

Current and Future Strategies of Bovine Respiratory Disease Diagnostics and Treatments

by

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Abstract

Bovine respiratory disease (BRD) is the most common and costly disease affecting cattle in the world today. The disease was first described in the late 1800s and is one of the most extensively studied diseases of livestock. BRD accounts for 65 – 80% of the morbidity and 45 – 75% of the mortality in some feedlots. Outbreaks typically occur around 10 days after transportation with the majority of deaths occurring within the first 45 days of arrival. Bacterial pathogens, physiologic stressors, and concurrent viral infections are all important factors causing BRD; other factors include seasonality, heritability, and breed tolerance. Diagnostic and treatment measures are continually being critiqued and researched. Even with continued research and the administration of antibiotics, BRD still continues to be a problem for the beef industry. Remote early detection and previous calf history are two resources that can help feedlots diagnose the disease earlier, or prevent it entirely. Feeding behavior and physical exams of the calves can also aid in early detection. New antibiotics and treatment methods have been developed, but the BRD problem still exists. Since the disease is most problematic in feedlot cattle, treatment of a large number of cattle in this setting can be costly, and often, performance and carcass traits are also affected. New preventative measures will be crucial to the industry with the continued problems and consequences of BRD. Improved treatment options and enhanced diagnostic tools will also be imperative for the control and treatment of BRD in the future.

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Dedication

This report is dedicated to my grandfather, Bob Bozworth. He gave me continuous support throughout my bachelor's and master's degrees. It was through him that I found my love for cattle and science.

Chapter 1 - Current and Future Diagnostics

Introduction

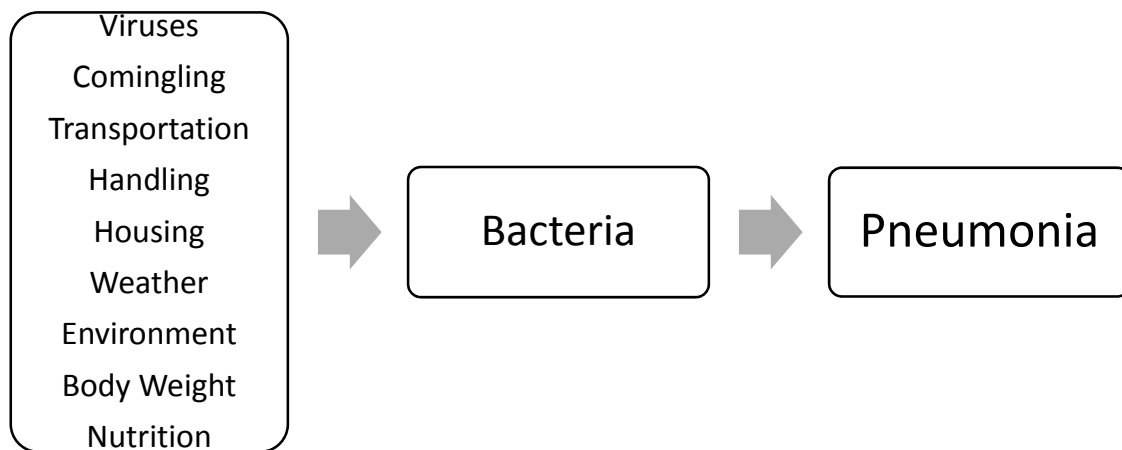
Bovine respiratory disease (BRD) is the most common disease syndrome in commercial feedlots. In the United States, the annual costs associated with BRD have been estimated to be \$4 billion, which includes the costs of treatment, prevention, and lost productivity (Cernicchiaro, 2012). Costs associated with BRD prevention, treatment, morbidity, and mortality have been estimated to be from \$13.90 to \$15.57 per head (Snowder, 2007).

Beyond the economic implications of BRD, animal welfare is another concern associated with these animals with this respiratory disease. Producers want and need their animals to experience the best care they can get to ensure the health and safety of all animals. Improved means of diagnosing this disease will allow animals to have less stress, lower rates of illness, and allow correct effective treatment. Cattle with BRD can potentially have decreased gains and meat quality. With improved methods of diagnostics, meat quality and feedlot efficiencies will increase.

BRD is caused by viruses or bacteria (Figure 1) infecting an animal with stressors of transportation, handling, housing, and weather conditions. Viruses that infect cattle, relating to BRD, are bovine herpesvirus type 1 (BHV-1), parainfluenza-3virus (PI3), bovine viral diarrhea virus (BVDV), and bovine respiratory syncytial virus (BRSV) (Grissett, 2015). *Mannheimia haemolytica* is the most common bacterial pathogen associated with BRD (Theurer, 2013). Other known bacterial pathogens infecting cattle are *Mycoplasma bovis*, *Pasteurella multocida*, and *Histophilus somni* (Grissett, 2015). Pathogens and cattle may react differently depending on several aspects. For example, each pathogen and individual cattle can have different incubation periods. Having knowledge of both infection and response time will lead to reducing the

negative impacts of BRD in populations. Prevention and control of BRD in cattle relies on implementation of health and production strategies designed to reduce stress, induce protective immunity, optimize nutrition, and minimize disease challenge (Nickell, 2010).

Figure 1: Causes of Bovine Respiratory Disease



The complex transportation organization of the beef cattle industry is one problematic area for BRD management and control due partly to the frequent transportation of animals. Minimal information is typically provided upon purchase of animals to determine history and preventative measures based on this information. Most cases of BRD tend to occur in the first 45 days after arrival to a feedlot. Timing of peak new case occurrence within a pen of animals can be highly variable due to the multifactorial nature of this disease complex (Nickell, 2010).

No one practice for reducing the effect of this disease exists. However, there are strategies or approaches that provide a basic foundation for intervention that can minimize the effect of this economically significant disease (Sweiger, 2010). One strategy includes the use of more effective modified live virus vaccines rather killed virus vaccines (Snowder, 2007).

Rationally-designed vaccines have also been added to vaccination programs. Despite these efforts, current vaccines for BRD do not confer complete protection against infection.

Improvements in diagnosing cattle with BRD are crucial so that animals are properly identified and treated to avoid extending and spreading the disease throughout the herd. Current methods for diagnosing BRD are lacking usefulness and effectiveness. Developing other means of diagnostics must be established in order to reduce BRD occurrence. Allowing a producer to be notified earlier and efficiently when an animal is morbid can make a difference in the severity of BRD and therapy outcome. Diagnosis is vital to BRD as it is commonly misdiagnosed or discovered too late. Having new and improved diagnostic tools will help producers tremendously as well as improve the animal welfare of cattle.

The objective of this report is to describe the diagnostic methods currently used by producers and veterinarians in the cattle industry. Immediate and distant future diagnostic tools are also discussed as options for controlling BRD that will aid in the proper treatment of animals.

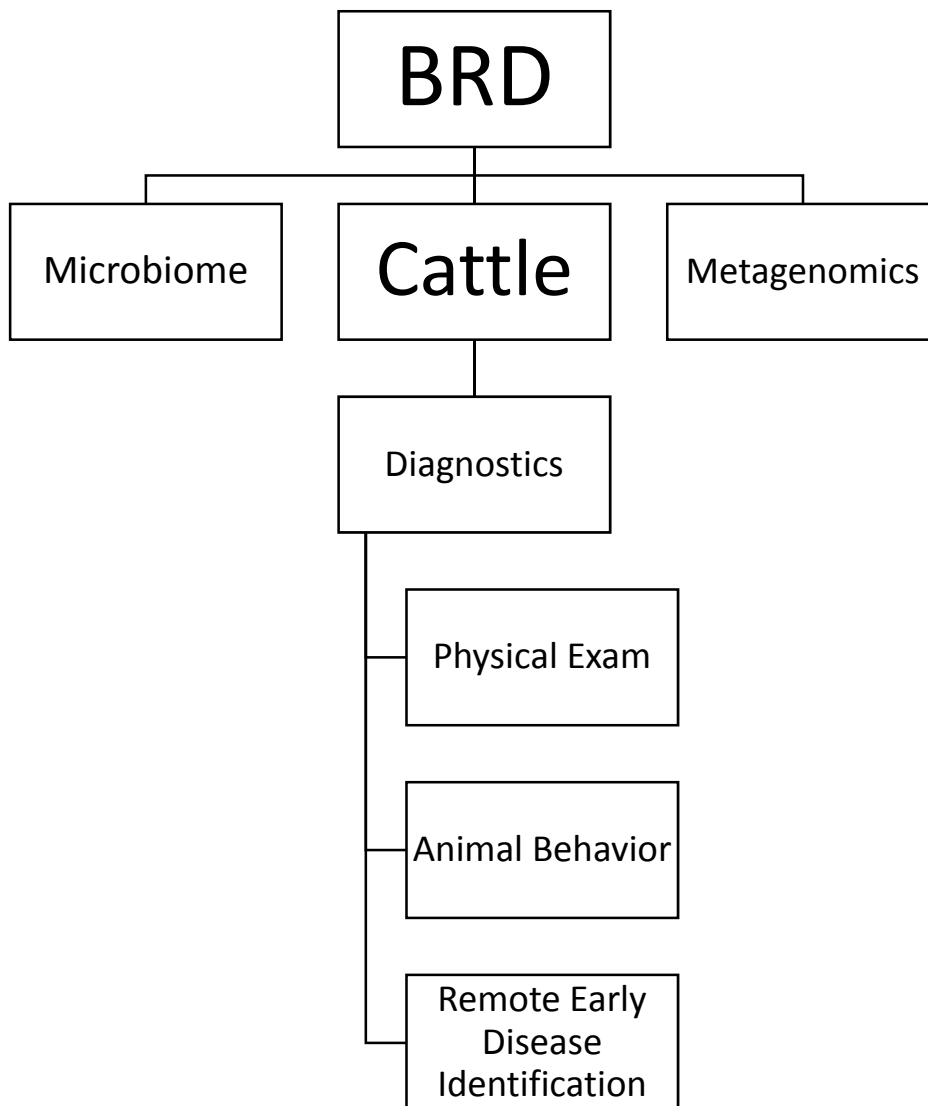
Materials and Methods

Search Terms and Criteria

Peer-reviewed articles were selected from PubMed, Web of Science, and Google Scholar databases. Published articles included years 1989 through 2016. Each database was searched using the terms displayed in Figure 2, beginning with "cattle BRD". After searching for cattle BRD, topics were narrowed to be more specific in the article search. Topics that did not have a significant amount of information were searched individually and did not include the word "cattle" (e.g., BRD microbiome, BRD whole genome sequencing, and metagenomics). A search was also conducted for "cattle microbiome" and "cattle whole genome sequencing" to find more articles covering the two techniques associated with other cattle diseases. Researched topics were

then divided into two categories as "immediate future" and "distant future" diagnostic methods. Applications included techniques that are within a short time frame of immediate future development, and longer time frame applications included methods that were early in the research stage, gaining popularity based on new understanding, and/or estimated to be applied in the distant future.

Figure 2: Search Terms Used to Collect Articles



Results

Current Diagnostic Methods

Case Definition

Researchers and producers have not described a widely accepted reference standard for visually diagnosing BRD. Having a sound case definition is essential when new technology is being tested or validated (Wolfger, 2015). Case definitions for BRD can vary and often depends on individual feedlots. Improvement of the clinical case definition of BRD may lead to a more accurate disease diagnosis, resulting in improved management strategies and enhanced treatment (Theurer, 2013). As an example, Table 1 describes common scoring criteria based on depression and respiratory scores. Depression and respiratory scores of ≥ 2 and a rectal temperature of $\geq 104.0^{\circ}\text{F}$ are used to define a calf is ill and requires treatment (Nickell, 2010).

Table 1: Depression and Respiratory Score

Depression Score Clinical Signs	
0	Normal: bright, alert and responsive
1	Mild Depression: may stand isolated with its head down or ears drooping, but will quickly respond to minimal stimulation
2	Moderate Depression: may remain recumbent or stand isolated with head down, may show signs of muscle weakness (standing cross-legged, knuckling or swaying when walking), depression obvious when stimulated
3	Severe Depression: may be recumbent and reluctant to rise, or if standing isolated and reluctant to move; when moving, is ataxic, knuckling or swaying evident; head carried low with ears drooping; eyes dull, possible excess salivation/lacrimation, obvious gauntness
4	Moribund: unable to stand; approaching death; highly unlikely to respond to any antimicrobial therapy
Respiratory Score Clinical Signs	
0	Normal: no abnormal respiratory symptoms. Respiratory rate and effort are appropriate for the environment
1	Mild Respiratory Distress: serous nasal or ocular discharge and/or cough
2	Moderate Respiratory Distress: mucous or mucopurulent nasal or ocular discharge and/or increase in respiratory rate or effort
3	Severe Respiratory Distress: marked increase in respiratory rate or effort, with one or more of the following: open mouth breathing, abdominal breathing and/or extended head.

Visual Observation

Current methods for identification of calves with BRD are mainly based on visual observations, but these methods have low sensitivity and specificity (Theurer, 2013). For example, in Table 1, feedlot employees use signs, such as reluctance to move, crusted nose, nasal or ocular discharge, drooped ears or head, and gaunt appearance, as indicators to support the diagnosis of BRD. The use of clinical signs or treatment records for classifying BRD has limitations. Diagnosing BRD based on clinical signs is inaccurate and has been estimated to provide diagnostic sensitivity and specificity values of only 61.8% and 62.8%, respectively (Nickell, 2010). Cattle are highly adept at concealing signs of sickness, and because of this, subjective assessment of sick cattle is highly variable. Therefore, animal caretakers potentially fail to identify each individual animal experiencing clinical or subclinical disease. Objective measures, such as rectal temperature, respiratory rate, or even changes in white blood cell counts have been used; however, there can also be limitations when using these methods. For example, white blood cell counts could be high due to a different infection resulting in a limitation for the accurate detection of BRD.

Physical Examination

Previous research has shown that *M. haemolytica* causes increases in both heart rate and respiratory rate and that the respiratory rate can be associated with the extent of lung consolidation (Friend, 1977; Reeve-Johnson, 2001). In contrast, another study demonstrated that heart rate and respiratory rate were not different between treatment groups (Hahn, 1997). Calves in this experiment were housed in extremely high ambient temperatures throughout the trial.

Increases in heart rate and respiratory rate may have been due to heat stress, making it difficult to use this parameter as a discriminator of BRD (Fuquay, 1981; Hahn, 1997).

Rectal temperatures are routinely obtained for calves with signs of BRD, and the final decision to treat a calf may be made on the basis of rectal temperature exceeding some predetermined threshold. Typically, the threshold for treatment is a rectal temperature $\geq 104.0^{\circ}\text{F}$ (Nickell, 2010). However, this quantitative measure does not provide an accurate diagnosis of the fever-causing disease and varies between operations.

Necropsy and Lung Lesions

Disease can often be definitively diagnosed at necropsy. At slaughter, the presence of lung lesions is a common method of determining previous respiratory lung infections. However, not all cattle with BRD symptoms will have noticeable lung lesions at the time of slaughter. At the same time, respiratory tract infections may produce permanent lung damage and only have an associated negative effect on growth and carcass traits (Snowder, 2007). One advantage of a post mortem examination would be that it would identify herds that are affected by BRD and inform producers of a respiratory bacterial disease issue in their operations.

Immediate Future Diagnostic Methods

Current methods for diagnosing BRD need to be improved. Developing other means of reliable diagnostics must be established in order to reduce BRD occurrence. Notifying a producer earlier and efficiently when an animal is morbid can make a difference in the outcome of BRD if therapy is initiated early in the disease process. Diagnostic tools are essential to the health of an animal and are vital to BRD as it is commonly misdiagnosed or discovered too late. Awareness of the disease will allow producers to treat early and effectively. Having new and improved diagnostic tools will help producers tremendously, and most importantly, improve the welfare of

cattle. Immediate future diagnostic developments are applications and techniques that have either been implemented or have recently been developed, and will probably be applied sometime within the next five years.

Quantitative Remote Monitoring Systems

Animal Behavior

Observing animal behavior has been suggested for monitoring the health of cattle. Remote monitoring tools have been developed and are used to detect quantitative changes in the health status of calves based on behavior and physiological responses. The behavioral and physiological responses of calves suffering from *M. haemolytica* pneumonia during periods of heat stress have not been described (Theurer, 2013). More information needs to be researched during a time of heat stress to determine if an increase in body temperature is due to illness or heat stress.

Behavior of animals is commonly analyzed to determine animal well-being. In one study, lethargy associated with BRD was apparent in grain bunk and hay feeder activity of *M. haemolytica*-infected calves compared with control calves (Gonyou, 1994). Similarly, previous studies have also shown *M. haemolytica*-infected calves spent less time near the grain bunk early on during the pneumonia period (Sowell, 1999; Hewson, 2011). Researchers were also able to detect a difference between treatment groups on day 1 after infection, where BRD-infected calves spent a relatively small amount of time per day at the grain bunk (Theurer, 2013). In the same study, a comparison between healthy and infected calves found that infected calves had a significant lower occurrence of time spent at the grain bunk, waterer, feeder, and shed (Theurer, 2013).

Feeding Behavior

BRD is also diagnosed in the feeding phase based on visual observation and general clinical signs of illness. Those signs include lack of rumen fill and apparent depression (Nickell, 2010). The inability to accurately identify all clinical BRD cases during the feeding phase is further demonstrated by several studies illustrating the presence of lung lesions at harvest in calves never treated for BRD. At time of slaughter, 33% of the sample population with lung lesions also displayed significantly reduced feed performance and inferior carcass characteristics compared with cattle without lung lesions (Gardner, 1999). This research suggests that large proportions of cattle suffering with BRD are overlooked and consequently fail to receive therapeutic BRD treatment.

Feeding behavior observations can and should be assessed for other economically important diseases. More research should evaluate the economic value of early disease identification in feedlots. Animal illness reduces feed intake in cattle. Feeding behavior, immediately after arrival to a feedlot, was compared between cattle with BRD and healthy cattle (Wolfger, 2015). One study has shown that the mean intake per feeding, mean feeding time, and frequency of feeding has merit in predicting the risk of BRD in feedlot cattle 7 days before visual detection (Wolfger, 2015). Feeding time was shorter in sick cattle in the first few days on feed. This information could be used to develop predictive algorithms for commercial application in feedlot settings (Wolfger, 2015). Feeding behavior systems record feeding times, or they can include weighing feed bunks corresponding to feed intake eaten by the animal. Reports quantifying changes in feeding behavior compared to the time of visual detection of disease are limited, but they could provide the knowledge needed for commercial development of automated disease detection systems.

Accelerometers

Accelerometers record how much time an animal spends lying down compared to standing. Accelerometers have been found to be useful in detecting differences in *M. haemolytica*-infected calves and control calves based on the percent of time lying down. The percent of time calves spend lying may be correlated to lethargy or depression. Lying behavior is expected to be one indicator of animal well-being. Previous trials indicate that calves challenged with *M. haemolytica* spend more time lying down than control animals (Hanzlicek, 2010). In *M. haemolytica*-infected calves, lying down time was inversely related to grain bunk and hay feeder behavioral activity. If producers could determine if calves were sick by the time spent lying down before the development of clinical signs, treatment could be initiated sooner, resulting in earlier resolution of the disease.

Pedometers

Pedometers record how many steps an animal takes in a given time period. Pedometers have not been useful for discrimination between *M. haemolytica*-infected calves and control calves (Theurer, 2013). This differs from previous research in which pedometers detected decreased number of steps traveled after challenge with *M. haemolytica* (Hanzlicek, 2010). From these studies, it appears that the increase in percentage of time spent walking and number of steps traveled on study day 0 may be attributed to the frequent movement that typically occurs during the intensive monitoring period following transport. Therefore, not all increased number of steps are directly related to disease. Potentially, producers may be able to track the number of steps as well as observe cattle that do not travel as much more closely for clinical signs of BRD.

Remote Early Disease Identification (REDI)

A remote early disease identification (REDI) system has been designed to monitor cattle behavior to identify potential BRD cases. This technology differs from pedometers because of the additional information the system gathers. Pedometers typically only keep track of how many steps an animal takes. Information from the REDI system includes steps taken, lying down time, feeding time, drinking time, and any other movement. Research studies have documented changes in feeding patterns during naturally occurring BRD cases. Algorithms can also be used to detect changes in cattle activity, location, and social patterns. For each day, a health status report can be obtained for individual cattle. However, this system also needs improvement. An improvement would be to decrease the time it takes to determine if a calf is ill based on data within the first 24 hours of disease. In one study, three days of data was collected before the REDI system determined that an animal was ill, whereas a visual observer made all disease calls within the first three days after arrival (White, 2015).

Alternatively, studies have also shown that fewer antimicrobials per calf were needed when using the REDI system compared to the conventional detection method. In one study, calves in the REDI group were treated earlier in the feeding phase than the conventional group by 6 days (White, 2015). Prophylactic treatment pull (gathering animals for treatment on first day of arrival) to first treatment pull (gathering and treating animals who are diagnosed with BRD after arrival) were reduced in REDI calves compared to visually diagnosed calves (White, 2015). Mean rectal temperatures were greater for the conventional group compared to the REDI group for each BRD case. Cattle that are ill have higher rectal temperatures, so this finding suggests that by using the REDI system, fewer cattle will be ill. Remote groups or conventional groups were not significantly associated with changes in the average daily gain (ADG). Also, the

number of treatments was negatively associated with weight gain. Calves that were never treated gained more weight than calves treated once, twice or three times (White, 2015). Remote detection calves treated twice for BRD had greater ADG compared to conventionally diagnosed calves treated twice for BRD. Future studies with increased sample size would be necessary to evaluate potential performance differences that could be related to early treatment of BRD. The REDI group had no difference in morbidity risk compared to the conventional group that received prophylactic treatment. This result could be due to the REDI system identifying BRD cases early, which would have also limited disease outbreak in the pen.

The REDI system has also been shown to identify sick calves up to 0.75 days earlier than a trained observer (White, 2015). Therefore, the producer could limit disease outbreaks by treating disease earlier using this system. Other advantages may include improved feedlot performance and implications in labor management by decreasing workload when treatment is required. Labor resources could also be efficiently focused on managing calves during a shorter well-defined period of BRD treatments.

The REDI system could also benefit producers most when a relatively high number of cattle need to be monitored such that the labor force is not overwhelmed with having to visually monitor and diagnose cattle. More specifically, this would occur between days 15 and 45 while on feed, as labor resources might be scarce and more focused on high-risk pens (White, 2015). One limitation of the REDI system is that it may not be as effective in monitoring for other diseases. For example, diseases that do not affect feeding behavior or movement could potentially have limited clinical signs captured by the REDI system.

A major finding with the REDI system is that cattle may not need to be treated at the time of arrival, only when disease is identified. This means that individual cattle would only need to

be treated once with antimicrobials, especially if disease was detected early by the REDI system. By not having to treat all animals with antimicrobials, it reduces the risk of developing antimicrobial resistance. This not only decreases the risk of antimicrobial resistance, it also reduces expenses, cattle stress, and labor, and it improves efforts toward antimicrobial stewardship. Additional studies are needed to assess the capabilities of the REDI system in a variety of field environments and disease challenges (White, 2015).

Infrared Thermography

Research findings suggest that infrared thermography of cattle is an effective animal welfare-monitoring tool. However, for the accurate detection of BRD, surface thermography would likely diminish the effectiveness in extreme ambient conditions commonly found in feedlots (Stewart, 2005). One study found that the nasal passage temperature exceeded the thermal limit in 5 out of 10 calves infected with BRD (Theurer, 2013). Thermography temperatures differed in nasal passage mucosal temperatures in calves that were challenged with *M. haemolytica* when compared to control calves, where *M. haemolytica*-infected calves had higher surface temperatures throughout the trial (Theurer, 2013). It was also noted in this study that behavioral changes lasted longer than temperature differences in this particular study.

Serum Biomarkers

Serum biomarkers may be an effective diagnostic tool for either early diagnosis of BRD or for use in assigning risk categories for calves being moved to feedlots. Cortisol is widely used as an indicator of stress in livestock. In one study, serum cortisol concentrations increased rapidly in a *M. haemolytica* challenged group of calves (Corrigan, 2007). This was paralleled by increases in rectal temperatures. Later, serum cortisol concentrations rapidly declined despite the progression to pneumonia. In previous studies, cortisol concentrations did not change after

challenge with *M. haemolytica* (Corrigan, 2007). Corrigan et al. (2007) demonstrated highly variable concentrations of cortisol after challenge and could not determine a difference between control calves and calves challenged with *M. haemolytica* until five days after challenge. Concentrations were under detectable limits until day 5 after infection (Hewson, 2011). Therefore, concentrations under the detectable parameter, even after the establishment of infection, would limit the use of cortisol as a diagnostic method. In addition, blood samples that are taken at different times throughout the day could give inconsistent results, limiting the usefulness of this method in a feedlot setting.

Haptoglobin (HP) has been found to be the most specific and reliable serum biomarker for differentiating *M. haemolytica*-infected calves from uninfected calves (Theurer, 2013). HP is a protein found in blood serum that removes hemoglobin from the blood. Control, uninfected calves had near 0 µg/mL HP concentrations throughout one trial, whereas *M. haemolytica*-infected calves had significantly greater HP concentrations (Theurer, 2013). These results agree with previous reports, where HP was shown to increase after exposure to *M. haemolytica* (Ganheim, 2003). In the same study, the first step after visual identification and verification of fever was measuring the HP concentration in serum (Theurer, 2013). It was discovered that a high number of steers with BRD had an elevated HP concentration as opposed to a relatively low number of steers without BRD, which resulted in the inclusion of HP in the disease definition of this study. More research needs to be performed to establish more precise reference ranges for calves with BRD in order to use HP concentrations as a diagnostic tool in the field (Theurer, 2013).

Other serum biomarkers, like serum amyloid A (SAA), has also been used to verify inflammation and tissue damage in cattle with BRD. Where HP had a sensitivity of 64% and

specificity of 71% in cattle with BRD, SAA was found to have a sensitivity of 100% and specificity of 46% in the same group of cattle with BRD (Wolfger, 2015).

The white blood cell count may not be a good parameter to confirm inflammation due to BRD (Nikunen, 2007; Richeson, 2013). In contrast, the red blood cell count was greater than the reference value in the majority of steers pulled from a pen due to clinical disease of BRD with little to no effect on the hematocrit (Fraser, 2014). Therefore, a high red blood cell count with a normal hematocrit in BRD affected cattle should be further investigated as a biomarker of BRD.

Distant Future Diagnostic Methods

Microbiome-Driven Diagnostic Methods

The microbiome is composed of microorganisms found in a specific environment, in the case of BRD, the respiratory tract. Microbiome studies use high-throughput sequencing of short fragments of the 16s rRNA gene or from all microbial DNA in a specific environment. The 16S rRNA gene is universal among prokaryotes and has several highly conserved domains, including bacteria and archaea. In addition to the domains, nine hypervariable regions, including primer binding sites, can be used to differentiate bacterial species. This is an ideal phylogenetic marker for characterizing the microbiota of a specific host in a specific environment.

Microbiome research is becoming more popular for humans. Animal scientists are now trying to carry over that research into cattle, specifically for BRD. The United States Department of Agriculture (USDA) recently awarded the University of Wisconsin a grant for defining the microbiome of the bovine upper respiratory tract with final data collection expected in September 2019 (USDA, 2016). This work will form a foundation for future studies in cattle, including studies associated with BRD susceptibility in feedlot cattle.

The nasopharynx microbiota is intricate, plays a role in respiratory health, and changes dramatically after cattle enter the feedlot operation (Timsit, 2016). Microbial unpredictability of the respiratory and digestive tracts has been linked to disease in other animals (Timsit, 2016). The impact of the nasal microbiota on the development of pneumonia in cattle is unknown, but there is evidence to suggest that the composition of the nasopharyngeal microbiota of cattle is related to the development of pneumonia. This research could allow development of a technique to change the microbiome of the nasopharyngeal to avoid disease. Culture-based surveys of the nasopharyngeal microbiota may yield valuable information about the fluctuating fraction. However, for some pathogenic bacteria, only a relatively small fraction of the bacteria are cultureable in the laboratory (Timsit, 2016). Therefore, the development of culture-independent methods to study microbial communities have been increasing since certain classes of bacteria may be too difficult to culture for research studies.

Metagenomics-Driven Diagnostic Methods

Metagenomic sequencing analyzes microbial community diversity, gene composition and function, as well as metabolic pathways associated with a specific environment. More specifically, viral metagenomics has been used to investigate the virome associated with complex disease syndromes, and bacterial microbiomes can be studied in the same way.

Metagenomic sequencing has been used to identify and characterize viruses associated with BRD. One study used metagenomic sequencing to characterize the virome of nasal swab samples collected from beef cattle with acute BRD and asymptomatic pen-mates (Mitra, 2016). Due to the small sample size, only associations between potential exposures and acute BRD in the population could be analyzed. Variance components of the random effects analyzed indicated that variability occurred between animals rather than as a group of cattle at the feedlot (Mitra,

2016). Such results potentially suggest that using cattle viromes for BRD diagnostics is unpredictable between animals because of biological differences. A larger number of samples would likely increase the ability of detecting significant differences between groups of cattle.

Potentially, metagenomics would be able to decrease the amount of time it takes for a disease to be detected and identified. This technology could also reveal other genetic attributes of a virus or bacteria that is needed for effective treatment other than the identification of the microorganism. Additional attributes could include the identification of resistance genes to antimicrobial medications and would allow for more applicable diagnostics (Hall, 2015).

Discussion

This report reviewed current diagnostic methods for BRD in feedlot cattle and explored potential future diagnostic approaches based on recent discoveries and new technology. With regard to future diagnostic capabilities, topics were separated into two parts, based on future development progress. Applications included techniques that are within an immediate future development phase, and other applications included distant future methods that are early in the research stage, gaining popularity based on new understanding, and/or estimated to be applied beyond five years from today.

Diagnostics techniques for BRD in feedlot cattle have traditionally been based on subjective visual observations of animal behavior, physical examinations, and lung lesions identified at necropsy. Strengths of necropsy for a diagnostic method include an accurate diagnosis after the inspection of the lungs for gross lesions; however, the diagnosis of BRD in an individual animal would be post-mortem. Treatment of pen mates of a necropsied animal may be indicated after the post-mortem diagnosis of BRD.

Current diagnostic tools use subjective measures, which makes diagnosing animals complicated compared to subjective definite measures. An improvement in the current case definition would solidify the BRD definition throughout the field. However, this could cause an education gap that needs to be addressed. Visual observations are the simplest way to diagnose BRD, but this method has low sensitivity and specificity due to the subjective observer. The use of a physical examination includes some objective measures; however, this method causes an increase in stress when sick cattle are handled.

Animal behavior is a great way to determine animal wellbeing. A downfall of this technique is that behavior could change for reasons other than BRD. The REDI system is a great addition to recording animal behavior, but again, it is not specific for the diagnosis of a single disease.

Infrared thermography has potential to diagnosis animals with a fever, but this technology will not work well in the summer months due to increased air temperature. Various serum biomarkers are being researched to determine their efficacy in the field. Disadvantages would include low specificity to BRD.

Current literature strongly supports the need to improve the BRD case definition to help producers and researchers diagnose the disease earlier. There was no specific research, based on statistics, on the misdiagnosis of BRD in feedlot cattle. However, there is strong evidence that the disease is not diagnosed until it is either too late to treat or more difficult for the animals to recover after treatment (Sweiger, 2010).

Future diagnostic options have been evaluated, but still need refinement to be advantageous in the field. Diagnostic methods, such as objective visual observations of animal behavior, accelerometers, pedometers, REDI systems, infrared thermography, and serum

biomarkers, show promise in the future. Each method will need to be evaluated for strengths and weaknesses after development and implementation. Determining the sensitivity and specificity of each method will be important in assessing effectiveness. Cost of using these methods will also be a driving factor in their use and application in the field.

The microbiome of cattle and the application of viral metagenomics and bacterial microbiomes has generated interest in their use for the early diagnosis of BRD in cattle as well as a way to evaluate BRD prevention strategies. If these methods are not economically feasible for producers, they will not be valuable to the beef industry. More research needs to be conducted to determine how this technology could be applied to the early diagnosis of BRD in the feedlot setting.

As stated above, there are many obstacles in the accurate and early diagnosis of BRD in feedlot cattle. If these obstacles are not overcome in the future, BRD could continue to worsen, resulting in exponential economic losses as well as the loss of an important food source. Antimicrobial resistance may continue to increase as more animals are being treated due to lack of effective diagnostic measures. This disease is a major problem in the industry for various reasons and needs to be resolved. The development of new diagnostic techniques that accurately diagnose BRD early in the course of disease could be one way to make an impact.

Chapter 2 - Current and Future Treatments

Introduction

Bovine respiratory disease (BRD) is the most common disease syndrome in commercial feedlots. In the United States, the annual costs associated with BRD were estimated at \$4 billion which includes the costs of treatment, prevention, and lost productivity (Cernicchiaro, 2012). Costs associated with BRD prevention, treatment, morbidity, and mortality have been estimated to be from \$13.90 to \$15.57 per head (Snowder, 2007).

Another concern affecting animals infected with this disease is animal welfare. Producers want and need their animals to have the best care they can get to ensure the health and safety of all animals. Improved means of treating this disease will allow animals to have less stress and lower rates of illness. Cattle with BRD can potentially have decreased gains and meat quality. With improved methods of treatment, meat quality and feedlot efficiencies will increase.

As shown in Figure 3, BRD is caused by viruses or bacteria infecting an animal with stressors of transportation, handling, housing, and weather conditions. Viruses that infect cattle, relating to BRD, are bovine herpesvirus type 1 (BHV-1), parainfluenza-3 virus (PI3), bovine viral diarrhea virus (BVDV), and bovine respiratory syncytial virus (BRSV) (Grissett, 2015). *Mannheimia haemolytica* is the most common bacterial pathogen associated with BRD (Theurer, 2013). Other known pathogens infecting BRD cattle are *Mycoplasma bovis*, *Pasteurella multocida*, and *Histophilus somni* (Grissett, 2015). Pathogens and cattle may react differently depending on several factors. For example, each pathogen can have different infection periods and individual cattle can have different immunological response times. Having knowledge of both infection and response time will lead to reducing the negative impacts of BRD in populations. Prevention and control of BRD in cattle relies on implementation of health and

production strategies designed to reduce stress, induce protective immunity, optimize nutrition, and minimize disease challenge (Nickell, 2010).

The general organization of the beef cattle industry is a problematic area for BRD management and control partly due to the frequent transportation of animals. Minimal information is typically provided upon purchase of animals to determine history and preventative measures based on this information. Most cases of BRD tend to occur in the first 45 days after arrival to the feedlot. Timing of peak new case occurrence within a pen of animals can be highly variable due to the multifactorial nature of this disease complex (Nickell, 2010).

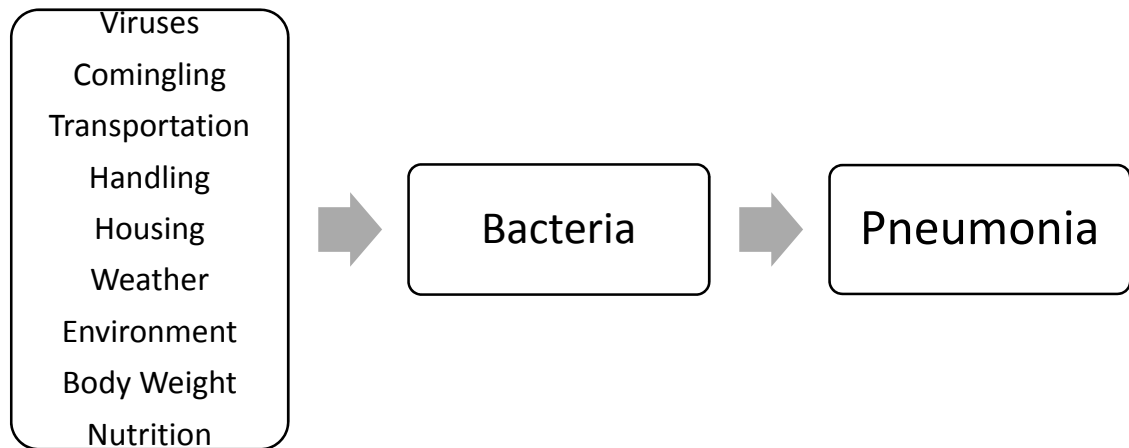
No one practice for reducing the effect of this disease exists. However, there are strategies or approaches that provide a basic foundation for intervention that can minimize the effect of this economically significant disease (Sweiger, 2010). These strategies include the use of more effective modified live virus vaccines rather killed virus vaccines (Snowder, 2007). Other vaccines, like chemically altered organisms, have also been added to vaccination programs. Despite these efforts, current vaccines for BRD do not confer complete protection against infection.

Currently, treatment of cattle with BRD is crucial for stopping disease progression as well as decreasing the spread of the disease throughout the herd. Current methods of treatment can be lacking due to various reasons. Developing new means of treatment must be established to more effectively reduce the outcome of BRD even further. Having new and improved treatment methods will also improve animal welfare.

The objective of this report is to describe treatment methods for BRD that are currently used by producers in the cattle industry. Immediate and distant future treatment methods are also

discussed as options for controlling BRD with the goal of improving the health and wellbeing of these animals.

Figure 3: Causes of Bovine Respiratory Disease



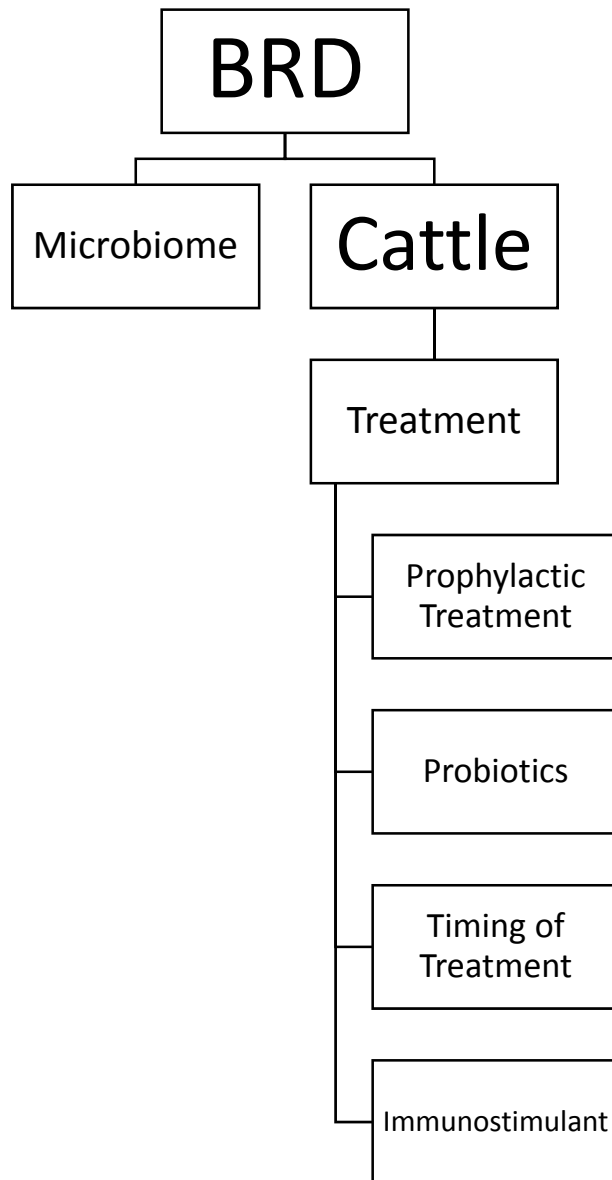
Materials and Methods

Search Terms

Peer-reviewed articles were selected from PubMed, Web of Science, and Google Scholar databases. Published articles included years 1989 through 2016. Each database was searched using the terms displayed in Figure 4, beginning with "cattle BRD". After searching for cattle BRD, topics were narrowed to be more specific in the article search. Topics that did not have a significant amount of information were searched individually and did not include the word "cattle" (e.g., BRD microbiome). A search was also conducted for "cattle microbiome" and "cattle probiotics" to find more articles researching these two treatment strategies for other cattle diseases. Research topics were then divided into two categories as "immediate future" treatment methods and "distant future" treatment methods. Treatment methods included those techniques

that are within a short time frame of immediate future development, and longer time frame applications included treatment methods that are early in the development stage, gaining popularity based on new understanding, and estimated to be applied in the distant future.

Figure 4: Search Terms used to Collect Articles



Results

Current Treatment Methods

Antimicrobial Treatment upon Arrival

One particular current management practice is antimicrobial treatment using antimicrobials upon arrival to a feedlot. In this setting, antimicrobial therapy has been defined as the mass treatment of animal populations that might be experiencing any level of disease before the onset of obvious illness. This treatment practice is commonly used to reduce the level of bacteria pathogen load that might exist in cattle populations acquired at any point of beef sector transportation. This practice entails the mass administration of an approved antimicrobial product to a population at risk of developing BRD with the intent to improve overall health and performance (Nickell, 2010). Table 2 lists the current FDA-approved antimicrobials labeled for BRD treatment.

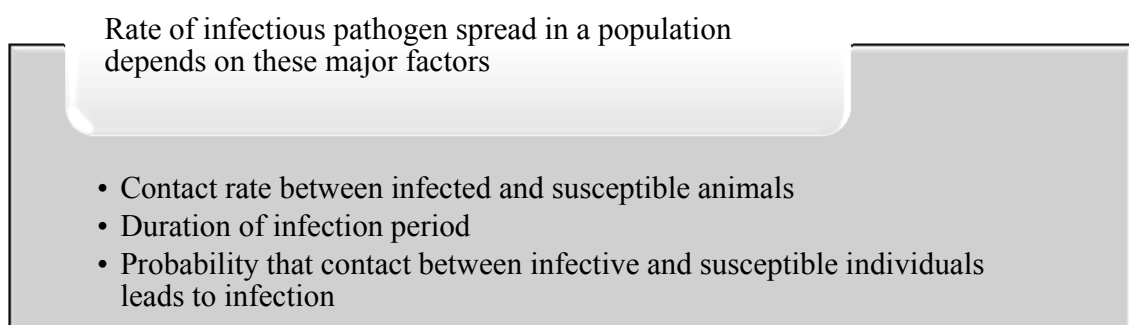
Table 2: Current Antibiotics Used for Bovine Respiratory Disease

Antibiotic Class	Antibiotic Name	Product Name	Manufacturer
Fluoroquinolone	Enrofloxacin	Baytril®	Bayer Animal Health
Macrolide	Tuluthramycin	Draxxin®	Zoetis
Macrolide	Tilmicosin	Micotil®	Elanco
Thiamphenicol	Florphenicol	Nuflor®	Merck Animal Health
Tetracycline	Oxytetracycline	Tetradure®	Merial
Cephalosporin	Ceftiofur	Excede®	Zoetis

Treatment with antimicrobials upon arrival can also be considered as curative treatment because cattle arriving to a stocker or feedlot facility not only may be at risk of developing BRD,

but they may already be in the early stages of infection. This management tool is based on the concept of medicating the entire population at a single point in time with the goal of treating subclinical cases. Treatment of the population is often preferable to selecting individuals for therapy due to the diagnostic challenges of identifying BRD in calves. As reviewed in the previous chapter, producers often fail to accurately identify sick cattle. Therefore, objective measures, such as rectal temperature and respiratory rate, could be used to identify clinically ill animals. In many beef producing systems, cattle are managed in co-housed populations. Disease dynamics have the potential to have a significant impact on overall health outcomes. The goal of treatment with antimicrobials upon arrival is not only to reduce individual cases of BRD, but also to reduce the overall disease challenge in the group. Figure 5 describes the three major factors associated with the rate of infectious pathogen spread in an animal population (Nickell, 2010).

Figure 5: Pathogen Spreading Factors



Medication of the entire pen at arrival has the potential to reduce the number of animals infected with a susceptible bacterial pathogen, clinical or subclinical, reducing the disease challenge in the environment for non-infected animals and limiting disease spread. For example, treatment with tilmicosin upon arrival has been shown to reduce the colonization rate of *M. haemolytica* within the nasopharynx in cattle compared with negative controls (Nickell, 2010). The use of antimicrobial treatment as a population control measure provides a tool for production

systems receiving calves at high risk for disease and compensates for the inability to successfully diagnose the true health status of calves at arrival to a feeding operation. The decision to administer pharmaceutical products to all animals is based on clinical signs, expected illness rates in the group, and prior evidence of product efficacy. BRD risk factors and high-risk cattle (Table 3) determine if prophylactic treatment will be administered. High-risk classification for BRD includes cattle that are light in weight, from multiple origins, have a poor health history, and have experienced long durations of travel before arrival at the stocker or feedlot facility. A prophylactic treatment decision is made based upon the given classification of either high-risk or low-risk. The goal is to strategically implement antimicrobial treatment therapy where it will provide optimum benefits.

General guidelines that have an impact on the decision to administer antimicrobial treatment for BRD include (1) the clinical appearance of the cattle on arrival, (2) current and expected morbidity/mortality patterns, (3) feed consumption, (4) elevated body temperature, and (5) efficacy of products labeled for the control of BRD (Nickell, 2010). The impact of treatment when administered at arrival will not likely be the same for groups where disease occurs at a later time point. If cattle are expected to be ill or become ill near the arrival time, antimicrobial treatment may decrease disease expression within the population. A previous study showed this by administering the antimicrobial agent before arrival to the feedlot or later in the feeding period (McClary, 1999). In another study, tilmicosin administered at arrival was superior to pre-shipment injection as well as a combination of pre-shipment and arrival medication (McClary, 1999). Similarly, morbidity risk was lower in cattle administered tilmicosin at arrival compared with before shipment (Duff, 2000). Overall, these studies consistently demonstrate that antimicrobial treatment administration at the time of arrival is ideal compared to other time

points of transportation. Research focusing on treatment three to five days after arrival should be conducted to determine if this is a more beneficial time to control for BRD.

Treating all animals upon arrival to feedlot with antibiotics has weaknesses. A major concern is the increase in antibiotic resistance due to using antibiotics to treat a disease that may or may not be infecting the animals. It also is a large cost associated with cattle arrival to a feedlot. The animals are typically handled upon arrival for other arrival procedures (for example, tagging, deworming) and so, this would not force another time through processing.

Table 3: Bovine Respiratory Disease Risk Factors

Cattle Risk Factors	High Risk Cattle
Weaning Status	Light Weight
Vaccination History	Multiple Origins
Comingling	Extended Travel
Environment	Previous Health

Future Treatment Options

Conventional management of calves that are at high risk for BRD often includes mass treatment with antimicrobials at arrival to the feedlot, followed by visual observation for diagnosing individual cases. These are effective methods, but control program efficacy is influenced by the accuracy of visual observation (White, 2015). Therefore, it is also important to have an effective antibiotic to treat individual cases focusing on the risk of resistance.

New treatment options would need to be developed to control BRD in the beef industry in the US and throughout the world. To reduce BRD incidence, improved treatment options need to be developed, including the development of new antibiotics. However, these also need to avoid the possibility of increasing antimicrobial resistance by overusing antibiotics. In this

section, the following topics will be discussed with regard to immediate future treatment methods: immunostimulants, development of new antibiotics, timing of treatment, and the use of probiotics.

Immediate Future Treatment Methods

Immunostimulants

Despite the fact that vaccines and antibiotics are available to treat and prevent BRD, producers still have difficulties overcoming the disease. For this reason, immunostimulants are of particular interest for producers, veterinarians, and pharmaceutical companies. Interest in immunostimulants has increased because of the recent antimicrobial resistance focus and the consumer demand on the decreased use of antibiotics in food animals. Immunostimulants can be used in conjunction with antibiotics and vaccines to give cattle the immune boost they need to overcome the disease. Immunostimulants also combat the immunosuppressive effects of stress (such as shipping or overcrowding) so that cattle can respond effectively to a pathogenic microorganism.

Innate immunity is a rapid, non-specific response, which provides immediate, short-lived protection against a non-specific pathogen until the development of a protective adaptive immune response to the same pathogen. Non-antibiotic products (like immunostimulants) stimulate the innate immune system to improve recognition and response to microbial pathogens that threatens the animal's health. An important innate immune cell population in cattle that would benefit from immunostimulants would be $\gamma\delta$ T cells. The cells encounter pathogens in the epithelial lining of the respiratory tract. (Hedges, 2016). Following a strong innate response, adaptive immunity to *M. haemolytica* involves the development of antibodies generated against specific antigens of secreted toxins and outer membrane proteins (Ayalew, 2013).

When cattle are subjected to environmental and physiological stressors, the animal's innate and acquired immune functions are compromised, allowing for pathogens to multiply in the respiratory tract, resulting in a need for an immune boost. Recently, a liposome complex injection for the treatment and prevention of BRD was developed that elicits a non-specific immune response. In a different study, scientists used an immunomodulator composed of DNA to elicit an innate immune response in cattle, which was effective alone or enhanced at least one biological agent (Abraham, 2014).

New Antibiotics

Antibiotics have played a primary role in the treatment and control of BRD. The most commonly used classes of antibiotics used to treat respiratory disease are fluoroquinolones, penicillins, tetracyclines, cephalosporins, phenicols, and macrolides (see Table 2) (Davies, 2016). Antibiotic resistance has also become a primary concern for the beef industry to limit the potential negative consequences of antimicrobial resistance. There is an urgent need to design and develop new antibacterial agents to treat BRD bacterial pathogens. New antibiotics are likely to include a combination of cell- and gene target-based approaches, for example, virulence genes or bacteria cell outer membrane proteins (Davies, 2016). Bacterial cells are complex and contain numerous proteins that play a role in the given bacterial infection. There is potential to develop new antibiotics that function by targeting newly discovered proteins in the outer membranes of bacteria. Development of the new antibiotics needs to include *in vivo* screening, because growth has a profound effect on gene transcription and may affect the expression of these potential drug targets (Davies, 2016). Animal health pharmaceutical companies are working to develop new antibiotics, but new chemical entities are scarce due to overlap in human medicine and the potential for causing resistant pathogens. A large problem with creating new antibiotics is that

new classes of antibiotics have not been discovered. The discovery of new classes of antibiotics would be an asset in treating resistant bacteria, like *Mannheimia haemolytica*, as well as aid in the treatment of BRD.

Timing of Treatment

Effective cattle health management should focus on foundational practices and avoid the distractions in managing the health of calves at high risk of developing BRD. Implementing a systems approach specific for the operation and focusing on the details of that system will maximize the effect of any health management protocol (Sweiger, 2010). Effective treatment must begin with a commitment to early identification and treatment of sick calves. Excluding cattle that are infected with antimicrobial resistant bacteria, most antibiotics are effective in treating BRD that reach therapeutic levels within two hours of administration (Sweiger,2010). Early treatment requires the ability to consistently recognize sick calves promptly in the course of disease and administer a proven antibiotic. If finding a faster acting antibiotic becomes a primary concern in treating calves with BRD, the concept of early treatment should be revisited with that new method. As reviewed in the previous chapter, there is an urgent need for accurate and rapid diagnostic tools to aid in early treatment.

Not all calves respond similarly to the same therapy. Calves requiring treatment usually respond well to efficacious antibiotics that are administered in a timely manner and continued for an adequate period of time. With a biologic system, there are always outliers and calf response to treatment is no exception. Calves may appear to respond to antibiotic therapy rapidly and completely, because they may have already recovered from the disease without the need for treatment. There may be a percentage of calves in any population that do not respond well to treatment regardless of the antibiotic used because of a poorly functioning immune system, poor

nutrition, weather conditions, and other influences. Continuing to administer additional antibiotics to a calf previously treated for BRD with efficacious antibiotics for an extended period of time only adds to the expense and stress of a calf that has already been adequately treated (Sweiger, 2010). As stated in the previous chapter, a diagnostic tool that confirms early infection would allow animals to be treated earlier to reduce the time it takes to recover and the amount of antibiotics used.

One study examined the effect of BRD antibiotic treatment on growth rate in different groups of feedlot cattle over a period of time, including an early group (1 through 40 days of 200 day feeding period), mid group (41 through 80 days), and late group (120 through 200 days) (Snowder 2007). The number of cattle treated in the late group for BRD was much less than the numbers of cattle requiring treatment in the early and mid groups. Cattle treated during the late period also tended to have heavier carcasses, more retail product, less fat trim and heavier bone weight than early and mid groups (Snowder, 2007). In a large study, scientists performed statistics for net returns, performance traits, and carcass traits on the basis of the number of antimicrobial treatments after initial diagnosis of BRD (Cernicchiaro, 2013). Within the first 100 days after arrival at the feedlot, 30,473 of 212,867 cattle had BRD; of those affected, 21,741 were treated only once, 5,836 were treated twice and 2,896 were treated ≥ 3 times (Cernicchiaro, 2013). Cattle that were treated once or less had higher net returns, and returns were higher for calves arriving in the fall or summer. Net return statistics were based on ADG, hot carcass weight (HCW), choice yield grade (CYG), and quality grade (QG) for economic evaluation.

In another study, 74% of BRD cases occurred in the first 42 days and cases peaked during week 2 post-arrival and then declined (Babcock, 2009). Researchers found that disease timing, when measured relative to arrival and slaughter, affects performance and health

outcomes. More studies need to be conducted to look at the relationship between BRD timing and performance and health variables that could lead to management options that more effectively mitigate the economic impact of this extremely important disease syndrome in feedlot production systems (Babcock, 2009).

Probiotics

The knowledge that some commensal bacteria have a role in maintaining health in the host has led to the rediscovery of probiotics as a disease management tool. For example, *Lactobacillus casei* supplementation improved the immune response against *Streptococcus pneumoniae* infection in the respiratory tract of mice (Villena, 2005). Similarly, a direct fed microbial, *Bacillus subtilis*, enhanced immune function in calves and broiler chickens (Molnár, 2011). There is evidence that certain *Lactobacillus* strains inhibit growth of *M. haemolytica* and stimulate a positive immune response in bovine epithelial cells *in vitro* (Subramanian, 2014). More research needs to continue in order to define efficacy of probiotics as a therapeutic based on the concept of competitive exclusion.

Distant Future Treatment Methods

Microbiome-Driven Treatment Methods

To facilitate new approaches to mitigate BRD and develop alternatives to antibiotics, a better understanding of the functionality of the bovine respiratory microbiota is needed. Studies using sequencing technologies to characterize the interaction of commensal respiratory bacteria with pathogens and the host will aid in targeted approaches to develop respiratory probiotics. Most studies in cattle have focused on bacterial pathogens in the gastrointestinal tract (Timist, 2016). Because of this, there is a scarcity of information regarding the structure of the nasopharyngeal microbiota and its role in maintaining health.

A recent study showing feedlot cattle that remained healthy during the first weeks after arrival had greater bacterial diversity and richness in their nasopharyngeal microbiota compared with cattle that developed bacterial pneumonia (Holman, 2015). The bacteria in the nasopharynx of feedlot cattle may have an important role on preventing the spread of pathogens. Several bacteria in the bovine nasopharynx may enhance the health of cattle and could be used in feedlot cattle through administration of nasal probiotics.

Commensal bacteria also have a key role in contributing to adaptive immunity against infections (Ichinohe, 2011). More studies need to be conducted to verify the hypothesis that commensal bacteria have a role in adaptive immunity and ensure product efficacy, as in the case of the use of probiotics. One study found that disease develops when a host and/or pathogen factors result in bacterial production and distribution to other body sites and as a result of a harmful host inflammatory response (Timsit, 2016). More in-depth studies are needed to examine both the microbial composition of BRD and the relative contribution of the immune system to the calf's health.

Heritability and Selection

Selection for disease resistance is one of several possible interventions to prevent or reduce the economic loss associated with animal disease and to improve animal welfare. Undesirable genetic relationships may exist between production and disease resistance traits. When examined the estimated heritability of BRD incidence was not significant (Snowder, 2007). Most correlations between phenotypic, environmental, and genetic correlations of the observed traits with BRD were insignificant. Hot carcass weight and weight of retail cuts had moderate, undesirable phenotypic correlations with BRD. Correlations of BRD and longissimus muscle (LM) palatability and average daily gain (ADG) were not detected. Low estimates of

genetic correlations conclude that selection to reduce BRD in feedlot cattle would have negligible correlated responses on growth carcass and meat palatability traits. Selection for those traits will have little effect on BRD susceptibility or resistance. Other livestock animals use selection to increase growth rate, increase immune performance, and increase mortality commonly seen in broilers and turkeys. In pigs, selection for percentage of carcass lean in pigs increased leg weaknesses, resulting in a selection disadvantage. In dairy cattle, milk yield has undesirable genetic correlations with mastitis, ketosis, and cattle disease records with cystic ovaries and metritis. However, phenotypic and genetic relationships between production and health traits in beef cattle have not been clearly established (Snowder, 2007). Before incorporating health traits into selection indices, potential genetic antagonisms between production and health traits must be understood. Differences in growth and carcass traits between treated and non-treated steers and between steers with or without lung lesions were generally similar. Unadjusted means and standard deviation (SD) for growth, carcass, and LM palatability traits are reported and are similar to those reported by Gregory et al. (1995) using an almost identical data set. Because data from heifers were included, the mean for ADG is less than that previously reported. Cattle treated for BRD had somewhat smaller means and SD for fat-related traits than the healthy group. Estimates of variance components and heritability were similar for the univariate and bivariate models. Therefore, the heritability estimate for BRD for this study agrees with a previous estimate by Snowder et al. (2006). Heritability estimates for carcass traits were moderate to high ranging from 0.26 to 0.68. Estimates for LM palatability traits were moderate, ranging from 0.23 to 0.31. Estimates for ADG, carcass and LM palatability traits were in close agreement with previous estimates, except for retail product weight and percentage as well as bone weight. These exceptions were due to differences in estimates of the additive

genetic variances. Means, SD, and phenotypic variances for retail product weight and percentage, and bone weight were similar to those reported by Gregory et al. (1995). The larger additive genetic variances resulted in heritability estimates greater than those reported by Gregory et al. (1995) for retail product weight and percentage and bone weight. Of related interest are the significant contrasts between healthy and period when treated for BRD groups for retail product weight and percentage and bone weight. In summary, the difference between these two studies suggests that health status can be considered as having a significant effect on some traits. Correlations of BRD with ADG, carcass, and LM palatability traits were usually low or near zero. Moderate correlations with BRD were estimated for HCW, retail cuts weights and bone weight. Phenotypic correlations with BRD ranged from -0.35 to 0.40 (Snowder, 2007). Hot carcass weight, weight of retail cuts and percentage of carcass bone were moderately correlated phenotypically with BRD. Most estimates of genetic correlations had large standard error (SE) and were not significantly different from zero. Therefore, the moderate estimates suggest that selection for resistance to BRD may have an undesirable correlated effect on shear strength and a reduction in the percentage of bone weight. In conclusion, these small and non-significant estimates of genetic correlations suggest that selection to reduce BRD in feedlot cattle would have negligible effects on growth carcass and LM palatability traits. Selection to reduce BRD would have minor economic consequences on production traits or product quality (Snowder, 2007).

Discussion

This report reviewed current treatment methods for BRD in feedlot cattle and explored potential future treatment tools based on recent discoveries and new technology. With regard to future treatment capabilities, topics were separated into two parts, based on future development

progress. Applications included treatment methods that are within an immediate future development phase, and other applications included distant future methods that are early in the research stage, gaining popularity based on new understanding, and/or estimated to be applied beyond five years from today.

Treatment methods for BRD in feedlot cattle are still effective in current processes, but without improvement, BRD will continue to be problematic. Despite current treatment methods for BRD, there continue to more deaths each year associated with this disease in feedlot cattle. Also, if continued, current treatment methods, like antimicrobial treatment upon arrival, will lead to more antibiotic resistance and eventually decline in efficaciousness, leading to more annual deaths. Implementing future effective treatment methods will strengthen, and hopefully, reduce current BRD treatment regimens.

Future strategies options have been evaluated, but they still need refinement to be advantageous in the field. Treatment strategies, such as immunostimulants, new antibiotics, and optimal timing of treatment, show promise in the future. Safety and efficacy are the most important evaluation tools for these new treatment methods. Cost and practical application of each treatment method will also be driving factors in determining their use in the field.

Studies of the respiratory microbiome of cattle and the application of metagenomics has generated interested in their potential use for treatment possibilities of BRD. If these methods are not economically feasible for producers, they will more than likely not be valuable to the beef industry and consumers.

Many obstacles stated above impact BRD and cattle producers as a whole. If these obstacles are not overcome in the future, BRD will continue to worsen, resulting in exponential losses. Without development of new treatment methods antimicrobial resistance will continue to

increase as more animals are continually being treated whether necessary or not. Subsequently, a major food source will be threatened as more animals become morbid from BRD that often results in death or euthanasia. BRD is a major problem in the beef industry and needs to be resolved by the development of new and effective treatments.

Chapter 3 - Conclusion

Bovine respiratory disease is an enormous problem for all cattle producers. To overcome this major problem both diagnostics and treatment methods will need improvement, as well as other potential influences such as preventative measures. As noted in the previous two chapters, research is being conducted to advance both diagnostic and treatment fields. There are certain aspects of BRD that producers cannot control, such as weather conditions. Producers do their best to protect animals from inclement weather but Mother Nature is often unavoidable.

A future research opportunity not discussed in this review is the development of a risk assessment tool for producers to determine risk categories of arriving cattle. Therefore, this could be considered a diagnostic tool to help producers determine cattle that need different means of treatment based on their higher or lower risk category. Another diagnostic tool that had little to no research published is the use of ultrasound to diagnose BRD. The expense of the machine and expertise needed to analyze the ultrasound image may be limiting factors for producers. However, often, large feedlots have an ultrasound onsite for other uses, and so, education on how to diagnose BRD using this machine could be beneficial.

Probiotics were previously discussed, but more specifically, the use of cytokines. Research has been conducted using cytokines in chickens to combat disease, improve weight, and health, but no current research was found relative to cytokine use in cattle (Luntz, 2003). The immune response generates cytokines in response to infection. Cytokines have the ability to block viral replication by using interferons as well as triggers the inflammatory response. Therefore, cytokines could be investigated for their ability to combat infection.

In conclusion, many different aspects are being explored to determine the best way to prevent, diagnose, and treat BRD. Researchers and pharmaceutical companies are taking action

to put forth means to aid in overcoming such a complicated and widespread disease. BRD will continue to be the frontrunner for research conducted at all levels in order to generate an effective solution or multiple solutions.

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