproductive and genomic records demonstrated that a bull will sire a larger number of calves in a multiple sire-pasture compared to other bulls in the same pasture. A further study was performed to determine if behavior differences existed among bulls in a multiple-sire pasture, and the ability of accelerometers to predict breeding behaviors. Machine learning techniques used classifiers on accelerometer data to predict behavior events lying, standing, walking, and mounting. The classifiers were able to accurately predict lying and standing, but walking and mounting resulted in a lower predictable accuracy due to the extremely low prevalence of these behaviors.

Finally, a new form of meta-analysis to the veterinary literature, a mixed treatment comparison, was able to accurately identify differences in metaphylactic antimicrobials on outcomes of bovine respiratory disease morbidity, mortality, and retreatment morbidity. The meta-analysis was not successful in determining the effects of metaphylactic antimicrobials on performance outcomes.

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Dedication

I dedicate this to my husband, Bobby.

Chapter 1 - A review of analytical methods for utilizing data for health and performance outcomes in the beef cattle industry

Introduction

Data are collected at an exponentially increasing rate from all aspects of the food animal industry, including the animal health and production sectors of the beef cattle industry. Group-level as well as individual-level data are collected and recorded daily throughout the industry. Emerging advances in data management and predictive analytics allow data to be transformed to aid quick and accurate operational and management decisions. Improved decision making can directly affect cattle health and performance thereby increasing overall profitability and efficiency of cattle operations.

Big Data analytics has become widely established in the human health industry, and analytical advances from this industry can be directly utilized in the food animal industry. This review will describe how data analytic methods are currently utilizing Big Data in the human and cattle industries.

Defining Big Data

The term Big Data is quickly being recognized in food animal veterinary medicine and this term is already being used extensively in the human health industry. The context-specific definition of Big Data is dependent on the industry of application. Currently, Big Data is defined based on volume, velocity, variety, and veracity of the dataset (Gandomi & Haider, 2015; Lycett, 2013).

Volume refers to the scale, magnitude, or quantity of data collected and analyzed, and data volume is currently measured in terabytes, exabytes, zetabytes, or pentabytes (Erevelles et

al., 2016; Gandomi & Haider, 2015; Kruse et al., 2016). A single volume threshold does not define Big Data across disciplines and applications, based on the variability in types of data that are collected. Also, based on expected technology advancements, what is deemed to be Big Data today, may not in fact be Big Data in a few years (Gandomi & Haider, 2015).

Velocity describes the need for real-time analysis of data based on the speed data are being collected, and speed of decisions. However in some industries, current speed of analysis and dissemination of results may not achieve the velocity desired (Kruse et al., 2016). This is very apparent in the food animal industry, where the structure and nature of the industry allows for immediate data recording, but not immediate analysis of data because of deficiencies within the current data analysis infrastructure.

Variety within Big Data datasets is based on the different forms and heterogeneity of the data within the data set. Data can be structured (e.g. spreadsheets and databases), unstructured (e.g. images and video), or semi-structured (Erevelles et al., 2016; Gandomi & Haider, 2015). An example of structured Big Data in the food animal industry would be USDA market reports of all cattle procured on a single day. Unstructured data such as pathology images are often harder to analyze based on lack of clearly identified organizational structure for the data.

Veracity is a recent term that has been used when defining Big Data, and it refers to the overall quality of the data, and the need to be cognizant of where the data originated. If data arises from human entry, the chance for error could increase which would decrease the quality of that data. Understanding potential sources for noise within a dataset is crucial when attempting to quantify patterns, trends, and outcomes.

Causal vs. Predictive Modeling

Before evaluating the different analytical methods for Big Data, the purpose of modeling outcomes needs to be divided into two categories, causal and predictive modeling. Causal modeling is defined as identifying potential causal associations between exposures and outcomes of interest (Dohoo et al., 2009). The goal of modeling for causal relationships is to determine how an independent variable affects the outcome or dependent variable, and determine the magnitude of effect of the relationship. Multicollinearity is a major concern that must be addressed when attempting casual modeling, because the goal is to obtain unbiased estimates of the coefficients.

Predictive modeling is performed to either predict future observations or understand relationships between predictors and an outcome of interest (Dohoo et al., 2009). Multiple variables are utilized to understand their relationship with the outcome of interest. Multicollinearity is tolerated more in predictive modeling, because it is modeling the prediction of the outcome of interest, and not as concerned with the individual coefficients estimates themselves, as it is in causal modeling.

An assumption of linear mixed models is that the variance components are homogeneous and constant across environments (Kutner et al., 2005). This assumption is valid when working with unadjusted or raw hierarchical data in livestock and human health systems, if the hierarchical structure is accounted for in the mixed model. Other predictive and causal modeling methods have the ability to model hierarchical or multilevel data sets as well as repeated measures data. Proper modeling of the heterogeneous variances can allow for greater accuracy of estimating mean differences, as well as identifying possible levels of production that could benefit from different management factors.

Analytical Methods

Statistical models

The statistical approach used in big data analysis needs to be appropriate based on the data structure, distribution, and desired outcomes (White et al., 2016). Regression modeling is a type of statistical estimation that can be performed for both causal and prediction models. In terms of Big Data, multivariable regression modeling has the advantage of utilizing as much of the data set as possible in order to predict an outcome, and to understand relationships between variables of interest with the outcome (Dohoo et al., 2009). For example, regression techniques can allow estimation of the effect of a one unit change in an independent variable x on a dependent variable y (Dohoo et al., 2009). Hierarchical data also can be accounted for with multivariable modeling, which is important because most biological datasets have some form of hierarchical structure (Dohoo, 2008).

Statistical software programs such as SAS (SAS Institute Inc., Cary, NC, USA), Minitab (Minitab Inc., State College, PA), or STATA (Statacorp LP, College Station, TX), can be used to perform statistical analysis on a given dataset. Prior to model building and statistical analysis, a given dataset needs to be structured and managed so that desired models can be built to predict outcomes with the highest possible accuracy. Programs such as Excel (Microsoft Corp., Redmond, WA), International Business Machines Corporation (IBM) Watson Analytics (IBMWA), SAS, STATA, and JMP (SAS Institute Inc., Cary, NC, USA) can allow for exploration of a dataset to discern possible distributions, trends, and patterns that may be worth exploring further in the model building process.

Machine learning

Machine learning is another form of statistical analysis that can predict outcomes based on algorithms created from large datasets (Hsu, 2006). A decision tree is a type of machine learning, and will incorporate a large data set, and splits the dataset based on desired outcomes (Gladwin, 1989). The decision to split the data a certain way are based on rules that maximize the outcome for the split data. The splitting is repeated multiple times, until the split data have the highest accuracy for predicting the desired outcome. For example, imagine a data set from a group of children in a classroom, and the outcome of interest is running or walking at recess. The independent variables used to predict the outcome of running or walking for each child includes knowing if the child is wearing tennis shoes, on a track team, the number of calories consumed at lunch, and enjoyment of running. The splitting of the dataset will be determined based on the number of yes and no answers within that dataset for the particular independent variables, in order to accurately predict the outcome. The decision tree algorithm may split the data first based on the child wearing tennis shoes, and determine that 80% of the students who are wearing tennis shoes, are going to run at recess. The next split will occur based on that 80%, and 40% of the 80% of children are on a track team, and so forth until the highest accuracy to predict running at recess is accomplished. An example as the one described is a very simple decision tree, but the basic principle can be extrapolated to demonstrate the value of a machine learning algorithm to enable complex splitting of Big Data datasets to determine real-time outcomes efficiently in a production setting.

Software programs containing machine learning methods include Knime Analytics, R (R Core Team, Vienna, Austria), and Insightful miner (Insightful Corp., Seattle, WA). Each program can be tailored based on the level of predictability needed for a given dataset. Predicting

an outcome with machine learning is different from regression techniques. Machine learning cannot make causal inferences or associations between the independent variables and dependent variable, whereas statistical models can model casual relationships. Although statistical estimation and modeling is used within machine learning, unlike statistical models, machine learning does not require basic assumptions about the data structure. For example, the distribution of the dependent and independent variables does not need to be known prior to algorithm building.

Machine learning has the ability to work with extremely large datasets to learn from millions of observations and to learn and predict simultaneously on those observations. A random forest classifier is similar to, but is more advanced than the decision tree in the ability to predict and learn. A random forest classifier learns in more ways than just simple splitting of single variables, as described in the example with the children running at recess (Breiman, 2001). Machine learning uses multiple iterations to learn and predict patterns within the dataset. Machine learning has a large range of analysis possibilities that go beyond the prediction of outcomes based on data collected in research trials (Boulesteix & Schmid, 2014). Machine learning has the ability to analyze data collected from social networks, audio, video, finance, marketing, and education (Gandomi & Haider, 2015).

Bayesian analysis

Bayesian methods add the consideration of prior probability in statistical analysis in order to model an outcome affected by known and unknown information. Bayesian analysis allows for probabilistic modeling of uncertainty around unknown parameters. The probability is deduced based on the true underlying nature of the parameter (Freedman, 1996). Bayesian analysis is also beneficial when evaluating diagnostics tests, when there is not a present gold standard (Dohoo,

2008). As with the earlier description of multivariable modeling methods, Bayesian analysis also has the ability to deal with the challenge of spatial and temporal clustering of hierarchical data. Bayesian methods are also available to be used for complex meta-analyses, which is currently practiced in the human health industry, and just becoming utilized in the veterinary medicine and the cattle industry (Dohoo et al., 2007). Bayesian analysis can be performed using the software programs previously discussed with statistical models and machine learning techniques.

Utilization in the Human Health Industry

The term Big Data was first introduced to the human health industry as recently as 2011 (Gandomi & Haider, 2015). The advancement of Big Data in the human health industry has been aided by initiatives by the International Business Machines Corporation (IBM) and other leading technology companies. Watson Analytics was released by IBM which has created platforms for quick visualization, data quality analysis, and statistical approaches for large data sets (Hoyt, Snider, Thompson, & Mantravadi, 2016). Federal government involvement has helped to increase the utilization and benefit of Big Data analytics in the health industry by providing provisions such as the Health Information Technology for Economic and Clinical Health (HITECH) component of the American Recovery and Reinvestment Act (ARRA) (Kruse et al., 2016; Services, 2010; Ward et al., 2014). The Act allows for billions of dollars in incentives for use of information technology in the health industry. The U.S. government also created a program to contribute millions of U.S. dollars to states that participate in the Health Information Exchange (HIE) Challenge Grant Program (Kruse et al., 2016; Services, 2011). The government incentives along with the platforms to analyze the data has led to sources of health care Big Data from the genomic industry, Electronic Health Records (EHR), medical monitoring and wearable devices, Laboratory Information Management Systems (LIMS), insurance claims and billing,

pharmacy, real-time locating systems, Radio Frequency Identification (RFID), and smartphone apps (Kruse et al., 2016; Ward et al., 2014).

Currently, Big Data in the human health industry is being used extensively in the field of genomics. A government funded initiative, Electronic Medical Records and Genomics (eMERGE) Network, uses EHR and DNA repositories of individual human DNA to identify underlying genetic factor information to incorporate into routine healthcare (McCarty et al., 2011). Big Data analytics is also being used to help determine cost effectiveness of treatments and medical policies. This form of research is called comparative effectiveness (CE) and is currently used in the medical health insurance field (Ward et al., 2014). Hospitals have demonstrated the benefits of Big Data analytics by decreasing health care costs, adverse health events, and patient readmissions, but have also been challenged by lack of analyst experience and high development cost of the analytics (Schaeffer, Booton, Halleck, Studeny, & Coustasse, 2016).

Predictive analysis algorithms have been used to predict and classify Diabetes Mellitus in humans and to provide a systematic way to determine availability and affordability of healthcare services to a specific population (Kumar et al., 2015). A specialized web portal has been created with the use of classification, regression, time series, and association algorithms to determine key performance indicators for particular supply chains in business networks (Stefanovic, 2014). Predictive algorithms can be continually evaluated and validated through the analysis of large datasets provided by outcomes collected over the following month, quarter, or year. Research within the specialty of emergency care was investigated for the potential benefit of Big Data analytics in the form of Bayesian networks, decision tree learning, and Markov and Monte Carlo simulations to improve decision making that enhances health care, improves meeting of patients'

needs, and increases cost-effectiveness (Janke et al., 2016). One issue that become apparent from early emergency care analysis was that data from this specialty may be error-filled and highly variable due to coming from disconnected data elements (Janke et al., 2016). Predictive analytics allow for an added tool of validation when the data sets are large enough to partition data to evaluate the models for clinical practice.

Technology, such as Radio-Frequency Identification (RFID) enhances the capability for real-time data management and analytics (Kruse et al., 2016; Ward et al., 2014). This technology is currently being used to track human patients admitted to a hospital, as well as to track paramedics and patients when a mass casualty event has taken place (Yu et al., 2010; Yu & Ganz, 2011). The use of a sensor-enabled low frequency RFID has been explored to enable identification of blood glucose levels in a diabetic patient (Moore, 2009). Technology such as RFID has the potential to not only provide real-time analytics, but also provide a large data base for the human health industry (Ward et al., 2014).

Utilization in the Cattle Industry

Big Data utilization in the beef cattle industry is currently a novel practice. The infrastructure of the beef industry is extremely diverse and disconnected, creating challenges for utilization of Big Data analytics compared to the human health industry.

Cow-calf operations that have 1 to 99 beef cows account for 90.4% of all farms with beef cows in the United States (USDA, 2011b). The low number of beef cows per farm leads to much of the variability that exists in cow-calf operations. Substantial heterogeneity exists among these different groups of animals based on environment, genetics, and management practices. Multivariable modeling can be used to assess where heterogeneity exists within a given production system. For example, comparing one facility system to another using multivariable

modeling can demonstrate how facility variation contributes to overall cow health and behavior (Simon et al., 2016).

Unlike the cow-calf and feedlot industries, the dairy industry has taken initiative to create large data banks for dissemination of information within the industry. The Animal Improvement Programs Laboratory collects data from dairy animals in order to improve efficiency through genetic evaluation and management characterization (USDA, 2014). The data from this system has allowed multiple research publications to report predictions on fertility, purchasing, culling, and estimated breeding value decisions (Mikshowsky et al., 2017; Tenghe et al,, 2016). The dairy industry is more integrated compared to the beef industry due to the structure of the industries themselves. In the beef cattle industry, animals can change ownerships multiple times throughout their life, whereas in the dairy industry, one calf may remain with the same owner or on the same farm throughout its lifetime. Despite inherent challenges, the beef cattle industry must continue to strive to collect quality data, and continue to enhance the productivity and efficiency of the operations.

One form of big data analytics, decision tree modeling, has been demonstrated to detect post-calving health problems in a dairy operation (Steensels et al., 2016). This form of modeling, if utilized in the cow-calf industry, could be very beneficial to predict outcomes such as dystocia, pounds of calf weaned, number of calves weaned per cow exposed for breeding, and the feasibility of the owner of the cow-calf operation retaining ownership of calves all the way though slaughter. In order to use data to model these decisions requires accurate records and a progressive attitude (White, 2005).

Although Big Data has not been utilized as extensively in the beef cattle industry as the human health industry, data mining practices have been reported. Data mining is defined as

extraction of implicit and potentially useful information or exploration and analysis of the data (Tan et al., 2006). Pattern recognition starts with data mining. Data mining takes large amounts of data about cattle health and performance and analyzes it over time to formulate predictions, similar to decision tree modeling (Hsu, 2006). Mining large data sets and analyzing trends and patterns over time has proven to help identify trade communities, shipment patterns, and disease surveillance (Gorsich et al., 2016). Pattern recognition has been used in a feedlot data set to analyze data on morbidity and mortality of feedlot calves to quantify risk factors that can change morbidity and mortality rates even by a few percentage points (Amrine et al., 2014; Moya et al., 2015).

Data from feedlots are considered to be large enough that simple analytics may not be optimal to create predictive outcomes (Cole et al., 2012). Even though predictive abilities exist, many feedlot operations may not be using available data this way, possibly because the amount of gathered data is greater than the current ability to analyze the data. Access to large enough data sets can allow for dataset partitioning in order to create predictive models on specific outcomes. The data can to be transformed to make predictions on how cattle will perform in relation to health and growth (Garcia, 2013). Recently published literature has taken large data sets to predict certain feedlot cattle outcomes such as time to disease events, risk factors for disease, and failure to finish a production cycle due to disease (Babcock et al., 2013; Babcock et al. 2009; Cernicchiaro et al., 2012; Cernicchiaro et al., 2013; Jenko et al., 2017). The data gathered must be accurate to identify potential relationships between variables collected, and lack of concise and accurate data can lead to bias in the results as well as increased error (I. Dohoo et al., 2009).

Tracking animals from one cattle industry operation to another has been discussed in recent years, and could provide a valuable information-driven dataset for the veterinary profession and the food animal industry. In 2006, the USDA announced a voluntary program, National Animal Identification System (NAIS), in order to track cattle to aid animal disease programs and to become a comprehensive information system (USDA, 2006). An information system in this form has proven to benefit the development of machine learning algorithms that accurately and rapidly trace back animals from a mock database (Scanga et al., 2007). A tracking system has proven to be successful in Australia to determine the influence of movement on disease spread in cattle (Iglesias & East, 2015). In the European Union, the National Cattle Register has demonstrated how tracking cattle movements can quantify associations with disease transmissions (Perrin et al., 2010). Technology, in the form of a tracking system, has been a valuable resource for data acquisition in the beef supply chain and a source of transparency for larger corporations in China (Liang et al., 2015).

Tags in the form of simple numbers or as advanced as electronic identification tags (RFID) are currently available to track and record animals in a production system. A successful tracking system utilizing RFID technologies in the cattle industry would be extremely beneficial, but currently lacks economic incentives for producers implementing the technology. In order to be successful, a government incentivized program, similar to the ones established in the human health industry, would be necessary. University of California Davis in 2010 began collecting data from the cattle industry with the use of RFID tags in order to analyze production from conception to carcass, and demonstrated the benefits of real-time data sharing (Van Eenennaam et al., 2010). Cow-calf producers and feedlots implementing this technology can utilize the data

within integrated companies, but dissemination of the data has not been widely accepted due to confidentiality concerns and competition among the different companies.

Bayesian analysis is very beneficial to begin to estimate outcomes when certain clinical trials have not occurred due to financial, logistic, or ethical constraints. One form of Bayesian analysis that is just beginning to be recognized in food animal production is mixed treatment comparison meta-analysis (O'Connor et al., 2013; O'Connor et al., 2016). Meta-analyses are currently utilized to combine estimates from multiple research trials making direct comparisons that address a specific hypothesis. The mixed treatment comparisons have the ability to combine not only direct comparisons between treatments, but also indirect comparisons where a clinical trial has not yet occurred (Jansen et al., 2008; Jansen et al., 2011). It is believed that Bayesian analysis will continue to advance the body of literature available to the food animal industry.

Conclusion

As demonstrated, the cattle industry infrastructure contributes to diversity of large amounts of data within the industry. Animal movement throughout the different operations within the industry account for a lot of the variability that exists within a production system. The beef cattle industry is currently not integrated, making tracking and following data at the animal-level extremely challenging. Big Data analytics allow researchers and producers to begin to understand where variability exists within operations, thereby allowing enhanced management decisions even in systems with extensive heterogeneity (Dohoo et al., 2001). The main difference between the current utilization of Big Data in the human health industry and the cattle industry is due to government incentives and the established infrastructure that exists in the human health industry. Understanding and addressing issues of transparency and confidentiality will lead to increased use of Big Data in the cattle industry. The cattle health industry has the potential to

utilize Big Data analytics to continue to expand on the prediction methods for quantifying management factor effects on health and performance.

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Chapter 2 - Calving distributions of individual bulls in multiple-sire pastures

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Abstract

The objective of this project was to quantify patterns in the calving rate of sires in multiple-sire pastures over seven years at a large-scale cow-calf operation. Data consisted of reproductive and genomic records from multiple-sire breeding pastures (n=33) at the United States Meat Animal Research Center (USMARC) from 2007 to 2013. Calving intervals were analyzed in 21-day periods. A ranking system for each bull was developed based on the calving rate per pasture over

the breeding season, with Rank 1 = the bull with greatest calving rate, Rank 3 = the bull with the least calving rate, and Rank 2 = all other bulls. A total of 179 bulls and 3,703 calves were successfully genotyped over seven years. A uniform distribution described the expected percentage of calves sired per rank within pasture. Rank 1 bulls sired 113% greater calves than the expected pasture-average, Rank 2 bulls sired 6% less than expected, and Rank 3 bulls sired 81% less than expected. A rank by calving interval interaction effect was identified ($P < 0.05$). A Rank 1 bull in calving interval 1 produced a greater average percent of the total calf crop over the entire season, compared to a Rank 2 and Rank 3 bull. The calving rate for individual sires is not homogeneous and there is a large difference between bulls siring the greatest and least number of calves. More research is needed to determine how rank changes over multiple breeding years and its association with dominance, libido, and fertility.

Introduction

In commercial cow-calf operations in the United States, multiple bulls are utilized within individual breeding pastures. On average there are 24 cows per mature bull and 17 cows per yearling bull (USDA, 2009). Bulls are expected to impregnate a high number of cows in a relatively short breeding season. Reproductive performance of bulls relies on the ability to detect cows in estrus, effectively mate cows, and successfully fertilize the oocyte to produce a viable fetus. The theory and practice of breeding soundness examinations is to screen bulls prior to the breeding season to assess some factors that impact reproductive success, such as sperm cell morphology and motility and musculoskeletal conformation (Chenoweth et al., 1984; Chenoweth et al., 1995). The desire of a bull to actively seek cows in estrous in order to mate is described as libido (Chenoweth, 1997). The number of estrous cows successfully mated is thought to be influenced not only by libido, but also by other bulls within the hierarchical nature of the herd,

more commonly known as social dominance (Blockey, 1979; Rupp et al., 1977). Understanding and quantifying social dominance has been attempted, with little success to accurately predict reproductive performance based on social dominance (Blockey, 1979; Ologun, Chenoweth, & Brinks, 1981; Whitworth et al., 2008). Although commercial cow-calf managers do not have simple methods to identify bulls with high libido or high social dominance, there may be genetic and economic benefits for identifying these bulls.

Variability in the number of offspring born per bull exists between sires in multiple-sire pastures. The reasons for the variability are currently unknown, but have been speculated to be due to differences in libido, social dominance, or conception success among bulls (Smith et al., 1981; Whitworth et al., 2008). If variability of reproductive success between bulls in multiple-sire pastures is due to libido or social dominance, an accurate understanding of bull behavior is needed. Serving capacity, as a proxy for libido, has been shown to be correlated with proportion of estrous cows mated by a bull in a single-sire pasture (Blockey, 1976). The effect of serving capacity on the number of offspring sired in a multiple-sire pasture may be mediated by the bull's hierarchical social ranking. If the number of cows in estrous is three or less, Blockey (1979) observed that a dominant bull is able to successfully prevent mating by other bulls, presumably regardless of competing bulls' libido (Blockey, 1979). If libido and social dominance rank are unrelated behavioral traits, then bulls with high libido and low social dominance or bulls with low libido and high social dominance are likely to negatively impact the number of calves sired by bulls with these characteristics in a multiple-sire pasture. Analyzing overall calving success by bull and patterns of calving success by 21-day intervals are necessary to investigate reasons for variability in progeny data. The objective of this study was to quantify patterns in the number of calves sired by bulls in multiple-sire pastures over multiple years at a

large-scale cow-calf operation. We hypothesized that patterns of calving success by 21-day intervals during the calving season would show that bulls siring the greatest number of calves had different calving patterns than other bulls within that pasture.

Materials and Methods

Herd description

Retrospective reproductive data were collected from cowherds housed at the United States Meat Animal Research Center (USMARC). Data consisted of reproductive and genomic records from multiple-sire breeding pastures (n=33) from 2007 to 2013. The breeding season began in June for each year analyzed and lasted for 63 days, and only one breeding season per year per bull was considered. Pastures consisted of cool and warm season grasses and ranged from 24.3 to 48.6 hectares in size. Rotational grazing was utilized to insure adequate nutrition. Each breeding pasture contained 23 to 243 cows with an average of 16 cows per bull (range 8 to 26). Bulls within each pasture were the same age. Breed of cows and bulls consisted of purebred as well as composites of approximately 16 breeds (ranging from 100% to 6.25% of any given breed). Breed within each breeding pasture was selected to produce the desired breeds and sire lines for genetic evaluation projects unrelated to this project. Breeding lifetimes averaged two years for bulls at USMARC, with a range of one to six years. A bull was culled during or after a breeding season based on injuries, reproductive performance, and/or genetic selection purposes. If a bull was removed during the breeding year, the length of total days the bull was in the breeding year was recorded.

Genotyping

All cows, bulls, and calves were genotyped using the animal's blood or semen with the Bovine SNP50 BeadChip to determine parentage (Stone et al., 2002). Genotyping was confirmed

by pedigree as previously described (Thallman, 2001a, 2001b). Only sires with successfully genotyped calves were included in the dataset. If a calf was not successfully genotyped, the calf was removed from the analysis.

Calving intervals, rank classification, calving distributions

Calving intervals were analyzed in 21-day periods within the calving season; interval 1 consisted of days 0 to 21, interval 2 consisted of days 22 to 43, and interval 3 consisted of days 44 to 63. An individual bull's reproductive performance as measured by calving rate was calculated as number of calves sired divided by the days the bull was in the pasture for the breeding year. For example, if a bull sired 10 calves and was in the breeding pasture the entire 63 days, then the calving rate would be calculated as 10 calves/63 days = 0.159 calves per breeding-day. If a bull was in the breeding pasture for less than 63 days, this number was used to determine the calving rate. For example, if a bull sired 7 calves, and was in the breeding pasture for 27 days, the calving rate would be calculated as 7 calves/27 days = 0.259 calves per breeding-day. Based on this calving rate, a ranking system for each bull over the entire breeding season was developed, with Rank 1 = the bull with greatest calving rate, Rank 3 = the bull with the least calving rate, and Rank 2 = all other bulls. If two bulls had the same greatest calving rate, both those bulls received a "Rank 1" as their rank score. If two bulls had the same least calving rate, those bulls received a "Rank 3" as their rank score.

A uniform distribution was used to describe the expected percentage of calves sired per rank within a pasture. Observed percentage of calves sired was determined based on total calves sired by individual bull rank per pasture. The standardized rate between the observed and expected percentage of calves sired for each rank for all breeding seasons was calculated by the following formula (Dohoo et al., 2003):

$$\frac{\text{(Observed \% of calves sired per rank per pasture-Expected \% of calves sired per rank per pasture)}}{\text{Expected \% of calves sired per rank per pasture}}$$

Statistical analysis

All descriptive analytics were performed in Excel (Microsoft Office Excel 2010, Microsoft Corporation, Redmond, WA). Statistical analysis was conducted to evaluate the overall calving distribution based on calving percent in each 21-day interval in each pasture, each year. The model was ran with the PROC GLIMMIX procedure (SAS Institute Inc., Version 9.4, Cary, NC, USA) and included the 21-day interval as a fixed effect and a random intercept term to account for clustering within pasture within year. Statistical analysis was conducted to evaluate differences between individual bull rankings within intervals of the total calving percent with the PROC GLIMMIX procedure (SAS Institute Inc., Version 9.4, Cary, NC, USA). The model included fixed effects for rank, interval, and a rank by interval interaction, a random intercept term was included to account for clustering within pasture within year, and a random residual term with compound symmetry covariance structure was included to account for repeated measures for each sire.

Results

Reproductive performance and calving distribution

A total of 3,703 calves were successfully genotyped, and a total of 179 bulls were individually analyzed. Average calving success (calves born per cow exposed for breeding) between the 33 breeding pastures was 89% (range of 67 to 100%) over all 7 years. Fig. 2.1 shows the calving distribution of the calving percent per 21-day interval for all individual bulls within pastures. The percentage of calves born per 21-day period decreased as the days in the breeding season progressed.

Sire rankings

The results on the observed percentage of calves sired for Rank 1 bulls and the expected percentage of calves sired if there was a uniform distribution between the percentages of calves sired between bulls per pasture is shown in Table 2.1. The standardized rate between the observed and expected percentage of calves sired for each rank indicates that Rank 1 bulls sired 113% greater calves than expected on average, Rank 2 bulls sired 6% less than expected, and Rank 3 bulls sired 81% less than expected.

The results of the calving percent difference between individual bulls by rank in 21-day intervals are shown in Fig. 2.2. A calving interval by bull rank interaction was present, $P < 0.05$. A Rank 1 bull in interval 1 produced on average 13% of the total calf crop, a Rank 2 bull produced on average 6% of the total calf crop in interval 1, and a Rank 3 bull produced 2% of the total calf crop in interval 1. The differences between the ranks of individual bulls within interval 1 were statistically significant, as were the differences between ranks within intervals 2 and 3. Overall, individual Rank 1 bulls sired the greatest percentage of calves in interval 1, 2, and 3, compared to Rank 2 and Rank 3 in the same intervals.

Rank changes between years for individual bulls based on the number of breeding years bulls are used are shown in Table 2.2. Breeding years ranged from one to six years, with a majority of the bulls being utilized for two breeding years. Only 19 bulls had a change in rank over breeding years. There were a total of 21 rank changes from all bulls because two of the 19 bulls had two rank changes over their breeding years. Most rank changes occurred for bulls used for 4 breeding years, and the rank change that occurred most commonly was a change from Rank 2 to Rank 1. There was one bull that had a rank change from a Rank 3 to Rank 1. There were 11

bulls which increased rank, and there were 10 bulls which decreased rank over the breeding seasons evaluated.

Discussion

The current study shows a reliable way to classify bulls with successfully genotyped calves in order to describe bulls in multiple-bull pastures with the greatest calving rate. This dataset was consistent with other reports demonstrating the variability in reproductive performance between bulls in multiple-sire breeding pastures (Fordyce et al., 2002; Holroyd et al., 2002; McCosker et al., 1989). One study of a breeding pasture with 27 herd sires found that five bulls produced greater than half of all viable offspring, and 10 bulls did not sire any calves (Van Eenennaam et al., 2007). Variability in bull reproductive success has also been demonstrated at a breeding farm in Northern Australia where 235 bulls were exposed to cows that sired 4,251 calves; of which, 14% of the bulls sired greater than 30% of the calves, and 6% of the bulls did not sire any calves (Fordyce et al., 2002). Some studies have shown that social dominance and scrotal circumference are highly heritable and related to herd fertility (Blockey, 1978; Meyer et al., 1990).Whereas, other research has shown no difference between social dominance and calf output, as well as between social dominance and libido (Farin et al., 1989; Holroyd et al., 2002; Ologun et al., 1981). Therefore, there is a need for technology (e.g. genotyping, GPS) to aid in understanding what is happening in breeding pastures before management strategies can be improved.

Factors, such as social dominance and libido, are evaluated on herd level data to predict fertility and reproductive success within a breeding season. The ranking system developed in the current study is not used as a prediction for calving rate or success. The ranking system is a way to evaluate calving rate differences between bulls at the end of the breeding season, and identify

those top and bottom producing bulls. Understanding more about the genetic and management of these ranked bulls may be advantageous for predicting reproductive success in a breeding season. Further research is needed to develop methods to accurately classify the rank of the bulls and identify the effect on calving rate. In the present study, we used parentage genotyping to begin to develop methods to rank bulls within a pasture using 21-day intervals.

Established, controlled breeding seasons for a herd increases productivity compared to long or year-around breeding seasons (Chenoweth, 2005). Analyzing the herd reproductive data from a single breeding season in 21-day intervals allows for an overall assessment of the herd to determine differences in reproductive success between 21-day intervals as the breeding season progresses compared to desired patterns (Larson, 1999). Analyzing the percent of calves being born over these intervals serves as a method to evaluate herd-level reproductive efficiency, but does not assess the reproductive efficiency of individual bulls. Assessing individual bulls by their rank within calving intervals serves as a method to determine the total contribution these bulls had to the overall calving percentage of the breeding season and how performance varied across the breeding season.

The ranking system described in this study identifies and compares those bulls with the greatest calving rate to the bulls with a lesser calving rate, and is the first attempt to classify bulls with this type of system to the author's knowledge. The Rank 1 bulls produced a greater percentage of the calving percent per 21-day interval per pasture. This is similar to other research studies that identified a higher percentage of calves sired by a lower percentage of the total bulls per pasture (Drake et al., 2011; Van Eenennaam et al., 2007). Rank was modified by the interval of the calving season with the magnitude of the effect of rank on the percent of calves sired per 21-day interval decreasing as the calving season progressed (Fig 2.2). There is value to identify

bulls with greater reproductive success compared to the least successful bulls. Our hypothesis was supported in that bulls that sired the greatest number of calves were consistently superior to lower ranked bulls for each 21-day interval of the breeding season. The least ranked bull produced the least calving rate within the three intervals analyzed, which could negatively influence pregnancy risk over an entire breeding season.

Possible management interventions for commercial herds that are able to identify the relative ranking of bulls could be to remove the bull with perceived greatest dominance from a breeding pasture after a prescribed period of time, if bull rankings over time do not change (i.e. once one-half the cows are expected to have been bred). Removing the most dominant bull would allow bulls with desirable genetic worth but less reproductive success to be able to sire an increased number of calves in spite of lower social dominance or other behavioral factors that limit calving success in multiple-sire breeding pastures. Similarly, bulls with less social dominance but desired genetic worth could be removed to a single-sire pastures where social dominance is not expected to influence reproductive success, and therefore be more efficient in their calving success (Farin et al., 1982). The effect of age on social dominance and behavior has been studied (Carpenter et al., 1992; Coulter & Kozub, 1989; Makarechian & Farid, 1985), and groups of bulls of the same age achieve higher pregnancy rates than groups of bulls of mixed age (Blockey, 1979). Effect of age on reproductive rank could not be assessed in the current study because the bulls within each pasture were the same age. Understanding how age of bulls effects rank over time would be beneficial. Additional research is needed to determine the genetic and management factors that are associated with variability in bull rankings before changes in sire selection or management of commercial cattle herds is suggested.

One of the limitations of our study was that bulls were most commonly used 2 breeding years due to the herd management established at USMARC. As shown in Table 2.2, most of the bulls ranking did not change over time. The low numbers of bulls that changed ranks did not allow us to evaluate potential reasons for changing ranks in this study. More research is needed to determine frequency and factors related to an individual bull changing ranks over multiple years. Another limitation of this study is the data can only be extrapolated to the study population available from USMARC, more research is needed to determine the association of different breeding management practices and individual bull rank.

Conclusion

This study demonstrates variability in the number of progeny by bull in multiple-sire pastures over seven years. Analyzing the percent of calves being born over 21-day intervals as a whole-herd assessment does not assess the reproductive efficiency of individual bulls. Ranking bulls by calving rate for the entire calving season is associated with number of calves sired by individual bulls in each 21-day period of the calving season. More research is needed in order to determine how rank changes for bulls over multiple breeding years, how to identify bulls with the greatest and least rank, and how calving rank is associated with dominance, libido, and fertility.

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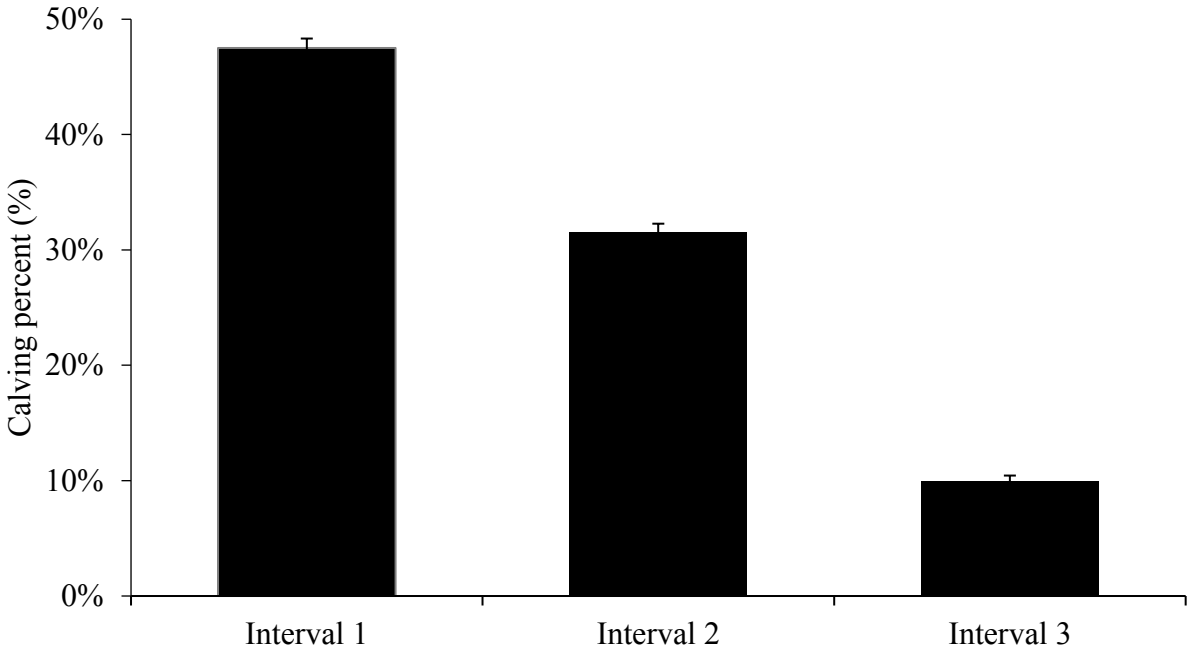
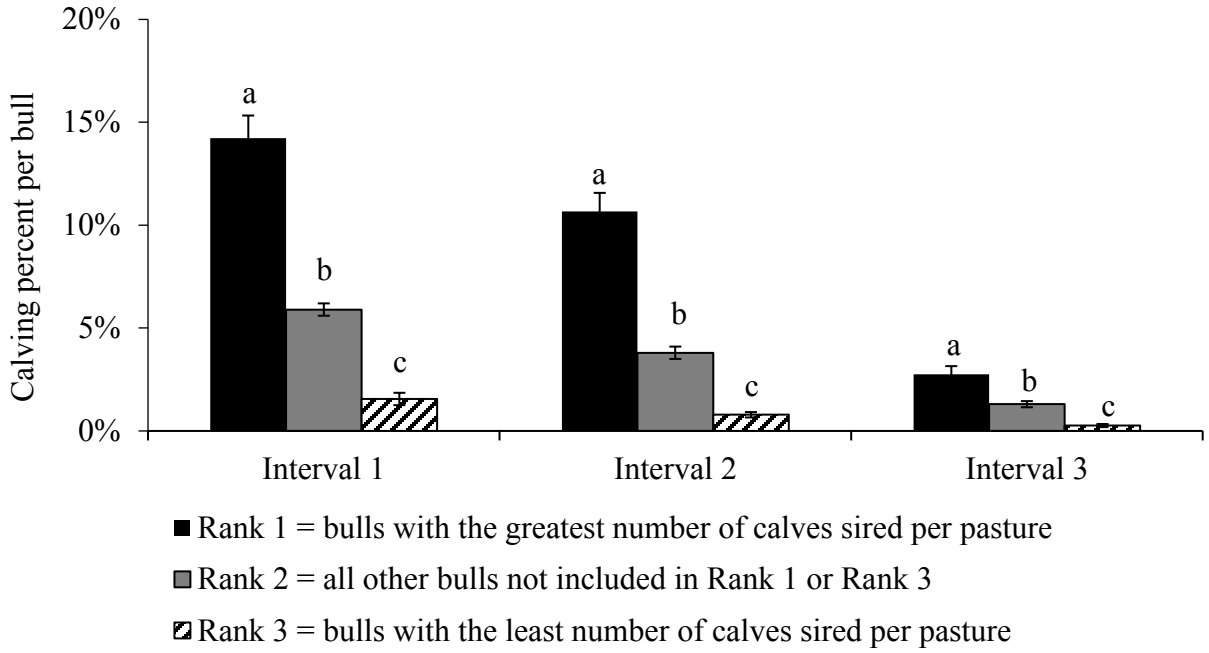
Figure 2.1. Model-adjusted least square means (±SE) calving percentage for each 21-day interval.



Interval 1 = days 0 to 21
Interval 2 = days 22 to 43
Interval 3 = greater than 43 days.

Figure 2.2. Model–adjusted calving percent (±SE) per bull by reproductive rank by 21-day intervals. An interaction based on rank and interval was identified ($P < 0.05$). Rank with non-connecting letters were significant ($P < 0.05$) within an individual interval.



Interval 1 = days 0 to 21
Interval 2 = days 22 to 43
Interval 3 = greater than 43 days.

Table 2.1. Average observed and expected percentage of calves sired per bulls categorized in the different ranking.

	Average observed percentage of calves sired per pasture	Average expected percentage of calves sired per pasture	Standardized rate between observed and expected percentage of calves sired
Rank 1[a]	34%	16%	113%
Rank 2[b]	15%	16%	-6%
Rank 3[c]	3%	16%	-81%

[a] Bulls with the greatest number of calves sired per pasture
[b] All other bulls not included in Rank 1 or Rank 3
[c] Bulls with the least number of calves sired per pasture

Table 2.2. Rank by year for individual bull counts. Breeding years correspond to the number of years a bull was used in a breeding season.

Rank change	Number of breeding years						Total
	1	2	3	4	5	6	
No change	47	92	5	15	0	1	160
1-2	0	0	1	3	0	0	4
1-3	0	0	0	1	0	0	1
2-1	0	0	4	2	0	0	6
2-3	0	1	2	2	0	0	5
3-2	0	0	2	3	0	0	5
Total	47	93	14	26	0	1	181

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Chapter 3 - Predicting bull behavior events in a multiple-sire pasture with video analysis, accelerometers, and classification algorithms

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Abstract

Parentage data from beef calves has shown that in multiple-sire pastures a disproportionate number of calves are born from a single bull. Investigating and accurately quantifying bull behavior within multiple-sire pastures will begin to determine reason(s) for the variability in the number of calves sired. The study objective was to assess accelerometer data and various classification algorithms to accurately predict bull behavior events in a multiple-sire

pasture. Behavior events of interest in this study included lying, standing, walking, and mounting.

Two bulls and ten estrous synchronized cows were used. True behavior events were determined during daylight hours with video analysis, and matched with accelerometer data. Accelerometers were attached to both ears, withers, and neck of both bulls. Accelerometer data were recorded for every second over 3 days. Accelerometer data were used to generate algorithms and accuracy was evaluated compared to known video behavioral data.

The prevalence based on the raw video data for lying was 32.6%, standing was 59.4%, walking was 7.4%, and mounting was 0.6%. The random forest classifier had the highest accuracy compared to other classifiers (random tree and decision tree) for each tag location and behavior of interest. The accuracies from the random forest algorithms ranged from 92 to 99% for lying, 85 to 90% for standing, 73 to 77% for walking, and 74% to 80% for mounting. The classification algorithm was able to accurately predict a lying and standing event, and predict a walking and mounting event with a lower accuracy. Further research is needed to determine how behaviors between bulls affects overall parentage data.

Introduction

Bull behavior can influence overall conception rates in multiple-sire pastures (Blockey, 1979). Libido, the willingness for a bull to breed a cow, and serving capacity have been identified as factors influencing fertility and conception rates in pasture breeding operations (Blockey, 1978; Chenoweth, 1981; Crichton and Lishman, 1988). The purpose of utilizing multiple bulls in a breeding pasture is to increase overall fertility and calving rates in a herd and reduce the number of pasture required compared to a single sire pasture breeding program. Once a bull services a female, she needs to conceive, maintain the pregnancy, and have a viable calf. If

a particular bull is not actively breeding cows or the act of mating does not result in a successful pregnancy, then that bull is not contributing to the overall productivity of that herd.

Parentage data from beef calves has shown that in multiple-sire pastures a disproportionate number of calves are born from a single bull (Fordyce et al., 2002; Holroyd et al., 2002; Van Eenennaam et al., 2007). The disproportionate parentage distribution shows that not all bulls are contributing equally to the number of calves being sired on the operation. Successful investigation of the factors influencing the variability in the number of calves born per bull requires accurate ways of quantifying bull behavior in a multiple-sire pasture. Previously, quantifying bull behaviors in a multiple sire pasture involved visual observations of the desired individual behaviors (Blockey, 1979; Boyd et al., 1989). Visual observation is labor intensive, increases the chance for human error by missing behavioral events in a given time period, and can influence the behavior of animals through human interaction (Theurer et al., 2013). Some investigations using visual observation to quantify bull behavior have been performed in controlled settings, such as small pens or within a limited time frame, e.g. 20 mins (Carpenter et al., 1992; Whitworth et al., 2008). The use of technology provides new tools to assess behavior accurately while decreasing the need for human observations, as well as increasing the time frame that animal behavior can be monitored.

Accelerometers can be used to assess lying and standing behaviors in cattle (Robert et al., 2009; Theurer et al., 2013). Using accelerometers to record specific behaviors of cattle in beef cow-calf herds in real-time provides advantages when investigating the bull's role and behavior in the reproductive efficiency of that operation. Understanding a bull's overall activity throughout a breeding season can be used to predict his contribution to the overall calving rate. It is hypothesized that actively breeding bulls will spend more time standing, walking, and

mounting and less time lying compared to bulls not mating as many females. The study objective was to assess accelerometer data and various classification algorithms to accurately predict bull behavior events for lying, standing, walking, and mounting in a multiple-sire pasture.

Materials and Methods

Animal population

All procedures were approved by the institutional animal care and use committee of University of Nebraska-Lincoln (IACUC # 1124). Two bulls, aged 3 years old were used in the project. One bull was Angus (designated bull #2) and the other was a composite of Red Angus, Simmental, and Gelbvieh (designated bull #1). Both bulls were placed in a rectangular pasture with 10 estrus-synchronized crossbred cows for three days (6/22/16 to 6/24/16). Three observations days were chosen due to the time period expected for cows to exhibit signs of estrus from estrus synchronized using the select-synch protocol (Patterson et al., 2003). All the cows exhibited signs of estrus during the observation period. The pasture was enclosed with electrical fencing and was 280 by 180 feet. A single movable oval water trough was placed in the pen and a rectangular feed bunk was used to provide ad libidum access to grass hay.

Accelerometer data collection

Accelerometer data were recorded with the use of Smartbow ear tags (MKW Electronic GmbH, Weibern, Austria). Accelerometer data recorded the three-dimensional location (x, y, and z axis) of each tag during each second of the study duration. Ear tags were attached to both bulls in four difference locations, the left and right ear, the withers, and the neck. Smartbow tags were attached to collars that fit around each bull's neck and were attached to each bull's wither with the use of glue, netting, and a cloth patch, and were attached to each ear with a button tag (Fig. 3.1).

Video analysis

Cameras (Axis Communications, Lund, Sweden) were attached the southwest and northeast corner of the pasture. The cameras were programmed to record activity of all cattle within the pasture in the camera frame, and to provide a one-second interval time-stamp during the 3 day trial. The camera time stamp was synched with the accelerometer time stamp at the start of the study to record data at the exact same hour:minute:second.millisecond.

With the use of only two cameras within the rectangular pasture, there were areas in the pen both bulls could be out of frame throughout the recording period. Video data were watched by a single investigator (KA) and logged (Noldus- Observer XT 11, Leesburg, VA) to quantify the exact onset time and duration of each behavior event by each of the two bulls. Behavior events of interest included lying, standing, walking, and mounting. Video recorded events were classified using the following definitions:

- *Lying* –Bull has all 4 legs tucked underneath the torso or lying on one side of its body for 1 s or longer. The lying period ended when the bull transitioned into another behavior.
- *Standing* –Bull has all 4 feet planted on the ground for 1 s or longer. Time spent grazing is included in this category, even if a small number of steps are taken during the grazing period. A period of time classified as standing ended when the bull transitioned into another behavior.
- *Walking* - Animal has taken 3 steps in a progressive direction, this behavior ends when the progressive movement stops.
- *Mounting* – Mounting event begins when the front feet of the bull leaves the ground, and ends when the front feet are back on the ground. During the mounting period, the animal being mounted stands in place during the mounting event in order to be bred.

- *Out of frame* – The bull is no longer visualized by either camera placed in the northeast and southwest corners of the pasture.
- *Other* – The bull does not display a defined lying, standing, walking, or mounting behavior.

Each event was mutually exclusive, meaning a bull identified as exhibiting one behavior could not simultaneously be classified as exhibiting another behavior. Each bull's behavior was recorded independent of the other bull's behavior.

Data preparation

Data from the accelerometer and video were exported as Excel spreadsheets (Microsoft Corp., Redmond, WA). Spreadsheets were imported into KNIME Analytics software as CSV files. Data were matched between the accelerometer and video log for each second of the study in order to create a combined dataset. The combined data set was partitioned into ear, wither, and neck sub-groups. The two ear tags were combined into a single dataset. Binary variables was created for each behavior of interest (lying, standing, walking, and mounting) and assigned a value of 1 (behavior occurred) or 0 (behavior did not occur) for each second of each sub-grouped dataset.

The prevalence for each behavior of interest (lying, standing, walking, and mounting) based on raw video data was determined by combining the number of video-recorded events for the four behaviors of interest for both bulls divided by the total number of behavior events. Behaviors logged 'out of frame' and 'other' were not included in the prevalence analysis for the raw video data. The final dataset used to build the algorithm included bull identification, accelerometer tag number, behavior onset time, behavior, and the x-axis, y-axis, and z-axis

accelerometer readings. A flow diagram of data preparation, refinement, partitioning, and classification is shown in Fig. 3.2.

Variable preparation and creation

Variables were created in order to increase the predictive accuracy of each behavior event. Multiple variables were created with the raw accelerometer data recordings for the x, y, and z, axis. The list of all created variables are in Table 3.1. Data points missed due to accelerometers not capturing every second, which occurred randomly throughout the study, were removed prior to variable manipulation, and was performed with the rule engine node in KNIME to remove cells containing missing data.

A pair-wise correlation analysis was performed on all variables created before the predictive algorithm building, with the use of the linear correlation node in KNIME (Berthold et al., 2008). A correlation statistic of |0.8| or higher was used to determine collinearity between two variables, and only one of the identified variables was selected and used in the predictive classification algorithm.

The animal identification, recording date, and tag number were removed from the data set prior to the predictive classification algorithm building. This was done to ensure that data was only being used in the algorithm that could be repeated in future studies.

Using a balanced datasets has been proven to optimize the performance of the classification algorithms (Japkowicz, 2000; Amrine et al., 2014). A balanced dataset was created for training of the classification algorithms for each sub-grouped dataset by tag location (ear, neck, wither) in terms of the binary variable created for each behavior of interest. An equal distribution node in KNIME was used to randomly under-sample the dataset by randomly

removing non-behavior events from the dataset until an approximately equal amount of behavior events and non-behavior events exist in each sub-grouped dataset.

Data partitioning

Data were partitioned into training, testing, and validation datasets based on 50%, 25%, and 25%, respectively from each sub-grouped dataset. Datasets were trained using three classifiers (decision tree, random tree, and random forest) to identify specific behavior events (lying, standing, walking, and mounting). Training a dataset involves utilizing created variables to learn and predict the outcome of interest with the highest accuracy possible. Validation data were used to determine accuracy, and accuracies were compared between the different classifiers for each sub-group.

Classification algorithms

Classification algorithms were determined using The Waikator Environment for Knowledge Analysis (WEKA) nodes within KNIME (Hall et al., 2009). The selected classification algorithm nodes used in each partitioned dataset included the decision tree classification, random forest classification, and random tree classification (Breiman, 2001; Maimon and Rokach, 2005).

Classifier accuracy

Overall accuracy for each classifier was determined based on the validation dataset. Predicted probabilities were generated for each behavior of interest as a 1 = lying, standing, walking or mounting for each different sub-grouped data set, and 0. Using these generated probabilities, a receiver operating characteristic curve (ROC) was created using the ROC curve node in KNIME. The ROC curve is a plot of the cutpoint sensitivity as measured by the classification algorithm versus the false positive rate of that same algorithm computed at a

number of different cutpoints, other than the standard generated by the algorithm (0.5). The optimum cutpoint is selected for distinguishing between the probability of a behavior event occurring and non-behavior event occurring (Greiner et al., 2000; Silipo et al., 2014). The predicted behavior event with a probability greater than or equal to the cutpoint probability was categorized as a 1, and those less than or equal to the cutpoint were given a behavior = 0.

Overall diagnostic performance was calculated using the predicted behavior of interest as determined by the classifier and the true behavior of interest as determined by the video logger to calculate the true positives (TP), false positives (FP), true negative (TN), false negatives (FN), sensitivity (Se), specificity (Sp), and accuracy (Acc) for each classifier. Accuracy was calculated as the sum of the TP and TN, divided by the sum of the TP, TN, FP, and FN.

Results

Descriptive Statistics

Combination of the accelerometer, video, and both bulls' data resulted in a full dataset with 1,963,207 event rows. One bull had a total of 1,011,590 matched events, and the other bull had 951,617 matched events. After removal of behavior logged as 'other' and 'out of frame' as well as removal of missing accelerometer data (n = 158,610), the final dataset included 1,804,597 event rows for all tag locations and all behaviors of interest (lying, standing, walking, and mounting).

Prevalence of behavior events

The prevalence based on the raw video data for lying was 32.6%, standing was 59.4%, walking was 7.4%, and mounting was 0.6%. The prevalence after the data was processed through the classification algorithms varied for individual behaviors and classifiers, but was similar to the raw video data prevalence. The variability in the prevalence between the sub-grouped data was

due to the approximate randomization from the equal size sampling node and the approximate partitioning of the datasets. The prevalence for lying behavior for individual data sets ranged from 29.5% to 33.1% (Table 3.2), standing behavior ranged from 58.4% to 61.6% (Table 3.3), walking ranged from 7.5% to 7.8% (Table 3.4), and mounting ranged from 0.6% to 0.7% (Table 3.5) for each of the different sub-groups (ear, neck, and wither).

Classification accuracy

Between all the three different classifiers evaluated, the best performing classifier for each location and behavior of interest was the random forest. The probability cutpoints, as determined by the ROC curves, varied 0.3 to 0.7, and a majority of the classifiers utilized the 0.5 cutpoint. The 0.5 cutpoint was the automated cutpoint used for each of the classifiers for the software. The location with the highest accuracy was wither based on the random forest classifier for lying (99.0%) and walking (77.1%) (Table 3.2 and 3.4). For standing and mounting, the neck had the highest accuracy (90.5% and 79.9%, respectively) (Table 3.3 and 3.5). The behavior with the highest accuracy between all locations was lying (99.0%), and the random forest classifier was able to predict almost every lying event that occurred (7893/8084) (Table 3.2). Sensitivity and specificity also ranged between 66.1% and 99.5% for all the sub-grouped data within each behavior of interest.

Discussion

Bull behavior related to reproductive performance varies greatly between bulls in a multiple-sire pasture (Farin et al., 1982; Farin et al., 1989; Chenoweth, 1997). It has been suggested that bulls with higher libido and serving capacity have a higher mating potential (Silva -Mena et al., 2000). Using accelerometers to quantifying bull behavior in a multiple-sire pasture as described in this manuscript is the first attempted to the authors' knowledge. This technology

allows bull behavior to be quantified without the need for visual observation. Using the results from this research, a researcher could accurately predict if a bull is lying or standing and when these events are occurring in real time, but could not accurately predict walking or mounting based on the proposed algorithm. Knowledge of behavioral events can be used to determine how bulls' behavior varies within a given breeding season, and begin to quantify the differences related to reproductive performance and the variability that exists in the number of calves sired.

Using classifier accuracy was proven to be misleading if it is the sole classification of overall predictability accuracy (Unruh et al., 2016). Sensitivity is the ability of the test to detect and true positive, and specificity is the ability of a test to exclude a true negative (Dohoo et al., 2003b). In order to determine the percentage of test positive or negative results that are truly positive or negative, assessment of the positive and negative predictive values is necessary (PVP, NVP). The best performing classifier as determined by accuracy was the random forest classifier, for lying behavior on the wither location (99.0%) (Table 3.2). The random forest classifier also has higher Se and Sp (97.5% and 99.5%, respectively), compared to the other classifiers for lying behavior on the wither location. The PVP for this same classifier in the same location is 98.9% and the NPV is 99.1%. The random forest classifier is able to detect a true positive based on the high Se, and if the test classifies an event as lying this is truly a lying event (98.9%). The inverse relationship is true in regards to Sp and NPV. The high PVP is related to the prevalence of the event (Dohoo et al., 2003a), and the prevalence of a lying event for the wither location was 30.4%. The accuracy of the test is reflective of the PVP. The same conclusion can be made when analyzing standing behavior for the best performing classifier in the neck location (Table 3.3). The PVP for standing was 91.1% and NPV was 89.6%.

An example where the accuracy is misleading towards classification ability is with the mounting behavior. The accuracy for the best performing classifier for mounting was 79.9% for the neck location (Table 3.5). The Se and Sp was 79.1% and 79.9%, respectively. Solely looking at the Se and Sp, one may determine this predictability to be moderate. The PVP of this classifier is 2.5% and the NPV is 99.8%. Therefore, when the algorithm predicts a mounting event, the likelihood that the event was truly a mount is only 2.5%, and when the algorithm predicts a non-mounting event, it is truly a non-mounting event for 99.8% of the predicted events. The reason for this low PVP is due to the low prevalence in the dataset (0.68%) which results in a high number of false positives (23,839) when specificity is not perfect. There were only 196 true mounting events in this dataset, and the high number of FP demonstrates that a lot of other behaviors appear similar to a mounting event in terms of the x, y, and z axis. Overall, the mounting event was extremely challenging to predict using accelerometer data due to the low prevalence in the dataset and the lack of unique movement through the x, y, and z axes during a mount compared to other behaviors. A similar conclusion can be made for the walking behavior. The wither location provided the best performing classifier (Table 3.4), however, the PVP was only 23.8% and NPV was 97.8%. Mounting and walking could be further tested in series, by creating a dataset which includes all predicted positive outcomes from the initial classifiers, reran through the same classifiers, and establish accuracy based on the outcome of the second classifier. Testing in series will increase Sp, but decreases Se (Dohoo et al., 2009). Series testing was not believed to improve the predictability of these behavior events because of the low prevalence in the dataset.

The location that had the lowest accuracy was the ear for each behavior of interest. This is most likely due to the ears having more movement that effect the x, y, and z axis readings

compared to wither and neck locations. The random forest classifier found that the ear location differed in overall PVP compared to the other locations with the same classifier by 15% for lying, 5.8% for standing, 5.2% for walking, and 0.5% for mounting. The differences are most likely due to the FP rates, and tag location does not appear to be great enough to prefer one location over another. It is believed tags placed on the ears, neck, or wither of the bulls would not have impacted the behavior events analyzed.

Limitations of this study include the cows utilized were synchronized prior to bulls entering the pasture. The study only lasted for 3 days because that was the duration cows were in estrus and mounting behavior occurred. It is common practice in cow-calf operations to utilize multiple bulls within a single breeding pasture, and breeding performance does change when comparing a single-sire versus a multiple-sire herd, and between different ratios of bulls: cows within a pasture (Farin et al., 1982; Neville et al., 1987). It is unknown how the predictability of accelerometer data will change based on a bulls' behavior when used in different pasture settings. The pasture used in this study was smaller compared to actual breeding pastures, and breeding behavior events may change in larger pasture settings. It is believed that the accelerometers would still be able to predict lying and standing behavior, although walking and mounting would still have a high risk of FP due to the lack of highly specific accelerometer readings for those behaviors. Further research is needed to clearly understand the role of classifying lying and standing behavior throughout a breeding season and the effect these behaviors could have on overall reproductive performance.

Conclusion

The objective of this study was to determine if classification algorithms could accurately predict behavior events from bulls in a multiple-sire pasture. The classification algorithm was

able to predict a lying and standing event with a high accuracy, Se, Sp, PVP, and NVP. The behaviors of walking and mounting have a lower accuracy, Se, Sp and this is due to the lower prevalence in each dataset as well as a high number of FP behavior event classifications, leading to a low PVP. Further studies are necessary to determine differences between bulls in multiple-sire pastures based on the number of offspring sired and certain bull behaviors.

Figure 3.1. Position of the three-dimensional Smartbow accelerometer tags on the left and right ear (a), attached to a collar on the neck (b), and attached to netting and a patch on the wither (c).

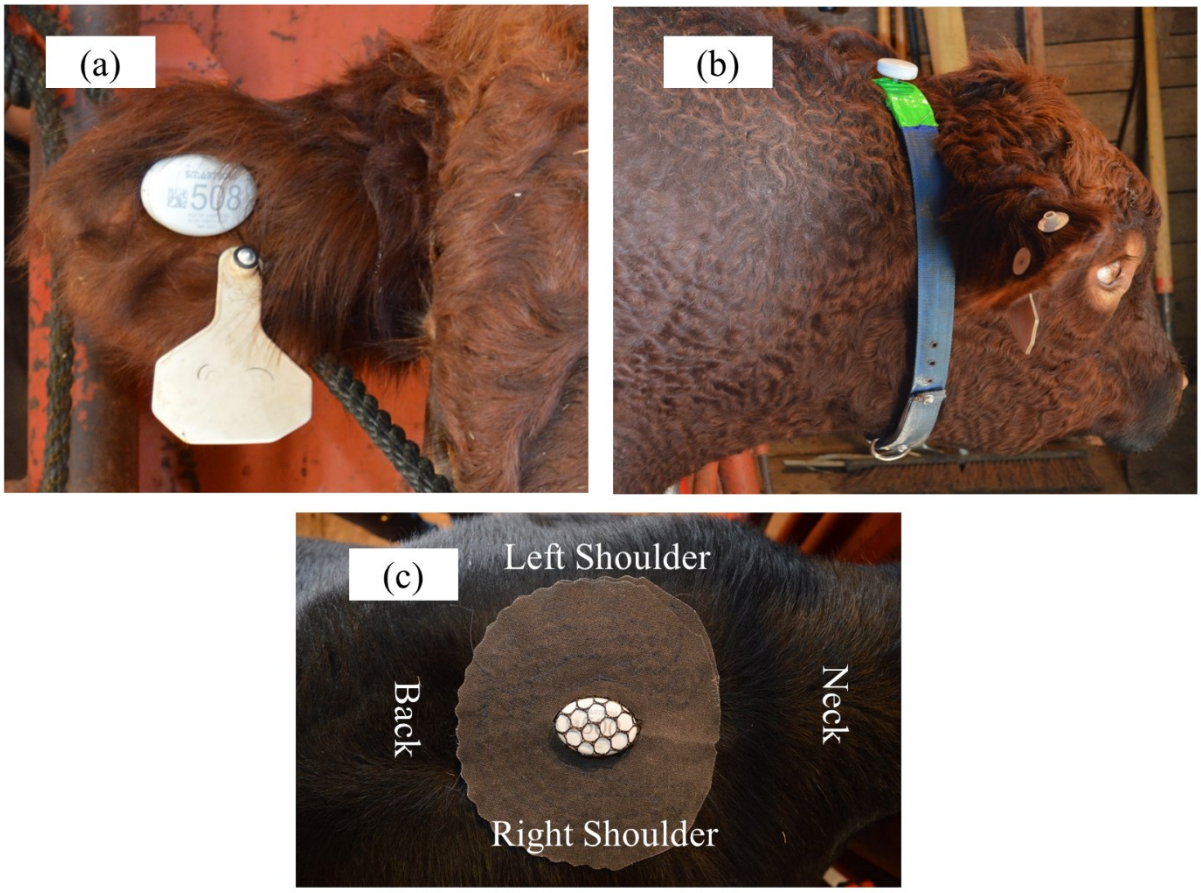
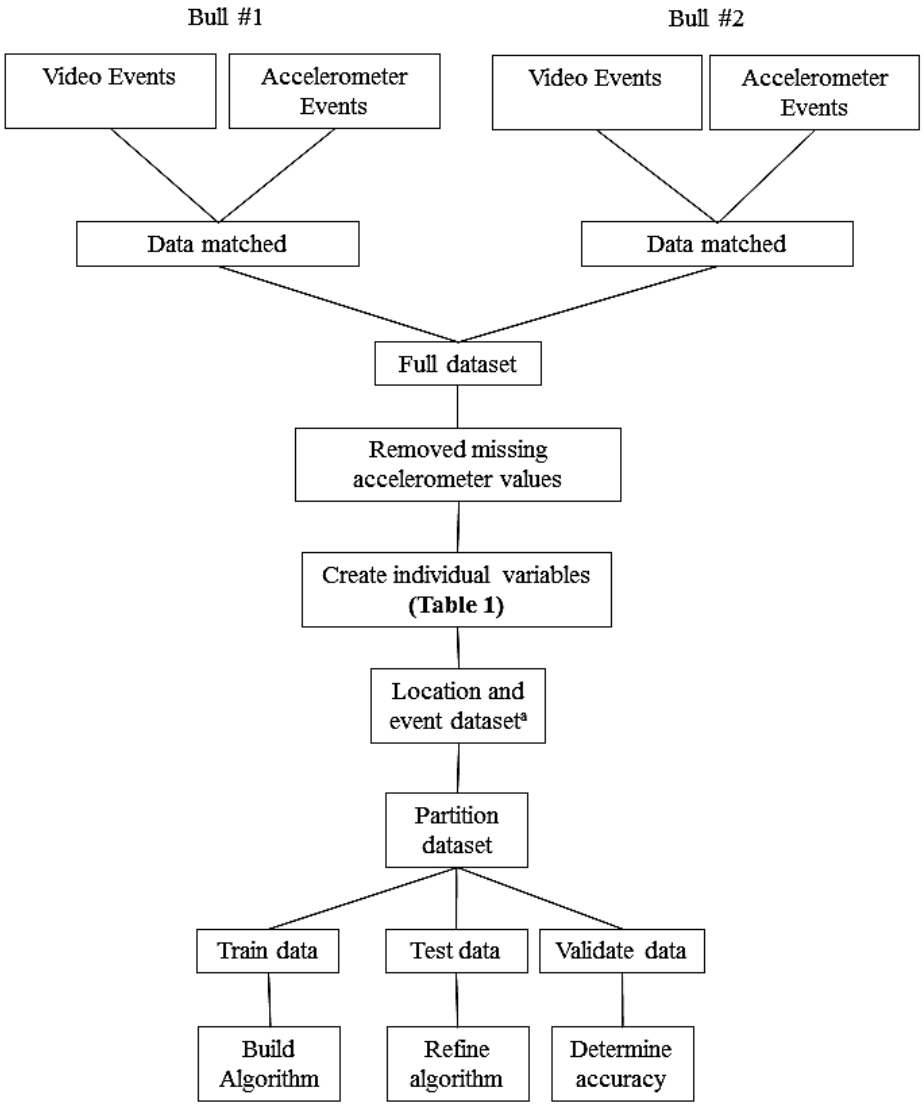


Figure 3.2. Flow diagram of data preparation, refinement, partitioning, and classification algorithm evaluations.



[a] The location and event dataset was repeated for each location (ear, neck, and wither) within each behavior event of interest (lying, standing, walking, and mounting) within three different classification algorithms (Random Tree, Random Forest, and Decision Tree) creating a total of 36 different classification algorithms evaluated.

Table 3.1. Variables created on full dataset that was used for the classification algorithm. This was performed after missing data and behaviors of non-interest were removed and prior to the data being sub-grouped by tag location within behavior event.

Variable	Description
Animal Identification	bull 1 and bull 2
Accelerometer Tag	unique number for each Smartbow accelerometer tag
Recording time	mm/dd/yyyy hh:mm:ss
Behavior	lying, standing, walking, mounting, other, out of Frame
xaccel	accelerometer reading for x axis
yaccel	accelerometer reading for y axis
zaccel	accelerometer reading for z axis
Accelerometer Location	left ear, right ear, neck, wither
Sumxyz	xaccel + yaccel + zaccel
Avgxyz	average(xaccel +yaccel + zaccel)
Mounting_0/1	mounting event = 1 non-mounting event = 0
MA(xaccel)	moving average, repeated for every 2, 5, 10, 15, 30, 60, and 120 rows of data within the xaccel column
MA(yaccel)	moving average, repeated for every 2, 5, 10, 15, 30, 60, and 120 rows of data within the yaccel column
MA(zaccel)	moving average, repeated for every 2, 5, 10, 15, 30, 60, and 120 rows of data within the zaccel column
MA(sumxyz)	moving average, repeated for every 2, 5, 10, 15, 30, 60, and 120 rows of data within the sumxyz column
MA(avgaxy)	moving average, repeated for every 2, 5, 10, 15, 30, 60, and 120 rows of data within the avgxyz column
Range(xaccel)	moving aggregation, range calculation for every 2, 5, 10, 15, 30, 60, and 120 rows of data within the xaccel column
Range(yaccel)	moving aggregation, range calculation for every 2, 5, 10, 15, 30, 60, and 120 rows of data within the yaccel column
Range(zaccel)	moving aggregation, range calculation for every 2, 5, 10, 15, 30, 60, and 120 rows of data within the zaccel column
Range(sumxyz)	moving aggregation, range calculation for every 2, 5, 10, 15, 30, 60, and 120 rows of data within the sumxyz column
Range(avgaxy)	moving aggregation, range calculation for every 2, 5, 10, 15, 30, 60, and 120 rows of data within the avgxyz column

Delta(xaccel)	difference between MA(xaccel) and xaccel values for every 2, 5, 10, 15, 30, 60, and 120 rows of data with those columns
Delta(yaccel)	difference between MA(yaccel) and yaccel values for every 2, 5, 10, 15, 30, 60, and 120 rows of data with those columns
Delta(zaccel)	difference between MA(zaccel) and zaccel values for every 2, 5, 10, 15, 30, 60, and 120 rows of data with those columns
Delta(sumxtz)	difference between MA(sumxyz) and sumxyz values for every 2, 5, 10, 15, 30, 60, and 120 rows of data with those columns
Delta(avgxyz)	difference between MA(avgxyz) and avgxyz values for every 2, 5, 10, 15, 30, 60, and 120 rows of data with those columns

Table 3.2. Diagnostic performance of classifiers[a] for lying behavior = 1 for each tag location.

Tag location	Classifier	ROC prob	TP[b]	FP[b]	TN[b]	FN[b]	Se (%)	Sp (%)	PVP[b] (%)	NVP[b] (%)	Acc (%)	Prev (%)
Ear	DT	0.5	13,728	4729	32116	1711	88.9	87.2	74.4	94.9	87.7	29.53
	RT	0.5	13,354	5281	31564	2085	86.5	85.7	71.7	93.8	85.9	29.53
	RF	0.6	13,662	2610	34235	1777	88.5	92.9	84.0	95.1	91.6	29.53
Neck	DT	0.5	9435	1118	18968	493	95.0	94.4	89.4	97.5	94.6	33.08
	RT	0.5	9228	1328	18758	700	92.9	93.4	87.4	96.4	93.2	33.08
	RF	0.5	9375	300	19786	553	94.4	98.5	96.6	97.3	97.2	33.08
Wither	DT	0.5	7,893	412	18131	191	97.6	97.8	95.0	99.0	97.7	30.36
	RT	0.5	7,883	511	18032	201	97.5	97.2	93.9	98.9	97.3	30.36
	RF	0.5	7,911	86	18457	173	97.9	99.5	98.9	99.1	99.0	30.36

[a] DT = Decision Tree, RT = Random Tree, RF = Random Forest

[b] TP = true positive, FP = false positives, TN = true negative, FN = false negatives, PVP = positive predictive value, NVP = negative predictive value

Table 3.3. Diagnostic performance of classifiers[a] for standing behavior = 1 for each tag location.

Tag location	Classifier	ROC prob	TP[b]	FP[b]	TN[b]	FN[b]	Se (%)	Sp (%)	PVP[b] (%)	NVP[b] (%)	Acc (%)	Prev (%)
Ear	DT	0.3	26,615	3465	16,591	5613	82.6	82.7	88.5	74.7	82.6	61.64
	RT	0.5	24,410	4647	15,409	7818	75.7	76.8	84.0	66.3	76.2	61.64
	RF	0.5	27,447	3213	16,843	4781	85.2	84.0	89.5	77.9	84.7	61.64
Neck	DT	0.5	15,126	1601	10,897	2390	86.4	87.2	90.4	82.0	86.7	58.36
	RT	0.5	14,940	1779	10,719	2576	85.3	85.8	89.4	80.6	87.6	58.36
	RF	0.5	16,246	1585	10,913	1270	92.7	87.3	91.1	89.6	90.5	58.36
Wither	DT	0.3	13,795	1634	8919	2279	85.8	84.5	89.4	79.6	85.3	60.37
	RT	0.5	13,489	1579	8974	2585	83.9	85.0	89.5	77.6	84.4	60.37
	RF	0.5	14,725	1669	8884	1349	91.6	84.2	89.8	86.8	88.7	60.37

[a] DT = Decision Tree, RT = Random Tree, RF = Random Forest

[b] TP = true positive, FP = false positives, TN = true negative, FN = false negatives, PVP = positive predictive value, NVP = negative predictive value

Table 3.4. Diagnostic performance of classifiers[a] for walking behavior = 1 for each tag location.

Tag location	Classifier	ROC prob	TP[b]	FP[b]	TN[b]	FN[b]	Se (%)	Sp (%)	PVP[b] (%)	NVP[b] (%)	Acc (%)	Prev (%)
Ear	DT	0.6	2756	15,725	32,504	1299	68.1	67.2	14.9	96.2	67.2	7.76
	RT	0.5	2773	16,357	31,872	1282	68.4	66.1	14.5	96.1	66.3	7.76
	RF	0.5	2931	12,803	35,426	1124	72.3	73.5	18.6	96.9	73.4	7.76
Neck	DT	0.5	1647	7689	20,065	613	72.9	72.3	17.6	97.0	72.3	7.53
	RT	0.5	1595	8343	19,411	665	70.6	69.9	16.0	96.7	70.0	7.53
	RF	0.5	1767	6620	21,134	493	78.2	76.1	21.1	97.7	76.3	7.53
Wither	DT	0.5	1627	6898	17,529	573	74.0	71.8	19.1	96.8	71.9	8.26
	RT	0.5	1585	7128	17,299	615	72.0	70.8	182	96.6	70.9	8.26
	RF	0.5	1776	5673	18,754	423	80.8	76.8	23.8	97.8	77.1	8.26

[a] DT = Decision Tree, RT = Random Tree, RF = Random Forest

[b] TP = true positive, FP = false positives, TN = true negative, FN = false negatives, PVP = positive predictive value, NVP = negative predictive value

Table 3.5. Diagnostic performance of classifiers[a] for mounting behavior = 1 for each tag location.

Tag location	Classifier	ROC prob	TP[b]	FP[b]	TN[b]	FN[b]	Se (%)	Sp (%)	PVP[b] (%)	NVP[b] (%)	Acc (%)	Prev (%)
Ear	DT	0.7	263	16,712	35,218	91	74.3	67.8	1.5	99.7	67.9	0.68
	RT	0.5	248	16,828	35,102	106	70.1	67.6	1.5	99.7	67.6	0.68
	RF	0.6	273	13,621	38,309	81	77.1	73.8	2.0	99.8	73.8	0.68
Neck	DT	0.5	141	7126	22,692	55	71.9	76.1	1.9	99.8	76.1	0.65
	RT	0.5	155	5979	23,839	41	79.1	79.9	2.5	99.8	79.9	0.65
	RF	0.5	155	5979	23,839	41	79.1	79.9	2.5	99.8	79.9	0.65
Wither	DT	0.5	137	7395	19,055	40	77.4	72.0	1.8	99.8	72.1	0.66
	RT	0.5	138	8310	18,140	39	78.0	68.6	1.6	99.8	68.6	0.66
	RF	0.6	143	5784	20,666	34	80.8	78.1	2.4	99.8	78.1	0.66

[a] DT = Decision Tree, RT = Random Tree, RF = Random Forest

[b] TP = true positive, FP = false positives, TN = true negative, FN = false negatives, PVP = positive predictive value, NVP = negative predictive value.

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Chapter 4 - A mixed treatment comparison meta-analysis of metaphylaxis treatments for bovine respiratory disease in beef cattle

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Abstract

The objective of this project was to evaluate the effects of antimicrobials approved for parenteral metaphylactic use in feeder and stocker calves on morbidity and mortality for bovine respiratory disease with the use of a mixed treatment comparison meta-analysis. An initial literature review was conducted in April 2016 through Pubmed, Agricola, and CAB for randomized controlled trials for metaphylaxis antimicrobial administered parentally to incoming feedlot or stocker calves within 48 h of arrival. The final list of publications included 29 studies, with a total of 37 trials. There were 8 different metaphylactic antimicrobials. Final event outcomes were categorized into BRD morbidity cumulative incidence d 1 to ≤ 60 of the feeding period, BRD morbidity cumulative incidence d 1 to closeout of the feeding period, BRD mortality cumulative incidence d 1 to closeout of the feeding period, and BRD retreatment cumulative incidence morbidity d 1 to closeout of the feeding period. Network meta-analysis combined direct and

indirect evidence for all the event outcomes to determine mean odds ratio (OR) with 95% credibility intervals (CrIs) for all metaphylactic antimicrobial comparisons. The "upper tier" treatment arms for morbidity d 1 to ≤ 60 included tulathromycin, gamithromycin, and tilmicosin. For BRD mortality cumulative incidence d 1 to closeout and BRD retreatment morbidity d 1 to closeout, classifying the treatment arms into tiers was not possible due to overlapping 95% CrIs. The results of this project accurately identified differences between metaphylactic antimicrobials, and metaphylactic antimicrobial options appear to offer different outcomes on BRD morbidity and mortality odds in feedlot cattle.

Introduction

Bovine respiratory disease (BRD) complex is a well-documented, multi-faceted disease syndrome involving environmental factors, host factors, and management practices affecting the health and performance of feedlot calves (Kelly & Janzen, 1986; Smith, 1998). Marketing and shipment of cattle are associated with stress prior to feedlot arrival, which increases the risk for BRD of fed cattle (Camp et al., 1981; Lofgreen et al., 1978). Mass medication, also known as metaphylaxis, has been used to prevent BRD in groups of cattle arriving at feedlots with over half of United States feedlots using metaphylaxis on at least some groups of cattle near the time of feedlot arrival (USDA, 2011a).

Multiple antimicrobials are currently available and used metaphylactically to decrease negative effects of BRD in groups of feedlot cattle, and the decision to implement a specific antimicrobial is dependent on the efficacy and cost effectiveness (Nickell & White, 2010). Clinical trials have been conducted to investigate the efficacy of antimicrobials for the treatment and control of BRD, and metaphylaxis uses have been investigated as a method to reduce morbidity and mortality associated with BRD in feedlot cattle (DeDonder & Apley, 2015; Ives &

Richeson, 2015). Meta-analysis and systematic reviews of the available literature have been previously performed to summarize published clinical trials for antimicrobial treatment of clinical BRD cases and for specific antimicrobials used metaphylactically, but no systematic review or meta-analysis has been published that summarizes clinical trials for all approved parenterally administered metaphylactic antimicrobials (Nickell & White, 2010; Van Donkersgoed, 1992; Wellman & O'Connor, 2007; Wileman et al., 2009).

A mixed treatment comparison (MTC) meta-analysis can assess indirect comparisons between antimicrobials where an actual clinical trial was not performed. (Higgins & Whitehead, 1996; Jansen et al., 2011; Lu & Ades, 2004b). The indirect comparison have been proven to be realistic estimates of disease risk when direct estimates are not available (O'Connor et al., 2016). The MTC of meta-analysis has been done frequently in the human medical field (Mills et al., 2009; Roever & Biondi-Zoccai, 2016; Shao et al., 2016), and has previously evaluated antimicrobial efficacy for treatment of BRD (O'Connor et al., 2013). The objective of this research was to evaluate the effect of parenterally administered metaphylactic antimicrobials approved for feeder and stocker calves on morbidity and mortality due to BRD using a MTC meta-analysis. These results should aid in the understanding of the effect of metaphylactic antimicrobial options on clinically important BRD outcomes.

Materials and Methods

Literature search

An initial literature review was conducted in April 2016 by a reviewer (KA) using, AGRICOLA (all years available), Commonwealth Agricultural Bureau (all years available), and Pubmed (all years available) for retrieval of topics relevant to the objective. The search terms included [beef OR cattle OR cow or OR bovine OR steer OR heifer OR calf OR calves] AND

[metaphyl* OR prophylactic]. An initial search revealed a total of 3,753 papers. Titles of peer reviewed papers published in English that included the search terms were examined for relevance. The initial search process was repeated with another independent reviewer (RL). Abstracts of relevant manuscripts were reviewed, and if agreed relevant, the full manuscript was acquired. Relevant manuscripts obtained by both reviewers were compared and only those relevant to the objective were fully reviewed. A third party reviewer was utilized if a disagreement between the first two reviewers occurred over the relevance of a manuscript.

Studies were excluded if randomization was not reported. In addition, metaphylaxis antimicrobial had to be administered parentally to incoming feedlot or stocker calves within 48 h of arrival. Studies using young, lightweight veal or dairy calves were excluded; however, if age, weight, or type of cattle were specifically described and were consistent with cattle arriving at U.S. feedlots, the study was included in the analysis. Metaphylactic administration had to be the only treatment variable. Only naturally occurring BRD was used as study outcome and challenge studies were excluded from the analysis. Blinding was reported in 24 trials, and was not reported in 16 trials, all trials were included in the statistical analysis regardless of blinding criteria. In two trials, blinding was reported to have not been possible due to the person implementing the BRD treatment protocol having prior knowledge of previous antimicrobials administered metaphylactically (Van Donkersgoed, 2012; Van Donkersgoed & Merrill, 2013a).

Data extraction

Outcome data comparing a metaphylactic antimicrobial to another antimicrobial or a control within each trial within each study was extracted (Larson & Step, 2012; Theurer et al., 2015). If a study contained multiple trials, the data from each trial were extracted separately. All data for each trial were extracted by a single reviewer (KA), and verified by a second reviewer

(RL). A treatment arm was considered a different antimicrobial for each trial. For example, if a trial consisted of antimicrobial A and B, this trial included two different treatment arms. For each trial, the following data were extracted: the interventions (antimicrobial) for each treatment arm, the number of animals enrolled in each treatment arm, and event occurrence for each treatment arm (Table 1). Event occurrence included morbidity, retreatment morbidity, and mortality related to BRD. Data were aggregated between treatment arms within a trial if the difference between those treatment arms was due to a difference in the post metaphylactic interval or route of antimicrobial administration. For example, if the difference between two antimicrobial groups was the dosage of the antibiotic (tilmicosin 10 mg/kg and 20 mg/kg), then antimicrobials were aggregated to a single antimicrobial group (tilmicosin) (Corbin et al., 2009). Also, if the difference between two treatments with the same antimicrobial was due to post-metaphylactic interval (ceftiofur 3 PMI and 7 PMI), then antimicrobials were aggregated to a single antimicrobial group (ceftiofur) (Booker et al., 2006).

BRD morbidity included calves that were enrolled in the trial and had to be treated for BRD. The protocol for BRD diagnosis needed to be described in the report, and had to include rectal temperature, clinical signs consistent with BRD, and administration of an antimicrobial. If this protocol was not outlined, the corresponding author was contacted for clarification of the protocol to diagnose BRD. Two corresponding authors were contacted and responded for clarification. If the results were given as a percent of animals in each treatment arm, then the event occurrence was extracted based on the total number of animals enrolled in that trial for each of the treatment arms. If the numerator and denominator used to calculate the percent could not be distinguished, the data were excluded in the analysis.

BRD retreatment morbidity was classified as animals initially diagnosed with BRD and treated with an antimicrobial that required an additional antimicrobial for BRD. If mortality data were not provided in the trial, or BRD mortality could not be distinguished from the overall mortality events, the mortality data were excluded in the analysis.

Treatment periods were established as either d 1 to ≤ 60 of the feeding period or d 1 to the end of the feeding period, and a single event could be classified as occurring in both treatment periods. The end of the feeding period is referred to as closeout. Day 1 included the day the metaphylactic treatment was given. If the monitoring period of the study was less than 60 d, the data were only included in the d 1 to ≤ 60 of the feeding period category. Trial days ranged from 7 – 60 d and this variability was accounted for in the analysis. If a trial included event results from d 1 to ≤ 60 over multiple periods, the event results closest to 60 d was included. Any trial data that did not fall into one of these categories were excluded.

Multiple treatment comparison analysis

The effectiveness of each individual treatment arm for the BRD morbidity d 1 to ≤ 60 was examined using the binomial likelihood, complimentary log-log (cloglog) link, random-effects model for combining direct and indirect evidence in mixed treatment comparisons using a Bayesian approach as previously described (Dias et al., 2010; Higgins & Whitehead, 1996; Lu & Ades, 2004b). This model assumes that the outcome for BRD morbidity d 1 to ≤ 60 is time dependent, and based on the differing lengths of each treatment arm the time until an event occurs has an exponential distribution (Dias et al., 2011). Differing days at risk were accounted for BRD morbidity d 1 to ≤ 60, for example if a trial period was 14 days, the days at risk would be 14/60 = 0.23 days at risk. Trial days were only accounted for in trials included in the BRD morbidity d 1 to ≤ 60 outcome. The effectiveness of each individual treatment arm for BRD

morbidity, BRD mortality, and BRD retreatment d 1 to ≤ closeout was examined using the binomial likelihood, logit link, random-effects model for combining direct and indirect evidence in mixed treatment comparisons using a Bayesian approach similar to d 1 to ≤ 60 d evaluation. (Dias et al., 2010; Higgins & Whitehead, 1996; Lu & Ades, 2004b). This model assumes that the proportional odds assumption holds, that all trials occur within the same time period, and further days at risk would not affect the differences between events (Dias et al., 2011). The code was called through WinBUGS with R to fit the model with the R2Winbugs package (Dias et al., 2011).

A homogeneous variance was assumed and uniformed priors were used for the standard deviation, σ for each of the BRD morbidity d 1 to ≤ 60 d, BRD morbidity d 1 to closeout, BRD mortality d 1 to closeout, and BRD retreatment morbidity d 1 to closeout models. Two uniform standard deviation priors were compared for each individual outcome model, σ ~ uniform (0, 5) vs. σ ~ uniform (0, 2), and based on narrower CrIs and lower deviance information criterion (DIC), σ ~ uniform (0, 5) was used in the final code. Gelman-Rubin diagnostics were performed to determine best convergence for chains (Gelman & Rubin, 1992). A total of two chains were used for each model, each with 120,000 iterations, with the first 20,000 interactions discarded. The output from the code was the posterior mean for odds ratio between the treatment arm comparisons with corresponding 95% CrIs. Treatment arms with the least OR and with corresponding overlapping 95% CrIs were classified as “upper tier.” Treatment arms with the greatest OR and with corresponding overlapping 95% CrIs were classified as “lesser tier.” Treatment arms in between the greatest and least OR and with corresponding overlapping 95% CrIs were classified as “middle tier.”

Results

After initial screening for relevant titles and abstracts, a final list of 170 publications were retrieved and evaluated. From these publications, 29 studies, with a total of 37 trials met all inclusion criteria. The length of the trial periods ranged from 7 to 293 days. Only BRD morbidity cumulative incidence is reported for treatment period d 1 to ≤ 60 of the feeding period and all event outcomes (BRD morbidity, mortality, and retreatment morbidity) are reported for treatment period d 1 to closeout.

Figure 4.1 shows a network of the different treatment arms included for each individual event outcome. BRD morbidity cumulative incidence d 1 to ≤ 60 included 62 treatment arms from 27 trials, BRD morbidity cumulative incidence d 1 to closeout included 37 treatment arms from 13 trials, BRD mortality cumulative incidence d 1 to closeout included 40 treatment arms from 14 trials, and BRD retreatment morbidity cumulative incidence d 1 to closeout included 26 treatment arms from 11 trials (Fig. 4.1). The maximum number of treatment arms within a trial were four (Booker et al., 2007; Harland et al., 1991; Morck et al., 1993; Tennant et al., 2014), all other trials contained two treatment arms. There were a total of 8 different metaphylactic antimicrobials (Table 4.1). All treatment arms were included in four or more trials except florfenicol, tildipirosin, and TMS. Florifenicol had three trials, tildipirosin had 1 trial, and TMS had 1 trial included. A placebo control was present in 25 trials.

Forest plots of the mean odds ratio (OR) comparisons between antimicrobial and control with 95% CrIs for each event outcome are shown in Fig 4.2. The dotted line in the center of each forest plot designates the OR equal to 1. If the OR are equal to 1, odds of the event occurrence are the same for the antimicrobial compared to the control; if odds are less than 1, the odds for the event occurrence are greater for the control compared to the antimicrobial; if odds are greater

than 1, the odds for the event occurrence are greater for the antimicrobial compared to the control. BRD morbidity cumulative incidence d 1 to ≤ 60 "upper tier" treatment arms were tulathromycin, gamithromycin, and tilmicosin. The "middle tier" included ceftiofur and oxytetracycline, and the "lesser tier" included florfenicol and TMS. Morbidity cumulative incidence d 1 to closeout "upper tier" treatment arms included tulathromycin, the "middle tier" include tildipirosin, gamithromycin, ceftiofur, tilmicosin, and oxytetracycline, and the "lesser tier" included TMS. Mean odds ratios (OR) for all comparisons between antimicrobials with 95% CrIs for each event outcome are shown in Table 4.2.

For BRD mortality cumulative incidence d 1 to closeout and BRD retreatment morbidity d 1 to closeout, classifying the treatment arms into tiers was not possible due to overlapping 95% CrIs. However, there were some differences between individual antimicorbials. In Fig. 4.2(c), the 95% CrIs for tulathromycin did not overlap with the 95% CrIs of tilmicosin and oxytetracycline. Overall, tulathromycin and tilmicosin has a lesser odds than the controls, and oxytetracycline is similar to the controls. The OR and 95% CrIs of the comparison of tulathromycin vs. tilmicosin is 0.26 (0.13-0.49) and tulathromycin vs. oxytetracycline is 0.20 (0.08 - 0.41) (Table 4.2(c)). OR for tulathromycin is different from tilmicosin and oxytetracycline, and the odds of mortality cumulative incidence d 1 to closeout of the feeding period is 4 times greater for tilmicosin than tulathromycin, and 5 times greater for oxytetracycline than tulathromycin.

Discussion

The results of the MTC meta-analysis were able to accurately identify differences between metaphylactic antimicrobials related to BRD morbidity, retreatment, and mortality. A wide variety of trials conducted between different antimicrobials were identified in the published literature. This MTC meta-analysis allows for simultaneous inference between treatment arms

based on the model estimates (Lu & Ades, 2004b). The data included in the MTC meta-analysis performs comparisons between the direct and indirect treatments and allows precision to increase with the assumption of consistency between these antimicrobials (Salanti et al., 2008).

Veterinarians and producers establish a metaphylactic treatment protocol based on prior knowledge of the incoming group of calves risk factors, season, weight, geographic origin, prior experience and published literature (Ribble et al., 1995; Sandersonet al., 2008; Snowder et al., 2006; USDA, 2011a). The overall goal of a metaphylactic antimicrobial is to decrease the risk and negative effect of BRD in feedlot cattle. The results from this MTC meta-analysis provide veterinarians and producers guidance to more accurately predict the expected outcomes when choosing among antimicrobials to use on incoming high-risk cattle in a feedlot or stocker operation. For example, tulathromycin has the least OR compared to all other treatment arms in BRD morbidity cumulative incidence d 1 to ≤ 60 d, BRD morbidity cumulative incidence d 1 to closeout, BRD mortality cumulative incidence d 1 to closeout, and BRD retreatment morbidity cumulative incidence d 1 to closeout outcomes when compared to controls (Fig. 4.2). Tulathromycin is also comparable to other antimicrobials for BRD morbidity cumulative incidence d 1 to ≤ 60, because the 95% CrIs of tulathromycin overlaps with gamithromycin and tilmicosin (Fig. 4.2(a)). These three "upper tier" treatment arms appear comparable in the effect differences between controls for the odds of disease. Results from a MTC meta-analysis can be applied to a group of incoming cattle, if this group has a predicted BRD morbidity of 30% within the first 60 days of the feeding period. If all cattle are administered at arrival an "upper tier" treatment with an OR 0.1 – 0.2, then the expected BRD morbidity would be about 4% to 8%, or a 80 to 90% reduction in odds of being diagnosed with BRD compared to controls. Overall, this

type of analysis has the potential to efficiently estimate the odds of disease which can be used to assess comparative health, performance, and economic outcomes of feedlot and stocker cattle.

Previous meta-analyses have indicated metaphylaxis can reduce BRD morbidity, and that reduction can be from 55% to 29% comparing control cattle to treated (Van Donkersgoed, 1992; Wileman et al., 2009). Mortality due to BRD has also been reported to be reduced from 3.8% to 1.8% for cattle not receiving metaphylaxis compared to those that do receive metaphylaxis (Wileman et al., 2009). The results from this MTC meta-analysis presented similar results; cattle treated with an antimicrobial have a reduced OR compared to controls for morbidity (Fig. 4.2) and allows producers and veterinarians to compare efficacy between antimicrobials, to determine antimicrobials that are similar (i.e. no difference), and antimicrobials that may be superior to other antimicrobials (i.e. a difference exists).

Event outcome for BRD mortality in Fig. 4.2(c) had overlapping 95% CrIs for all the treatment arms making full interpretation of these antimicrobial comparisons challenging. The lack of identified differences between multiple treatments arms may be due to the low incidence of mortality in feedlots (Snowder et al., 2006), and the incidence was low in the studies included in the analysis which most likely contributes to the overlapping CrIs. The lack of differences does not imply observed differences would not be higher in populations at a higher risk for BRD mortality.

In the US, 59% of all feedlot cattle are treated with a metaphylactic antimicrobial at arrival (USDA, 2011a). Analyzing retreatment of cattle diagnosed with BRD after metaphylactic administration is beneficial in determining the overall affect the metaphylactic antimicrobial has on BRD morbidity, treatment success, and mortality. Retreatment for the present study refers to animals initially diagnosed with BRD and treated with an antimicrobial that required an

additional antimicrobial for BRD. The results from this MTC meta-analysis for the BRD retreatment morbidity cumulative incidence were challenging to interpret, event outcome for BRD retreatment morbidity in Fig. 4.2(d) had overlapping 95% CrIs for all the antimicrobial arms. An analysis to compare retreatment protocols after initial metaphylactic administration was attempted, but was unsuccessful due to few trials with similar BRD retreatment morbidity protocols that could be compared.

The prevalence of BRD morbidity differs among days following feedlot arrival (Babcock et al., 2010). The reported trial days in the treatment period d 1 to ≤ 60 were variable in the total days at risk for calves. Accounting for variability days at risk for treatment periods is necessary when analyzing the odds of disease for a MTC meta-analysis which we accomplished using the binomial likelihood, complimentary log-log (cloglog) link, random-effects model for combining direct and indirect evidence in mixed treatment comparisons using a Bayesian approach. While this model accounts for days at risk, it cannot account for a skewed distribution of morbidity case occurrence in the first 60 days.

When a study is published, reporting all aspects of the design, such as blinding, randomization, and allocation to treatment units, is crucial to perform a MTC meta-analysis. Because of incomplete reporting, making decisions based on published literature can be hampered due to limited data and subjective prediction (Jackson, 2006; Pollreisz et al., 1991). Previous publications have reported lack of reporting of crucial aspects of trials and the influence the inclusion or exclusion of specific trials have on the final analysis of a systematic review or meta-analysis (O'Connor et al., 2013; Theurer et al., 2015; Van Donkersgoed, 1992). A limitation of this project included the limited published literature for many of the metaphylactic treatments. Inconsistency may increase when later publications are combined with earlier

publications due to changes in cattle, pathogens, or management over time, and careful consideration should be made when interpreting results from a MTC meta-analysis if the data between trials appears to be inconsistent (Mills et al., 2012).

Summary and Conclusions

The results from this MTC meta-analysis identified differences between parenteral metaphylactic antimicrobial options currently available. Metaphylactic antimicrobial options appear to offer different effects on BRD morbidity and mortality odds in feedlot and stocker cattle. Further research is needed to determine the effects of different metaphylactic antimicrobials on the BRD mortality, retreatment morbidity, performance, and economics of feedlot cattle.

Table 4.1. Data extracted from 37 individual trials and 29 studies included in the mixed treatment comparison meta-analysis for each outcome event.

[1] Experimental units per antimicrobial group
[2] Allocation weight in kilograms
[3] BRD morbidity cumulative incidence d 1 to ≤ 60 of the feeding period
[4] BRD morbidity cumulative incidence d 1 to close out of the feeding period
[5] BRD mortality cumulative incidence d 1 to closeout
[6] BRD retreatment cumulative incidence d 1 to closeout

Treatment Arms	Number of animals	EU's/group[1]	Wt[2] (kg)	BRD morb to 60[3]	BRD morb to closeout[4]	BRD mort to closeout[5]	BRD retreat to closeout[6]	Trial
ceftiofur/gamithromycin	1853	931/922	205	354/295	-	-	-	(D. Amrine et al., 2014)
control/gamithromycin	87	44/43	582	12/8	-	-	-	(Baggott et al., 2011)
control/gamithromycin	242	121/121	390	32/8	-	-	-	(Baggott et al., 2011)
control/gamithromycin	227	114/113	430	32/6	-	-	-	(Baggott et al., 2011)
tilmicosin/oxytetracycline/tulathromycin	9910	3304/3302/3304	300	-	464/562/113	62/84/10	179/218/26	(Booker, Abutarbush, Schunicht, Jim, Perrett, et al., 2007)
tilmicosin/ceftiofur	11,605	3870/7735	256	-	1116/2120	423/626	713/1222	(Booker, Abutarbush, Schunicht, Jim, Perrett, et al., 2007)
control/tilmicosin	1000	200/800	207	-	68/164	27/54	23/58	(Corbin et al., 2009)

control/tilmicosin	997	200/797	265	-	137/374	1/14	53/107	(Corbin et al., 2009)
control/tilmicosin	64	32/32	224	23/15	-	-	-	(Duff, Walker, Malcolm-Callis, Wiseman, & Hallford, 2000)
control/oxytetracycline	1793	893/900	120	71/30	-	-	-	(Fazzio, Giuliodori, Galvan, Streitenberger, & Landoni, 2015)
control/florfenicol	60	30/30	230	13/10	-	-	-	(Frank, Briggs, Duff, Loan, & Purdy, 2002)
control/florfenicol	42	21/21	230	12/9	-	-	-	(Frank et al., 2002)
control/tilmicosin	57	28/29	170	13/0	-	-	-	(Galyean, Gunter, & Malcolm-Callis, 1995)
control/tilmicosin	116	58/58	191	19/7	-	-	-	(Galyean et al., 1995)
control/tilmicosin	121	62/59	232	27/7	-	-	-	(Galyean et al., 1995)

control/tilmicosin	400	200/200	273	113/51	123/60	0/2	12/8	(C. A. Guthrie et al., 2004)
control/TMS/oxytetracycline	900	300/300/300	325	139/133/97	172/169/140	10/9/6	-	(Harland et al., 1991)
control/gamithromycin	308	154/154	293	64/34	-	-	-	(Lechtenberg et al., 2011)
control/gamithromycin	159	53/106	256	34/15	-	-	-	(Lechtenberg et al., 2011)
control/florfenicol	108	54/54	271	16/18	-	-	-	(Martin et al., 2007)
control/tilmicosin	199	100/99	215	54/15	-	-	-	(McClary & Vogel, 1999)
control/tilmicosin/oxytetracycline	1806	601/602/603	300	254/117/157	-	-	-	(Morck et al., 1993)
tilmicosin/tulathromycin	293	147/146	219	100/48	-	20/5	-	(Nickell, White, Larson, Blasi, & Renter, 2008)
control/gamithromycin	250	125/125	350	43/6	-	-	-	(Rossi, Vandoni, Bonfanti, & Forbes, 2010)
oxytetracycline/gamithromycin	470	235/235	345	34/4	-	-	-	(Rossi et al., 2010)
tulathromycin/gamithromycin	1136	568/568	325	83/53	-	-	-	(Rossi et al., 2010)

control/tilmicosin	305	154/151	337	35/8	-	-	-	(Schumann, Janzen, & McKinnon, 1990)
control/tilmicosin	205	103/102	269	21/2	-	-	-	(Schumann, Janzen, & McKinnon, 1991)
tilmicosin/oxytetracycline	10,989	5494/5495	281	-	1064/1239	77/85	409/454	(Schunicht, Guichon, et al., 2002b)
tilmicosin/ceftiofur	385	194/191	-	14/18	-	-	-	(Step et al., 2007)
control/tilmicosin/tulathromycin	2336	783/784/769	312	-	112/45/16	24/11/8	-	(Tennant et al., 2014)
tulathromycin/gamithromycin	2529	1266/1263	230	274/361	-	-	-	(Torres, Thomson, Bello, Nosky, & Reinhardt, 2013a)
tilmicosin/gamithromycin	5000	2500/2500	312	-	480/320	10/15	81/44	(Van Donkersgoed, 2012)
tilmicosin/tildipirosin	4500	2250/2250	336	-	608/338	20/20	79/54	(Van Donkersgoed & Merrill, 2013a)
control/tilmicosin	4314	2157/2157	348	-	259/173	9/2	53/33	(Van Donkersgoed & Merrill, 2013b)

tilmicosin/tulathromycin	4494	2250/2244	274	-	315/67	5/1	28/7	(J. Van Donkersgoed, J. K. Merrill, & S. Hendrick, 2008)
control/tilmicosin	1096	550/546	259	298/165	317/185	23/9	50/22	(G. J. Vogel et al., 1998)

Table 4.2. The mean odds ratio with 95% credibility intervals for BRD morbidity cumulative incidence d 1 to ≤ 60 of the feeding period (a)[1], BRD morbidity cumulative incidence d 1 to close out of the feeding period (b)[2], BRD mortality cumulative incidence d 1 to closeout (c)[2], and BRD retreatment cumulative incidence d 1 to closeout (d)[2] of the mixed treatment comparison meta-analysis. The metaphylactic antimicrobial on the left for all odds ratio comparisons is the reference category.

[1] Binomial likelihood, complimentary log-log (cloglog) link, random-effects model
[2] Binomial likelihood, logit link, random-effects model
[3] The antimicrobial on the left of each comparison is the denominator in the ratio, and the antimicrobial on the right is the numerator. If the OR are equal to 1, odds of the event occurrence are the same for each antimicrobial; if odds are less than 1, the odds for the event occurrence are greater for the antimicrobial on the left; if odds are greater than 1, the odds for the event occurrence are greater for the antimicrobial on the right.

	Comparison[3]	OR	95% CrIs		
(a) BRD morbidity d 1 to ≤ 60	tilmicosin vs. TMS	3.59	1.19	-	9.30
	tilmicosin vs. oxytetracycline	2.16	1.11	-	3.92
	tilmicosin vs. florfenicol	3.15	1.26	-	6.68
	tilmicosin vs. tulathromycin	0.59	0.27	-	1.14
	tilmicosin vs. ceftiofur	1.10	0.43	-	2.43
	tilmicosin vs. gamithromycin	0.69	0.39	-	1.15
	TMS vs. oxytetracycline	0.74	0.24	-	1.74
	TMS vs. florfenicol	1.11	0.26	-	3.03
	TMS vs. tulathromycin	0.21	0.05	-	0.57
	TMS vs. ceftiofur	0.39	0.09	-	1.14
	TMS vs. gamithromycin	0.24	0.07	-	0.58
	oxytetracycline vs. florfenicol	1.57	0.54	-	3.56
	oxytetracycline vs. tulathromycin	0.30	0.11	-	0.63
	oxytetracycline vs. ceftiofur	0.55	0.18	-	1.26
	oxytetracycline vs. gamithromycin	0.34	0.16	-	0.62
	florfenicol vs. tulathromycin	0.22	0.07	-	0.53
	florfenicol vs. ceftiofur	0.41	0.11	-	1.12
	florfenicol vs. gamithromycin	0.25	0.09	-	0.55
	tulathromycin vs. ceftiofur	2.05	0.65	-	5.07
	tulathromycin vs. gamithromycin	1.26	0.64	-	2.27
	ceftiofur vs. gamithromycin	0.73	0.29	-	1.55
(b) BRD morbidity d 1 to closeout	tilmicosin vs. TMS	2.07	1.11	-	3.56
	tilmicosin vs. oxytetracycline	1.29	0.94	-	1.77
	tilmicosin vs. tulathromycin	0.23	0.16	-	0.32
	tilmicosin vs. ceftiofur	0.97	0.54	-	1.62
	tilmicosin vs. gamithromycin	0.64	0.35	-	1.08
	tilmicosin vs. tildipirosin	0.50	0.27	-	0.83
	TMS vs. oxytetracycline	0.67	0.37	-	1.14
	TMS vs. tulathromycin	0.12	0.06	-	0.22
	TMS vs. ceftiofur	0.51	0.21	-	1.04
	TMS vs. gamithromycin	0.34	0.14	-	0.69

	TMS vs. tildipirosin	0.26	0.11	-	0.53
	oxytetracycline vs. tulathromycin	0.18	0.12	-	0.27
	oxytetracycline vs. ceftiofur	0.77	0.39	-	1.36
	oxytetracycline vs. gamithromycin	0.51	0.25	-	0.92
	oxytetracycline vs. tildipirosin	0.39	0.20	-	0.70
	tulathromycin vs. ceftiofur	4.43	2.17	-	7.88
	tulathromycin vs. gamithromycin	2.94	1.41	-	5.28
	tulathromycin vs. tildipirosin	2.27	1.10	-	4.06
	ceftiofur vs. gamithromycin	0.71	0.30	-	1.43
	ceftiofur vs. tildipirosin	0.55	0.23	-	1.12
	gamithromycin vs. tildipirosin	0.84	0.35	-	1.70
(c) BRD mortality d 1 to closeout	tilmicosin vs. TMS	1.35	0.28	-	3.84
	tilmicosin vs. oxytetracycline	1.44	0.74	-	2.70
	tilmicosin vs. tulathromycin	0.26	0.13	-	0.49
	tilmicosin vs. ceftiofur	0.88	0.25	-	2.02
	tilmicosin vs. gamithromycin	1.96	0.44	-	5.43
	tilmicosin vs. tildipirosin	1.21	0.32	-	3.17
	TMS vs. oxytetracycline	1.64	0.37	-	4.82
	TMS vs. tulathromycin	0.31	0.06	-	1.00
	TMS vs. ceftiofur	1.07	0.14	-	3.56
	TMS vs. gamithromycin	2.86	0.25	-	8.95
	TMS vs. tildipirosin	1.52	0.17	-	5.41
	oxytetracycline vs. tulathromycin	0.20	0.08	-	0.41
	oxytetracycline vs. ceftiofur	0.74	0.15	-	1.75
	oxytetracycline vs. gamithromycin	1.52	0.27	-	4.60
	oxytetracycline vs. tildipirosin	1.02	0.19	-	2.70
	tulathromycin vs. ceftiofur	3.81	0.83	-	9.42
	tulathromycin vs. gamithromycin	8.41	1.45	-	25.26
	tulathromycin vs. tildipirosin	5.39	1.03	-	14.73
	ceftiofur vs. gamithromycin	3.38	0.42	-	10.70
	ceftiofur vs. tildipirosin	2.01	0.30	-	6.41
	gamithromycin vs. tildipirosin	1.15	0.12	-	3.58
(d) BRD retreatment morbidity d 1 to closeout	tilmicosin vs. oxytetracycline	1.00	0.59	-	1.60
	tilmicosin vs. tulathromycin	0.50	0.22	-	0.98
	tilmicosin vs. ceftiofur	0.82	0.39	-	1.52
	tilmicosin vs. gamithromycin	0.86	0.37	-	1.70
	tilmicosin vs. tildipirosin	1.38	0.60	-	2.69
	oxytetracycline vs. tulathromycin	0.52	0.22	-	1.01
	oxytetracycline vs. ceftiofur	0.90	0.34	-	1.85
	oxytetracycline vs. gamithromycin	0.93	0.33	-	2.05
	oxytetracycline vs. tildipirosin	1.67	0.54	-	3.24
	tulathromycin vs. ceftiofur	2.04	0.62	-	4.65
	tulathromycin vs. gamithromycin	2.06	0.59	-	5.13

	tulathromycin vs. tildipirosin	3.39	0.97	-	8.09
	ceftiofur vs. gamithromycin	1.30	0.37	-	2.88
	ceftiofur vs. tildipirosin	1.94	0.61	-	4.53
	gamithromycin vs. tildipirosin	2.01	0.55	-	4.77

Figure 4.1. Network of treatment arms for the metaphylactic antimicrobial for BRD morbidity cumulative incidence d 1 to ≤ 60 of the feeding period (a), BRD morbidity cumulative incidence d 1 to closeout of the feeding period (b), BRD mortality cumulative incidence d 1 to closeout (c), and BRD retreatment morbidity cumulative incidence d 1 to closeout (d) in the mixed treatment comparison meta-analysis. The width of the lines corresponds to the number of direct comparisons between antimicrobials, the size of the dot indicates the number of antimicrobials within each arm, and number in parenthesis corresponds to the number of comparisons for each antimicrobial.

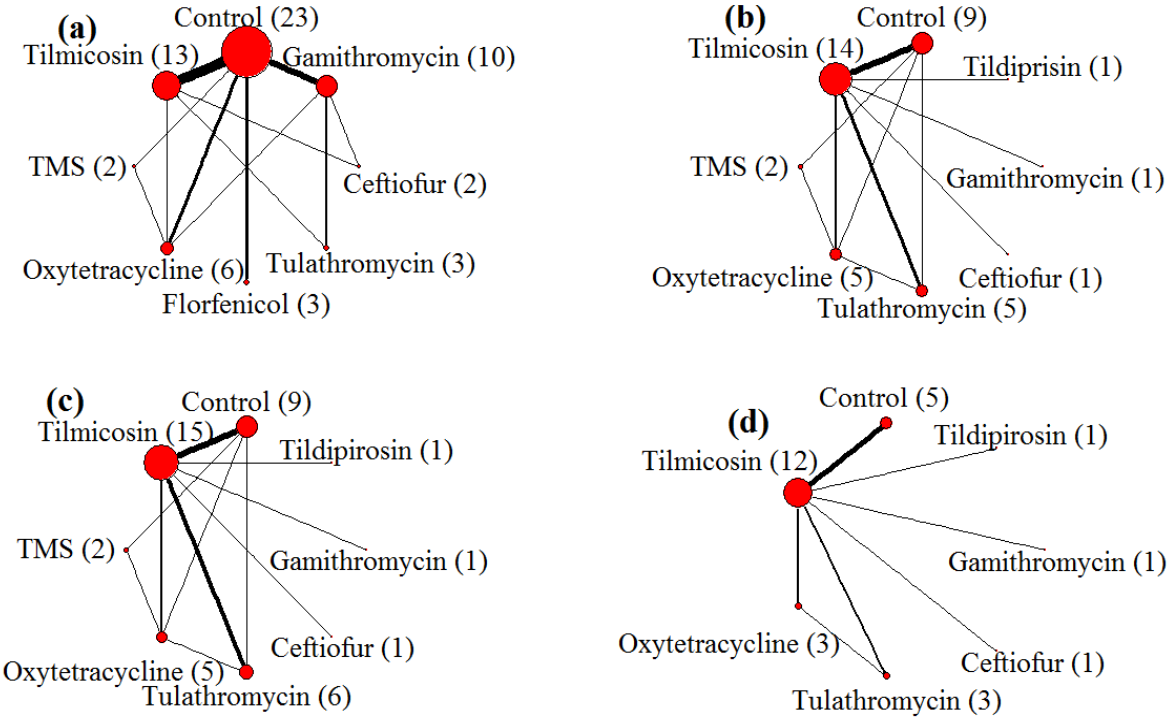
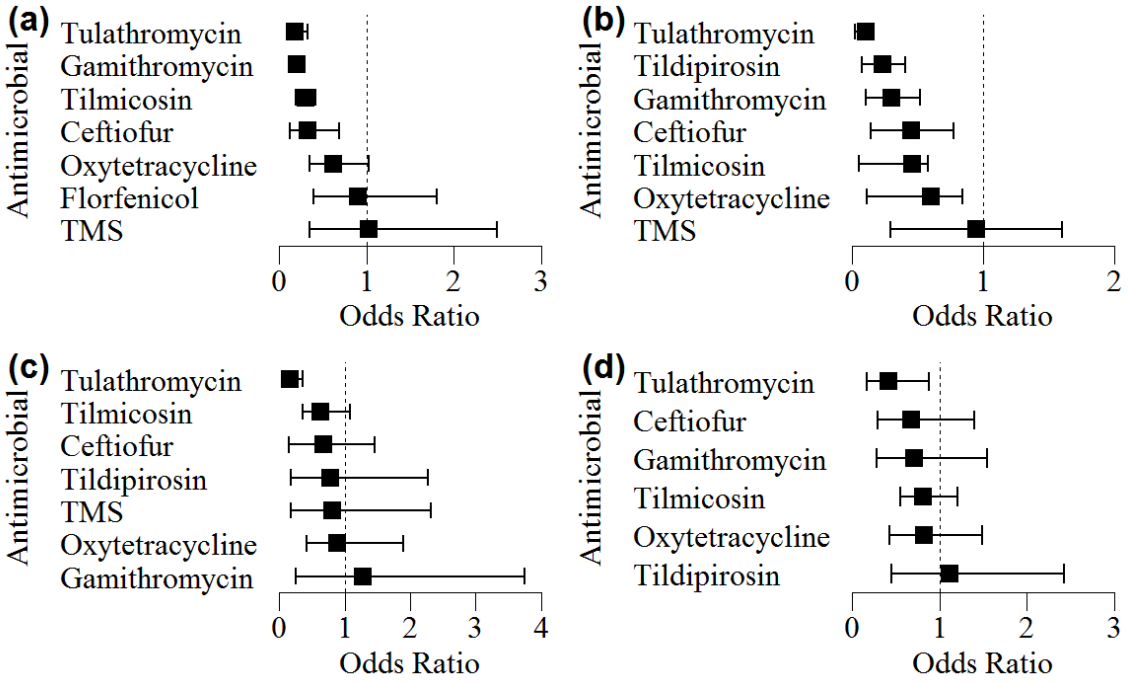


Figure 4.2. Forest plots of the odds ratio comparison between individual antimicrobials and control in the mixed treatment comparison with a 95% CrIs for BRD morbidity cumulative incidence d 1 to ≤ 60 of the feeding period (a)[1], BRD morbidity cumulative incidence d 1 to close out of the feeding period (b)[2], BRD mortality cumulative incidence d 1 to closeout (c)[2], and BRD retreatment morbidity cumulative incidence d 1 to closeout (d)[2].

[1] Binomial likelihood, complimentary log-log (cloglog) link, random-effects model
[2] Binomial likelihood, logit link, random-effects model



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Chapter 5 - A mixed treatment comparison meta-analysis of metaphylaxis treatments for bovine respiratory disease and the effects on performance outcomes in beef cattle

Introduction

Bovine respiratory disease (BRD) leads to economic losses due to mortality, treatment costs, decreased performance, and carcass value (Griffin, 1997; Schneider et al., 2009). Multiple methods to combat BRD have been researched and performed in order to minimize the negative impact of BRD in incoming feedlot calves, one example is metaphylaxis. Metaphylaxis treatment options have been shown to decrease the risk of BRD morbidity and mortality in feedlot cattle as well as improve treatment response rates in calves (Abell et al., 2017; O'Connor et al., 2016). Differences between multiple treatment options has been analyzed using a mixed treatment comparison (MTC) meta-analysis in order to make direct and indirect comparisns among antimicrobial treatments. A MTC meta-analysis has proven to generate results comparable to direct clinical trials (O'Connor et al., 2016). Direct comparisons between trials using meta-analysis techniques has shown calves treated with a metaphylactic antimicrobial had a greater average daily gain (ADG) of 0.11 kg/d compared to controls (Wileman et al., 2009). Performance measurements such as dry matter intake (DMI), feed to gain ratio (F:G), and carcass measurements (hot carcass weight (HCW), quality and yield grade) would be beneficial to analyze the differences between animals treated with different metaphylactic antimicrobials in order to understand the effects metaphylaxis may have on cattle performance.

The objective of this research was to evaluate the effect of metaphylactic antimicrobials approved for feeder and stocker calves to be administered parenterally for the prevention of BRD, on performance outcomes using a MTC meta-analysis. The results from this analysis

should contribute to the understanding of performance outcomes from calves metaphylactically treated at arrival to a feeder or stocker operation.

Materials and Methods

Literature search

A literature search was performed as previously described (Abell et al., 2017). Manuscripts were included from trials where a metaphylactic antimicrobial was randomly administered parentally to incoming feedlot calves within 48 h of arrival and performance measurements were collected at the end of the feeding period, or closeout. Performance measurements included ADG, DMI, F:G, HCW, quality grade choice or better, and yield grade 1-2.

Data extraction

Outcome data were extracted from trials that included data to the end of the feeding period. The end of the feeding period did not need to be defined by actual days, but had to be specified as closeout, terminal sort, end of feeding period, or slaughter. Data from trials within the same study were extracted separately. Data were extracted by a single reviewer (KA). Data were extracted for each antimicrobial within each trial and individual antimicrobials were classified as individual treatment arms. The following data were extracted from each trial: the antimicrobial for each treatment arm, number of animals enrolled in each treatment arm, number of animals processed for each treatment arm, and event occurrence for each performance outcome for each treatment arm (Table 5.1 and 5.3). Data were not included if performance analysis was not specified as deads included or deads excluded, or variability of means, standard deviation (SD) or standard error (SE), were not reported. For two trials, the variability (SE/SD) for a given mean was zero, and the zero was changed to 0.0001 for purpose of model

convergence (Booker et al., 2006; G.J. Vogel et al., 1998). Event occurrence included ADG, DMI, F:G, HCW, quality grade choice or better, and yield grade 1-2. Two trials included in the quality and yield grade analysis were performed in Canada and had different grading systems for quality and yield grade (Booker, et al., 2007; Schunicht et al., 2002a). Canada AAA was categorized as choice or greater, Canada prime was included in the choice or greater category, Canada 1 was categorized as yield grade 1, and Canada 2 was categorized as yield grade 2 (Processors, 2016). Data reported as prime and choice grade were combined to create the outcome choice or greater. The raw data from yield grade 1 was combined with the raw data from yield grade 2 to create the outcome yield grade 1-2. Data were aggregated as previously described, if the difference between treatment arms within a trial was due to a difference in post metaphylactic interval or route of administration (Abell et al., 2017). Results reported as percentages for each treatment arm were extracted based on the number of animals enrolled as deads-included or deads-excluded, or the number of animals that were processed. Data were excluded from the analysis if the number of animals enrolled or processed could not be determined.

Multiple treatment comparison analysis

The effectiveness for each individual treatment arm for ADG, DMI, F:G, and HCW was examined using the normal likelihood, identity link, random effects model in order to combine the direct and indirect evidence in the mixed treatment comparison meta-analysis with a Bayesian approach (Dias et al., 2010; Higgins & Whitehead, 1996; Lu & Ades, 2004a). The effectiveness for each individual treatment arm for quality grade choice or better and yield grade 1-2 was examined using the binomial likelihood, logit link, random effects model. Based on the known ordinal relationship of carcass outcomes, only quality grade choice or better was

analyzed, and yield grade 1 and 2 were combined for the analysis (Osterstocket al., 2010). The code was called through WinBUGS through R with the R2Winbugs package to fit the model for all event outcomes (Dias et al.2011).

A homogeneous variance was assumed for all models and uniformed priors were used for the standard deviation, σ. In order to determine the best fitting model, two uniformed standard deviation priors were tested, σ ~ uniform(0, 5) vs σ ~ uniform(0, 2). The σ ~ uniform (0, 5) proved to have narrower credibility intervals as well as a lower deviance information criterion (DIC) compared to σ ~ uniform (0, 2), therefore σ ~ uniform (0, 5) was used in the final code. Best convergence chains were determined based on visualization of Gelman-Rubin diagnostics (Gelman & Rubin, 1992). The final model for all event outcomes included 2 chains, each with 150,000 iterations, the first 50,000 of those were discarded. The final model output for ADG, DMI, F:G, and HCW included the posterior mean between treatment arm comparisons with corresponding 95% credibility intervals (CrIs). The final model output for quality grade choice or better and yield grade 1-2 included the posterior mean for odds ratio between treatment arm comparisons with corresponding 95% CrIs.

Results

The initial screening of the literature revealed 170 publications, with a total of 11 trials meeting all inclusion criteria (Table 5.1 and 5.3). A placebo control was present in 4 trials for ADG, DMI, F:G, and HCW analysis, and a placebo control was present in 3 trials for quality and yield grade analysis. The maximum number of treatment arms per trial was 3 (Booker et al., 2007; Tennant et al., 2014), and the remaining trials contained 2 treatment arms. The treatment arms analyzed between all models included Tilmicosin, Oxytetracycline, Ceftiofur, Tulathromycin, Tildipirosin, and Gamithromycin. Tilmicosin was included in 10/11 of trials

included in the ADG, DMI, F:G, and HCW analysis, and included in all trials in the quality and yield grade analysis.

The model for ADG with deads-included consisted of a total of 8 trials with 4 different treatment arms analyzed (Table 5.1) (Gamithromycin, Tildipirosin, Tilmicosin, and Tulathromycin). Posterior mean comparisons with 95% CrIs between metaphylactic antimicrobials and controls are shown in Fig. 5.1(a). All posterior mean antimicrobials are greater than 0, or animals that were treated with one of the 4 antimicrobials included in the MTC meta-analysis had a greater ADG compared to controls by approximately 0.05 kgs. The lower limit of the 95% CrIs for Tildipirosin and Tulathromycin are less than 0, and is approximately 0 for Gamithromycin.

The model for ADG with deads-excluded consisted of a total of 8 trials with 5 different treatment arms analyzed (Table 5.1) (Ceftiofur, Gamithromycin, Tulathromycin, Tilmicosin, and Oxytetracycline). Posterior mean comparisons with 95% CrIs between metaphylactic antimicrobial and controls are shown in Fig 5.1(b). The posterior mean ADG for all antimicrobials is greater than 0 compared to controls and ranges between 0.02 to 0.05 kgs. The lower limits of the 95% CrIs for all antimicrobials is less than 0, with Gamithromycin having the widest CrIs of -0.04 to 0.12 kgs.

The number of trials included for DMI deads-included analysis was 6 and for DMI deads-excluded was 5. The posterior means for all antimicrobials included in the DMI deads-included analysis were greater than 0 compared to controls, but the lower limit of all 95% CrIs were less than 0 for all antimicrobials (Fig. 5.2(a)). Tildipirosin had the widest 95% CrIs of -0.70 to 0.85 kg. The posterior means for the antimicrobials included in the DMI deads-excluded analysis had

wide 95% CrIs that included 0 within the interval. Ceftiofur had a posterior mean less than 0 for the DMI deads-excluded analysis of -0.11 kg.

The analysis for F:G deads-included and deads-excluded analysis both had 7 trials and 4 different antimicrobials (Table 5.1). All posterior means for the 4 different antimicrobials in the F:G deads-included analysis outcome were less than 0 compared to the controls with the upper 95% CrIs greater than 0. The widest 95% CrIs was Gamithromycin compared to controls, -0.23 to 0.42 (Fig. 5.3(a)). The posterior means for all 4 different antimicrobials compared to controls for the F:G deads-excluded analysis were very similar, the posterior mean range of treatments was -0.01 to 0.02 (Fig. 5.3(b)).

Hot carcass weight (HCW) was included in 4 different trials. The reason for the small number of trials for this outcome was due to the outcome or a measure of variability (SE/SD) not being reported. The antimicrobials included in this analysis were Tulathromycin, Ceftiofur, Tilmicosin, and Oxytetracycline (Fig 5.4). All posterior mean comparisons between the metaphylactic antimicrobial and control, and the associated 95% CrIs were greater than 0 except for Oxytetracycline. The 95% CrIs for Oxytetracycline was -1.93 to 11.9 kg. All pairwise comparisons between the antimicrobials posterior means with 95% CrIs for ADG, DMI, F:G, and HCW are shown in Table 5.2.

The analysis for quality and yield grade included 6 different trials (Table 5.3). The model for yield grade did converge, but the results were not believable due to the odds ratio computed was outside of the 95% CrIs. The results for yield grade 1-2 are not shown, but the raw data is provided in Table 5.3. Figure 5.5 shows the forest plot of the log odds ratio (OR) comparison between individual antimicrobials and control in the MTC meta-analysis. An OR equal to 1 indicates the odds of event occurrence are the same for both antimicrobial and control; an OR

less than 1 indicates the odds for event occurrence are greater for the control compared to the antimicrobial; an OR greater than 1 indicates the odds of event occurrence are greater for the antimicrobial compared to controls. The lower limit of the 95% CrIs for all antimicrobials were less than 1 compared to controls. The mean odds ratios between each metaphylactic antimicrobial are shown in Table 5.4.

Discussion

The results from the mixed treatment comparison meta-analysis were able to identify differences between the performance outcomes of ADG, DMI, F:G, HCW, and quality grade choice or better for cattle treated with metaphylactic antimicrobials versus controls. The analysis was not able to identify differences in yield grade 1-2 due to unrealistic mean odds ratios produced from the model. The results presented are the first to the authors' knowledge that compare indirect and direct evidence of the effect of metaphylactic antimicrobials on performance outcomes in feedlot calves.

The purpose for administering a metaphylactic antimicrobial at arrival to feedlot cattle is to prevent BRD (Young, 1995), and it is important to recognize that the antimicrobials are not labeled to be given in order to influence performance outcomes in calves. In the current study, the outcomes were analyzed to determine if differences existed in performance outcomes at the end of the feeding period between antimicrobials and controls, as well as between different antimicrobials. The results presented should not be interpreted as evidence for and an endorsement of administration of a metaphylactic antimicrobial to obtain a desired performance outcome.

When evaluating the outcome ADG, the posterior mean comparison between metaphylactic antimicrobial and control show a slightly lower ADG advantage for metaphylactic

antimicrobial treatment compared to controls when calculated as deads-excluded versus when calculated as deads-included (Fig. 5.1). A previous meta-analysis demonstrated calves treated with an metaphylactic antimicrobial versus control had a greater ADG of 0.11 kg/d (Wileman et al., 2009). In the current study, the largest posterior mean comparison between an antimicrobial versus control was Ceftiofur, 0.05 kg/d, which is lower than the direct meta-analysis results combining all cattle receiving a metaphylactic antimicrobial versus control cattle reported by Wileman et al (Wileman et al., 2009). Reasons for the discrepancy with this study may be because Wileman et al. included trials that ended prior to the end of the feeding period and antimicrobials administered orally. The outcome F:G shows that the deads-included posterior means compared to controls are lower compared to the deads-excluded calculations (Fig. 5.3). The posterior means for the DMI deads-included and -excluded appear very similar (Fig. 5.2). Reasons for the similarity between the DMI deads-included and deads-excluded analysis may be due to the small number of trials reporting that outcome, which may also be the reason for the wide 95% CrIs for each antimicrobial. The 95% CrIs are overlapping between antimicrobials in all performance outcomes, making full interpretation between antimicrobials difficult.

Figure 4 shows the differences between treatments compared to controls and the effect on HCW. All treatments were greater than 0, except for Oxytetracycline. The total number of trials to determine the HCW outcome was 4, and the differences between each treatment arm versus the control were robust enough to demonstrate a difference in the MTC meta-analysis.

The results for quality grade choice or better shows there are overlapping 95% CrIs for antimicrobials versus control, as well as between antimicrobials (Fig. 5.5). Table 4 shows the results of the mean OR between antimicrobials, and the OR for each comparison are very close to 0, meaning the odds of quality grade choice or greater is the same for each antimicrobial. All

the 95% CrIs for each comparison contains 1, except for Tilmicosin versus Oxytetracycline. Tilmicosin was presented in each trial included in the MTC meta-analysis, and one paper does estimate the direct differences between Tilmicosin and Oxytetracycline, and the difference is not statistically significant ($P > 0.05$) (Schunicht et al., 2002). The discrepancy between the indirect estimate created by the MTC meta-analysis and the direct comparison from the manuscript demonstrates the need to interpret the results from this study with caution. The estimates created from this analysis may not be robust due to the small number of trials included in the analysis. Estimates were not believable for the yield grade 1-2 outcome and may be due to the small number of studies included in the MTC meta-analysis. The raw data may be added to future research comparing different antimicrobials administered to cattle and the effects on performance outcomes. The raw data could potentially be used in an economic evaluation to determine cost differences between metaphylactically treated cattle and the effect on performance outcomes.

Overall, the number of studies evaluated for each outcome were small, with the greatest number of trials included in the ADG outcome analysis (8 trials). Interpretation of the results from this MTC meta-analysis should be performed with caution due to potential publication bias and inconsistencies between the combined data to produce the presented outcomes. The data included in this analysis were from trials that followed cattle to the end of the feeding period. The definition for the end of the feeding period may be different between studies, and may be a source of confounding bias in the analysis. For example, in one study, calves were followed to terminal sort, which means that some animals may have been on feed for an additional 30 to 40 days (Van Donkersgoed & Merrill, 2013a). The differences between feeding days between trials may confound the results presented in this study, therefore the results should be interpreted with

caution. The performance outcomes were usually secondary outcomes in each of the trials included in the analysis, with health outcomes (morbidity and mortality) being the primary outcomes. The trials included in the current study ranged from the years 1998 to 2015, and there is a potential risk in combining results from performance outcomes in calves that were fed in feedlots in different countries, environments, rations, etc.

Conclusion

In summary, the results of this study demonstrated the use of a MTC meta-analysis to determine the effects on performance outcomes of different metaphylactic antimicrobials used in feedlot calves. Unfortunately, the estimates were not robust enough to determine differences among antimicrobials for ADG, DMI, F:G, HCW, quality grade choice or better, or yield grade 1-2, due to an insufficient number of trials included in the analysis. Further research is needed to determine the effects of different metaphylactic antimicrobials on performance outcomes and possible economic differences that may exists in feedlot cattle.

Table 5.1. Data extracted from 11 individual trials included in a mixed treatment comparison meta-analysis for ADG, DMI, F:G, and HCW performance event outcomes. Deads-excluded is defined as mortalities and railers throughout the feeding period were not included in the analysis. Deads-included is defined as mortalities and railers throughout the feeding period were included.

[1] Average daily gain (kg)

[2] Daily dry matter intake (kg)

[3] Feed to gain conversion (kg/kg)

[4] Hot Carcass Weight (kg)

Treatment Arms	ADG[1] Deads in.	ADG Deads exl.	DMI[2] Deads in.	DMI Deads exl.	F:G[3] Deads in.	F:G Deads exl.	HCW[4]	Reference
Control/Tilmicosin	1.29/1.36 (±0.01)	1.44/1.46 (±0.0001)	7.4/7.5 (±0.1)	7.4/7.5 (±0.1)	5.75/5.39 (±0.04)	5.15/5.18 (±0.05)	-	(G.J. Vogel et al., 1998)
Tilmicosin/Oxytetracyline	-	1.35/1.35 (±0.0001)	-	8.65/8.65 (±0.03)	-	6.45/6.43 (±0.02)	-	(Schunicht, Guichon, et al., 2002a)
Control/Tilmicosin	1.46/1.50 (±0.03)	1.52/1.56 (±0.014)	-	8.55/8.55 (±0.17)	5.74/5.62 (±0.14)	5.63/5.50 (±0.1)	353.6/359.7 (±1.51)	(C.A. Guthrie et al., 2004)
Tilmicosin/Ceftiofur	-	1.23/1.26 (±0.009)	-	8.14/7.97 (±0.05)	-	6.46/6.47 (±0.03)	401.0/404.2 (±1.59)	(Booker et al., 2006)
Tilmicosin/Oxytetracycline/Tulathromycin	-	1.17/1.16/1.20 (±0.005)	-	7.99/8.03/8.34 (±0.04)	-	6.80/6.92/6.94 (±0.04)	334.4/333.4/338.4 (±0.73)	(Booker, Abutarbush, Schunicht, Jim, & Perrett, 2007)

Tilmicosin/Tulathromycin	1.33/1.32 (±0.004)	1.30/1.30 (±0.004)	-	-	6.87/6.95 (±0.06)	6.97/7.02 (±0.05)	-	(J. Van Donkersgoed, J. Merrill, & S. Hendrick, 2008)
Tilmicosin/Gamithromycin	1.40/1.38 (±0.014)	-	8.68/8.64 (±0.03)	-	6.52/6.63 (±0.07)	-	-	(Van Donkersgoed, 2012)
Tilmicosin/Tildipirosin	1.52/1.52 (±.014)	-	8.77/8.77 (±0.03)	-	5.77/5.77 (±0.05)	-	-	(Van Donkersgoed & Merrill, 2013a)
Control/Tilmicosin	1.82/1.88 (±.005)	-	10.68/10.59 (±0.08)	-	5.84/5.62 (±0.05)	-	-	(Van Donkersgoed & Merrill, 2013b)
Tulathromycin/Gamithromycin	1.52/1.52 (±0.03)	1.2/1.2 (±0.01)	7.3/7.4 (±0.08)	-	-	-	-	(Torres, Thomson, Bello, Nosky, & Reinhardt, 2013b)
Control/Tilmicosin/Tulathromycin	1.47/1.53/1.55 (±.04)	1.53/1.56/1.57 (±0.04)	8.31/8.50/8.53 (±0.11)	-	5.65/5.56/5.56 (±0.003)	5.43/5.46/5.43 (±0.004)	398.5/406.0/470.1 (±2.6)	(Tennant et al., 2014)

Figure 5.1. Forest plot of posterior mean comparisons between metaphylactic antimicrobial and control in the mixed treatment comparison meta-analysis with 95% CrIs for average daily gain with deads-included (a) and deads-excluded (b)[1].

[1]Normal likelihood, identity link, random effects model for multi-arm trials.

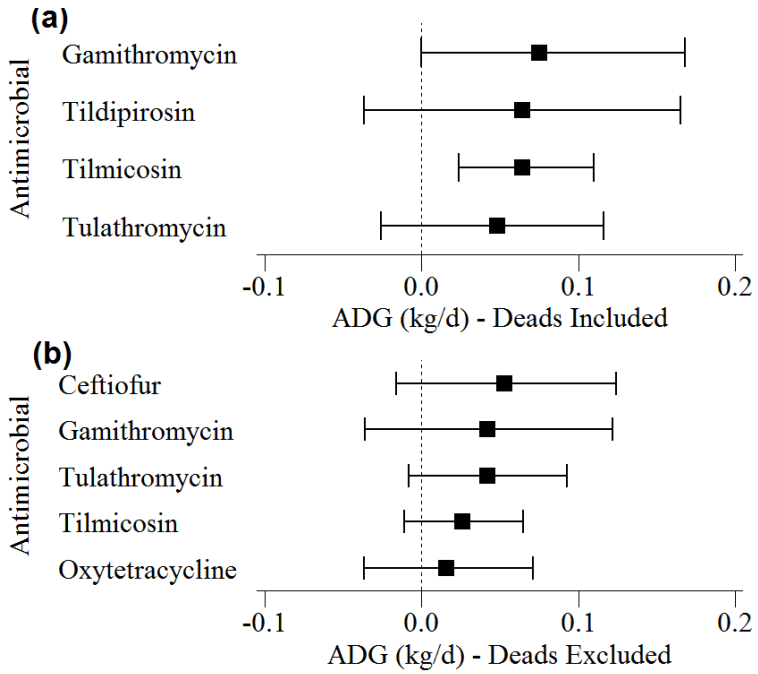

Figure 5.2. Forest plot for posterior mean comparisons between metaphylactic antimicrobial and control in the mixed treatment comparison meta-analysis with 95% CrIs for daily dry matter intake with deads-included (a) and deads-excluded (b)[1].

[1]Normal likelihood, identity link, random effects model for multi-arm trials.

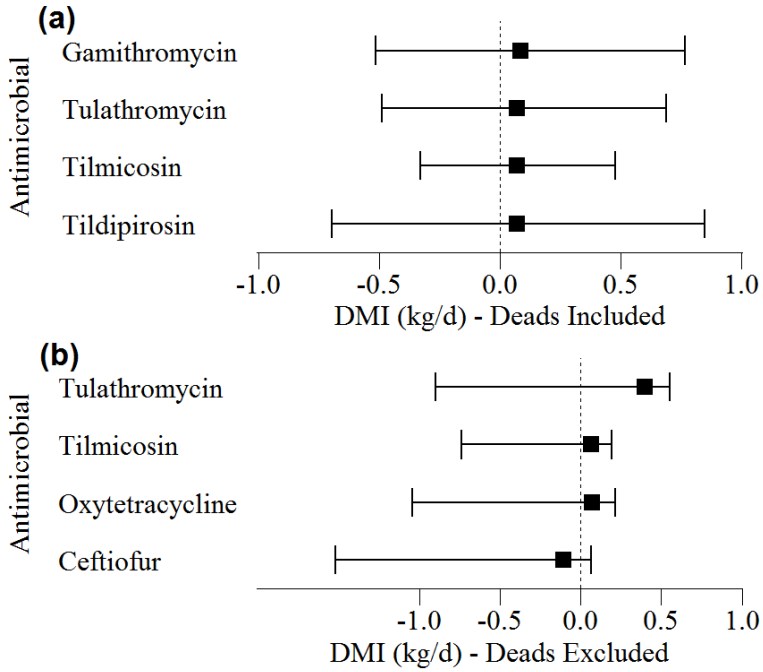

Figure 5.3. Forest plot of posterior mean comparison between metaphylactic antimicrobial and control in the mixed treatment comparison meta-analysis with 95% CrIs for feed to gain ratio with deads-included (a) and deads-excluded (b)[1].

[1]Normal likelihood, identity link, random effects model for multi-arm trials.

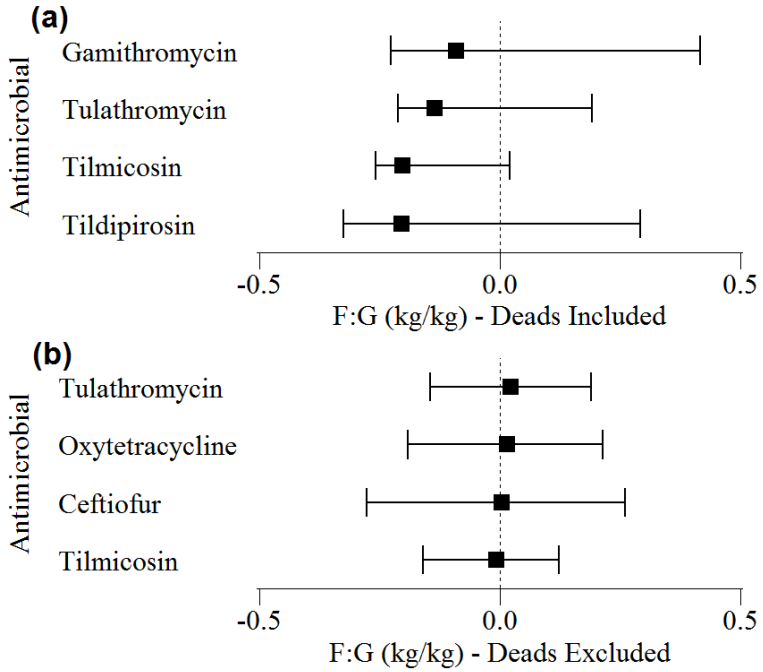

Figure 5.4. Forest plot of posterior mean comparison between metaphylactic antimicrobial and control in the mixed treatment comparison meta-analysis with 95% CrIs for hot carcass weight (HCW) (kg)[1].

[1] Normal likelihood, identity link, random-effects model

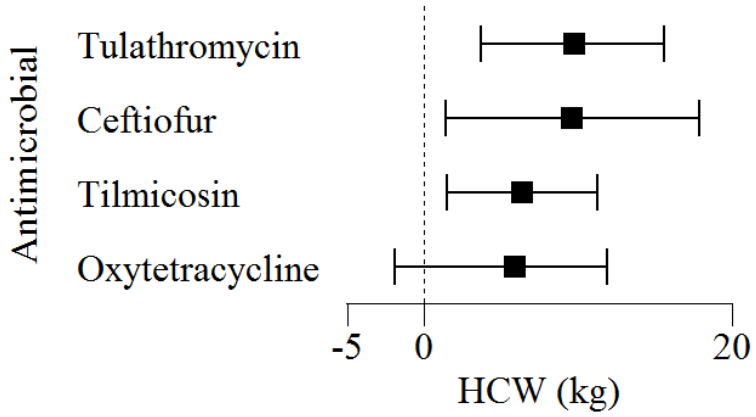

Table 5.2. Pairwise comparison results between metaphylactic antimicrobials for each performance event outcome with 95% credibility intervals of the mixed treatment comparison meta-analysis[1]. Posterior means for each metaphylactic antimicrobial comparison are included for ADG with deads-included (a), ADG with deads-excluded (b), DMI with deads-included (c), DMI with deads-excluded (d), F:G with deads-included (e), F:G with deads-excluded (f), and hot carcass weight (HCW). The metaphylactic antimicrobial on the left for all mean comparisons is the reference category.

[1] Normal likelihood, identity link, random-effects model

Event Outcome	Comparison	Mean	95% CrIs
	Tilmicosin vs. Tulathromycin	-0.02	-0.08 - 0.04
	Tilmicosin vs. Gamithromycin	0.01	-0.05 - 0.09
(a) ADG	Tilmicosin vs. Tildipirosin	0.00	-0.09 - 0.09
Deads included	Tulathromycin vs. Gamithromycin	0.03	-0.04 - 0.12
	Tulathromycin vs. Tildipirosin	0.02	-0.09 - 0.13
	Gamithromycin vs. Tildipirosin	-0.01	-0.13 - 0.09
	Tilmicosin vs. Oxytetracycline	-0.01	-0.05 - 0.03
	Tilmicosin vs. Tulathromycin	0.02	-0.02 - 0.05
	Tilmicosin vs. Ceftiofur	0.03	-0.03 - 0.09
	Tilmicosin vs. Gamithromycin	0.02	-0.06 - 0.09
(b) ADG	Oxytetracycline vs. Tulathromycin	0.03	-0.02 - 0.07
Deads excluded	Oxytetracycline vs. Ceftiofur	0.04	-0.03 - 0.11
	Oxytetracycline vs. Gamithromycin	0.03	-0.05 - 0.10
	Tulathromycin vs. Ceftiofur	0.01	-0.06 - 0.08
	Tulathromycin vs. Gamithromycin	0.00	-0.06 - 0.06
	Ceftiofur vs. Gamithromycin	-0.01	-0.10 - 0.08
	Tilmicosin vs. Tulathromycin	0.00	-0.52 - 0.57
	Tilmicosin vs. Gamithromycin	0.01	-0.51 - 0.61
(c) DMI	Tilmicosin vs. Tildipirosin	-0.001	-0.67 - 0.68
Deads included	Tulathromycin vs. Gamithromycin	0.01	-0.55 - 0.58
	Tulathromycin vs. Tildipirosin	-0.001	-0.88 - 0.84
	Gamithromycin vs. Tildipirosin	-0.02	-0.91 - 0.83
(d) DMI	Tilmicosin vs. Oxytetracycline	0.04	-0.58 - 0.68

Deads excluded	Tilmicosin vs. Tulathromycin	0.35	-0.49 - 1.19
	Tilmicosin vs. Ceftiofur	-0.18	-1.11 - 0.72
	Oxytetracycline vs. Tulathromycin	0.31	-0.54 - 1.16
	Oxytetracycline vs. Ceftiofur	-0.22	-1.35 - 0.87
	Tulathromycin vs. Ceftiofur	-0.53	-1.77 - 0.66
	Tilmicosin vs. Tulathromycin	0.07	-0.23 - 0.36
	Tilmicosin vs. Gamithromycin	0.11	-0.35 - 0.57
(e) F:G	Tilmicosin vs. Tildipirosin	-0.001	-0.45 - 0.43
Deads included	Tulathromycin vs. Gamithromycin	0.04	-0.50 - 0.59
	Tulathromycin vs. Tildipirosin	-0.07	-0.06 - 0.45
	Gamithromycin vs. Tildipirosin	-0.11	-0.75 - 0.53
	Tilmicosin vs. Oxytetracycline	0.02	-0.13 - 0.18
	Tilmicosin vs. Tulathromycin	0.03	-0.09 - 0.17
(f) F:G	Tilmicosin vs. Ceftiofur	0.01	-0.22 - 0.24
Deads excluded	Oxytetracycline vs. Tulathromycin	0.01	-0.17 - 0.19
	Oxytetracycline vs. Ceftiofur	-0.01	-0.30 - 0.26
	Tulathromycin vs. Ceftiofur	-0.02	-0.29 - 0.23
	Tilmicosin vs. Ceftiofur	3.24	-3.39 - 9.85
	Tilmicosin vs. Oxytetracyline	-1.29	-6.86 - 3.78
(g) HCW	Tilmicosin vs. Tulathromycin	3.43	-1.36 - 7.57
	Ceftiofur vs. Oxytetracycline	-4.53	-13.17 - 3.72
	Ceftiofur vs. Tulathromycin	0.19	-8.03 - 7.79
	Oxytetracycline vs. Tulathromycin	4.72	-0.76 - 9.81

Table 5.3. Data extracted from 6 individual trials included in a mixed treatment comparison meta-analysis for quality grade choice or better and yield grade 1-2 event outcome.

Treatment Arms	Animals processed/group	Choice or better	YG 1-2	Reference
Tilmicosin/Ceftiofur	3286/6829	2343/5114	1602/3359	(Booker et al., 2006)
Tilmicosin/Oxytetracycline	5345/5342	1047/996	5200/5230	(Schunicht, Guichon, et al., 2002a)
Tilmicosin/Oxytetracycline/Tulathromycin	3142/3103/3229	1545/1476/1670	2693/2715/2715	(Booker, Abutarbush, Schunicht, Jim, & Perrett, 2007)
Control/Tilmicosin	164/721	59/251	84/622	(Corbin et al., 2009)
Control/Tilmicosin	179/734	60/295	76/327	(Corbin et al., 2009)
Control/Tilmicosin/Tulathromycin	759/773/761	358/349/372	370/313/331	(Tennant et al., 2014)

Figure 5.5. Forest plot of the odds ratio comparison between individual antimicrobials and control in the mixed treatment comparison[1] meta-analysis with a 95% CrIs for quality grade choice or better.

[1] Binomial likelihood, logit link, random-effects model

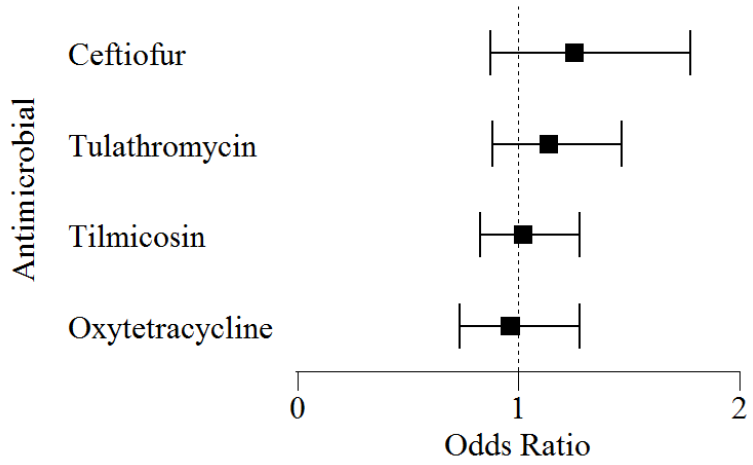

Table 5.4. The mean odds ratio with 95% credibility intervals for quality grade choice or better[1].

[1] Binomial likelihood, logit link, random-effects model
[2] The antimicrobial on the left of each comparison is the denominator in the ratio, and the antimicrobial on the right is the numerator. If the OR are equal to 1, odds of the event occurrence are the same for each antimicrobial; if odds are less than 1, the odds for the event occurrence are greater for the antimicrobial on the left; if odds are greater than 1, the odds for the event occurrence are greater for the antimicrobial on the right.

Event Outcome	Comparison[2]	OR	95% CrIs
Choice or better	Tilmicosin vs. Oxytetracycline	0.94	0.77 - 0.98
	Tilmicosin vs. Tulathromycin	1.11	0.90 - 1.16
	Tilmicosin vs. Ceftiofur	1.22	0.90 - 1.27
	Oxytetracycline vs. Tulathromycin	1.19	0.93 - 1.24
	Oxytetracycline vs. Ceftiofur	1.33	0.91 - 1.36
	Tulathromycin vs. Ceftiofur	1.10	0.77 - 1.16

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Chapter 6 - Dissertation conclusions

Emerging advances in data management and predictive analytics allow data to be transformed to aid quick and accurate operational and management decisions in veterinary medicine. The purpose of this dissertation was to evaluate current analytic methods utilizing Big Data in the cattle health industry. Data analytic techniques such as statistical estimation with regression, machine learning techniques, and Bayesian analysis are currently being utilized to understand relationships between variables and desired outcomes. These results help quantify how data is being analyzed currently, as well as novel analyses available that will continue to advance the veterinary research profession.

Cow-calf production commonly utilizes multiple bulls within a single breeding pasture. The variability that exists in the number of progeny by bull was analyzed over time and demonstrated the changes that exist between bulls. Categorizing bulls by rank identified associations with the number of calves sired by individual bulls in each 21-day period of the calving season. Data management and further analytics will help quantify how rank changes for bulls over multiple breeding years, how to identify bulls with the greatest and least rank, and how calving rank is associated with dominance, libido, and fertility. To perform an analysis of this scale, a dataset is needed that provides accurate reproductive records of bulls over multiple breeding seasons, along with progeny records of all calves sired. A dataset as robust as the one required to quantify rank changes would be acquired from a large cow-calf production operation, and an initial predictive model could be generated based on initial data inquiries, and data could be added to the model over the years to provide an accurate estimation of overall individual bull

rank changes. Unfortunately, a dataset of this size would require funding to not only generate the overall reproductive records, but also progeny testing of individual bulls and calves.

Machine learning allows predictive algorithms to be created on a large amount of data. Predictive modeling in this form has been proven to be accurate for identifying behaviors for lying and standing in bulls in a multiple-sire pasture. Understanding behaviors of animals allows for further evaluation of animal health and performance in the beef cattle industry. Machine learning can further identify how diagnostic sensitivity, specificity, positive predictive value, and negative predictive value changes based on the accuracy of a given classifier algorithm. Machine learning also has the advantage of removing a sub-set of the data for validation of the algorithm generated without having to conduct a separate research study. Removing a sub-set of the data for validation purposes deems more challenging in small datasets that utilize simple analytic techniques.

Simple analytic techniques, such as linear and logistic regression will remain invaluable for analyzing clinical trial, retrospective, and prospective data in veterinary medicine. A dataset that is not great enough to be considered Big Data can still be analyzed to determine relationships between variables and outcomes of interest. Variables such as temperature, behavior, and social interactions can be analyzed using regression techniques to understand associations with outcomes such as morbidity and mortality in beef cattle.

Bayesian analysis will continue to be utilized in the beef cattle industry considering prior probability in statistical analysis to model an outcome with known and unknown information that may not be as accurately and fully analyzed with regression techniques. The mixed treatment comparison meta-analysis presented in the previous chapters used Bayesian techniques to identify differences between parenteral metaphylactic antimicrobial options currently available

in feedlot cattle. Metaphylactic antimicrobial options appear to offer different effects on BRD morbidity and mortality odds in feedlot and stocker cattle. We were unable to identify performance and carcass differences between treatments due to a small number of trials available for the analysis.

Large amounts of data will continue to be collected in every aspect of the beef cattle industry, but actually implementing that data into daily management decisions may be lacking in certain areas. Knowing that advanced analytics, such as machine learning and Bayesian analysis exist allows a greater level of knowledge to be gained on desired outcomes. It is believed that these techniques will continue to be utilized and advance research in the cattle industry. Furthering the breadth of knowledge and understanding how to utilize advanced analytical techniques is critical for the beef cattle industry and the animal research industry. The human health industry continues to strive in advancing their management system based on real-time Big Data analytics. The veterinary health industry has the potential to advance as well, and even perform research that may not be possible in the human health industry due to regulatory constraints. The veterinary profession and cattle health industry have the potential to utilize Big Data analytics to continue to expand on the prediction methods for quantifying management factor effects on health and performance.