Novel approaches for combating bovine respiratory disease

by

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Abstract

Bovine respiratory disease (BRD) is the leading cause of illness and death in cattle throughout North America, costing producers $800 to $900 million each year. Over the past 30 years, there has been extensive research conducted to study BRD, but few advances have been made to reduce the negative effects of the disease. The significant impact of BRD on the cattle industry creates opportunities for new and novel approaches for combating the disease to be explored and researched. The objective of this paper is to provide an overview of current BRD understanding and traditional approaches for treating and preventing the disease. Additionally, this paper will provide a discussion on novel approaches to mitigate risk of BRD by understanding the impact of animal genetics, and managing environmental and animal social factors. Bovine respiratory disease is classified as a multifactorial, complex disease caused by both bacterial and viral pathogens. Major risk factors for development of BRD include: presence of disease-causing infectious agents, host factors that increase susceptibility of animal, and external environmental factors. Scenarios when all risk factors are present indicate ideal environments for BRD-causing pathogens to infect cattle. High stress environments post transport, post weaning, or any activity that requires movement of animal from its pen (i.e. vaccination, treatment, sorting pens, etc.) often create the described ideal environment. Identification of risk factors associated with BRD is an important step in preventing and managing disease. Prevention can also be obtained through early vaccination protocols, biosecurity, metaphylaxis and other animal management practices. In the US, over 90% of large feedlots reports BRD as the most frequent disease resulting in increased medication costs and death. Nearly 20% of beef cattle in the United States will require clinical treatment of BRD at some point in their lives. Clinical signs can include nasal discharge, lethargy, inappetence,

coughing and labored breathing. Early detection of clinical signs is crucial in treating and preventing the spread of disease. A diagnosis of BRD in cattle is made using clinical signs, history, and/or laboratory testing. Treatment practices include antimicrobial therapy, but with increasing public concern regarding antimicrobial use in cattle, novel approaches to combating the disease are needed. Novel approaches to combat BRD include understanding the importance of genetics and genomics when selecting cattle, implementing new protocols to circumvent environmental risk factors, and by providing disease preventative animal management and biosecurity practices at each stage of production.

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Chapter 1 – Introduction to bovine respiratory disease

As of January 1, 2023, there were 89.3 million head of cattle and calves on U.S. farms according to the Cattle report published by the USDA's National Agricultural Statistics Service (NASS). According to the USDA, the U.S. beef cattle industry is divided into two sectors: cow-calf operations and cattle feeding. Cow-calf operations mainly maintain a herd of cows for raising calves. The 2017 Census of Agriculture shows that cow-calf production occurs on 729,046 farms with an average herd size of 44 head. Cowherds are widely distributed in size with 27.2% of cows in herds of less than 50 cows, 55.6% in herds 50 to 500 cows and 17.2% in herds greater than 500 head (USDA-NASS, 2017). Calves are weaned at 3 to 7 months of age and can move through the value chain in several different ways. After calves are weaned and replacement heifers or bulls are retained as breeding stock, the remaining animals are sold into the feeding system for slaughter. There are different ways for these new steers and heifers to grow to market weight. The calves may enter a stocker program where they will graze on grass for 3 to 4 months before being placed in a feedlot. Another option is to move animals into a 30 to 60-day preconditioning program. Through a pre-conditioning program, animals are put through a health protocol for deworming, dehorning, and vaccination. Calves can then be started on feed to ensure they are healthy in the next stage of the value chain. Another option is for the calves to be backgrounded for 90-120 days, placed in pens or lots and fed dry forage, silage and grain before entering a feedlot. On January 1, 2020, the top five cattle feeding states of Nebraska, Texas, Kansas, Iowa and Colorado accounted for 72.1% of total feed lot inventories (USDA-NASS, 2020). As of January 1, 2023, the total number of cattle on feed in U.S. feedlots of all sizes was 14.2 million head (USDA, 2023).

Bovine respiratory disease (BRD) is the leading cause of mortality in beef calves 3 weeks of age to weaning and morbidity and mortality in beef feeding and finishing systems. Bovine respiratory disease costs producers in North America $800 to $900 million each year (Sanchez, 2022). According to Dr. Matthew Scotts, an assistant professor of microbial ecology and infectious disease at Texas A&M College of Veterinary Medicine, nearly 20% of all cattle raised for beef production will require clinical treatment for BRD at some point in their lives (*The Cattle Battle*, 2022). Bovine respiratory disease is not limited to beef cattle. Dairy producers raising heifer calves report challenges with treatment costs, increased calf mortality, and decreased production over the lifetime of the animal. Dairy heifers diagnosed with BRD as calves are reported to have increased risk of being culled from the herd prior to their second calving.

Bovine respiratory disease is a multifactorial disease complex because multiple factors play a significant role in its development, such as suppression of the immune system, exposure to stress, and exposure to bacterial, viral and/or parasitic pathogens. Broadly, BRD refers to and encompasses any disease of the upper or lower respiratory tracts of cattle. Bovine Respiratory Disease is considered a polymicrobial disease, which means that it arises from infections with a combination of bacteria and viruses. In addition, several other factors influence the susceptibility of an animal to developing BRD. Any one risk factor alone may not trigger BRD, but several risk factors together form an additive effect that can predispose the animal to BRD. Viruses that can cause BRD include bovine herpes virus (IBR), bovine parainfluenza virus (PI-3), bovine respiratory syncytial virus (BRSV), bovine viral diarrhea virus (BVDV) and bovine coronavirus (BCV). Viral infection commonly causes the initial BRD infection and predisposes the animal to subsequent bacterial BRD infections. Bacterial infections often related to BRD include *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni* and *Mycoplasma bovis*. Parasite involvement could include lungworm.

Host factors refers to the characteristics of an animal that makes it more prone to the disease. This includes age, nutritional status, immune status, prior exposure to pathogens, and genetics. The environmental conditions can also increase the risk factors for disease. Stress from transportation, bringing cattle together from multiple different sources, also called comingling, or even adverse weather or temperature fluctuations can make a difference in the stress levels of the animal in susceptibility to the disease. Cattle transported from cow-calf operations to feeding operations are at an increased risk of developing BRD. Commonly referred to as "shipping fever", BRD occurrence in the feedlot generally occurs within two weeks of arrival. In feedlots, BRD is the primary cause of morbidity and mortality, with 60% to 90% of all morbidity and mortality attributed to the disease (Smith, 1998; Hay et al., 2014; Baptista et al., 2017). Approximately 0.64% to 0.74% of cattle on feed in North America die due to BRD (Miles, 2009; Baptista et al., 2017). Between treatment costs and production loss attributed to BRD, cattle producers lose valuable time and money fighting this disease. According to the USDA (2015), 23.9% (917,090) of all cattle deaths are due to respiratory disease each year.

In the dairy industry, research is limited, but nationwide surveys have estimated BRD affects 22% of pre-weaned dairy calves in the United States and is a leading cause of preweaning mortality in dairy calves (Dubrovsky, 2020). Based on producer diagnosis, BRD prevalence in these studies ranged from 0 to 52%, with many cases occurring before weaning. Studies reported BRD was also associated with increased calf death rates (Guterbock, 2014). The cost of calf hood BRD in a dairy heifer calf is reflected in the immediate cost of treatment as well as lifetime decreases in productivity of that animal. Decreased productivity often contributes to increased likelihood of affected cattle leaving the herd before their second calving (Dubrovsky, 2020).

Historical perspective

Most cattle feeding in the United States before the 1960s was conducted in the corn belt, where corn production dominated the area. Beef packing plants were located near rivers or highly populated areas for ease of transport to beef products to urban areas. Cattle feeding in the western United States did occur, but these feedlots were far from packing plants presenting challenges for transport of animals and beef products. However, cattle feeding continued to grow and prosper in the Great Plains and High Plains, despite the issues marketing these finished cattle. During the 1950s there were 15 sizable feed yards in Texas and the industry was growing in Kansas, the Oklahoma Panhandle and Colorado.

In the 1960s and through the early 1970s, cattle population numbers continued to grow in the High Plains. Favorable weather in this area compared to the Corn Belt, made this area attractive to raise animals. Additionally, the cost to ship the corn to cattle rather than the cattle to corn was more economically favorable. Meat packing plants moved to the western United States to follow the concentration of cattle production. Trains and other means of transportation followed as packing plants moved further from primary water ways which had previously served as method for transport of beef products. The invention of the refrigerator car revolutionized the industry by providing efficient and reliable transport for chilled, packaged meat and removed the old system of transporting livestock, saving immeasurable amounts of money (Smith, 2019). Although cattle were still scattered throughout the United States in the 1960s and 1970s, these years were known to many as the Golden Age of Cattle Feeding on the High Plains.

The size and number of feedlots continued to grow, and efficiencies came along with these expansions. Larger feedlots attracted nutritionists and veterinarians with the skills and knowledge to develop needed health programs using the first "consulting veterinarian" models. Prevention and treatment protocols were tailored to each feedlot's individual health status and need. By the early 1980s, descriptive statistics, computerized records, improved residue avoidance, and ongoing employee training were becoming the norm (Smith, 2020). In the 1980s the early Beef Quality Assurance (BQA) programs were formalized. These programs were established, first centering on drug residue avoidance (Smith, 2020). In the 1990s, BQA provided guidance on multiple health and production practices, such as injection site lesion avoidance, cattle handling, and antibiotic stewardship. Beef Quality Assurance certification was not only for the feedlot but for the cow-calf and stocker operations as well. The dairy industry created a BQA equivalent known as Farmers Assuring Responsible Management (FARM) in 2009 (Smith, 2020). Despite these advancements, research, and education, BRD continues to plague the cattle industry due to the complex nature of the disease. Mortality from BRD has shown little to no improvement, and by some measures, it is considered greater today than during the Golden Age of Cattle Feeding (Smith, 2020).

The recognition of BRD as a major challenge in the cattle industry today has led to extensive research conducted on methods to reduce the impact of the disease on health and productivity. A breakthrough in understanding the disease in the feedlot cattle came when Canadian researchers reliably and repeatedly generated the typical pathology of fibrinous pneumonia (Jericho and Landford, 1978). An experimental aerosol challenge was conducted on recently weaned beef calves with bovine herpesvirus-1 (BHV-1) followed by aerosol challenge with *Mannheimia haemolytica* four days later. Primary challenge with parainfluenza type 3 (PI3) virus followed by *M haemolytica* induced similar pathology, while challenge with either virus or *M haemolytica* alone did not (Jericho, 1979). This discovery solidified that BRD was a polymicrobial disease with many pathogens causing clinical disease. Following this breakthrough, researchers performed a series of experiments testing the effects of duration of time between weaning and transport and challenge. Differences in ambient temperature and humidity at or after the challenge indicated that environmental factors were not as important as the time interval between primary and secondary exposure and coinfection. Four or more days, between exposure of both viral and bacterial pathogens was required for challenged cattle to develop fibrinous lobar pneumonia. Less than four days between exposure to pathogens did not impact development of fibrinous lobar pneumonia. This four-day period was presumed to be the length of time required for virus-induced impairment of host defense mechanisms to increase susceptibility to bacterial infection (Jericho, 1978). Experimental vaccination with some but not all BHV-1 or *M haemolytica* vaccines greatly mitigated disease, leading to the belief that BRD could be eliminated or decreased substantially by proper vaccination (Jericho et al., 1982; Darcel, 1981; Jericho, 1990). As a result of these findings, over the next 20 years intense research focus was applied to determine the virulence mechanisms of BHV-1, *M haemolytica*, and other agents of BRD. It was a priority to develop and test vaccines to prevent infection and resulting disease.

Understanding each virus or bacterial pathogen related to the BRD complex is essential in diagnosing disease. During this time, bovine respiratory syncytial virus (BRSV) was recognized as a pathogen, and in the 1980s, a vaccine was first developed and marketed. Both intranasal and parenteral vaccines for BRSV are available today. Since the 1940s, bovine viral diarrhea virus (BVD) had been recognized as a pathogen causing death primarily in cattle six month to two years of age (Olafson et al., 1946). Today, it is accepted that BVD is a virus involved in BRD complex. A major step in understanding BVD infections and manifestations, were research reports describing the mechanism for persistently infected animals with BVD, therefore tying together fetal infection, immunotolerance, and mucosal disease (Ramsey et al., 1953; McClurkin et al., 1984). Diagnostic tests were then developed for detection of persistently infected animals used skin samples taken from the ear, making sample collection easy and simple (Njaa et al., 2000). More diagnostics tests followed along with the importance of involving a diagnostic laboratory in disease identification and diagnosis was crucial when treating and managing animals with respiratory illness.

With the recognition of BVD type 2, vaccine manufacturers incorporated BVD types 1 and 2 into vaccines and sub-genotypes were described. Combining antigens from both BVD types broadened the spectrum of immunity provided by the vaccine against natural BVD challenges. In addition to adding BVD type 2 to vaccines, control programs were developed as an additional step to control the disease, including identification and removal of persistently infected cattle, biosecurity measures, and vaccination protocols (Fulton, 2005; Kelling et al., 2000).

In the 1980s, *Histophilus somni* bacterins were introduced. Investigators have concluded that the risk of BRD was not affected by vaccination against this pathogen with currently available vaccines (Larson and Step, 2012). Conclusions from a meta-analysis conducted by Larson and Step (2012) agreed with an early systematic review by Perino (1997) that reported conflicting effects on morbidity and no significant effect on mortality among studies.

Mannheimia haemolytica is a major bacterial pathogen in the BRD complex. Various types of vaccines protecting cattle from the pathogen have been brought to the market over the past few decades. A meta-analysis evaluating morbidity cumulative incidence and mortality relative risk in field trial with *M haemolytica* vaccines found a statistically significantly lower risk of morbidity but not mortality for feedlot cattle. The BRD mortality was reduced by 28% and 50% in two large scale trials in feedlots comparing vaccinated *M haemolytica* toxoid vaccinated cattle to controls. Vaccinated and controls were comingled within pens and cattle were monitored until harvest (Smith, 2020).

Since the 1970s, research to develop and test vaccines against specific BRD agents has had mixed effects. Variation exists within morbidity and mortality data following BRD vaccination (Martin et al., 1982). Ultimately, the knowledge and tools gained have not been associated with recognizable decrease in BRD mortality according to USDA National Animal Health Monitoring System (NAHMS) surveys. Through research, its continually proven that the risk factors for BRD are complex.

Understanding the cause of bovine respiratory disease

At the beginning of the twentieth century, BRD was believed to be solely caused by bacterial infections and was referred to as “bovine pasteurellosis” (Gaudino, 2022). The first descriptions of the disease in the late nineteenth century was referred to as “hemorrhagic septicemia.” As research advanced, scientists were unable to replicate disease with bacteria alone and noted that viral agents were also needed to replicate disease seen in the field. Bacteria could be cultured from apparent healthy animals after they were stressed in shipment but also during overcrowding weaning and weather variations. Bovine respiratory disease has been frequently referred to as “shipping fever” during the last century because of these issues experienced after the stressful events shipping causes for cattle. In the 1950’s, the theory of viral causation gained support in North America when viruses IBR and PI-3 were isolated from cattle with shipping fever (Gaudino, 2022). During experimental infection, PI-3 mimicked natural pneumonia with bacterial superinfections often accentuating the clinical signs and lesions in cattle (Gaudino, 2022). Bovine respiratory disease is now globally recognized as a polymicrobial disease, with bacterial infections known to affect morbidity and mortality during viral respiratory infections. In healthy cattle, the bacteria and viruses responsible for BRD can naturally reside in nasal passages, but it is the combination of those pathogens, host factors, and environmental factors that ultimately causes disease. A common scenario for the development of BRD involves the combination of an immunocompromised animal (typically due to stress), and exposure to an immunosuppressive viral agent. Viral immunosuppression creates opportunity for infection by bacteria, which commonly resides in a healthy animal's respiratory tract. As these opportunistic bacteria migrate and colonize in the lower respiratory tract, they create pulmonary compromise, pneumonia, and lesions throughout the respiratory tract (Edwards, 2010). Pneumonia refers to inflammation of the lungs. It may be accompanied by inflammation of the larger airways (bronchioles) and referred to as bronchopneumonia. It can also be referred to as pleuropneumonia, or inflammation of the pleura, the outer surface of the lung, adjacent to the chest wall. Causation factors of BRD can be placed in three main categories: host factors, infectious agents, and environmental factors.

Host factors refer to the characteristics of an animal that can increase susceptibility to disease. Factors include age, nutritional status, immune status, prior exposure to pathogens, and genetics. Pneumonia is a leading cause of sickness and death in cow-calf herd especially after the first few weeks of life (Smith, 2021). In a study with health records representing over 9900 calves from 28 cattle management groups, researchers analyzed the effect of calf gender and age of the dam and their potential risk of BRD (Smith, 2021). Surveys of beef producers and veterinarians indicate that pre-weaning BRD is a problem for approximately one out of five cattle producers (Smith, 2021). Pre-weaning BRD may affect up to 10% of all US beef calves, resulting in the death of 0.6-1.4% of all calves (Smith, 2021). Calves affected by pre-weaning BRD weigh 17-37 pounds less at weaning compared to calves not affected with BRD. Maternal immunity is important for protecting young calves against respiratory pathogens, but maternal antibodies wane with time. Approximately every 16-20 days after ingestion of colostrum, the serum concentration of maternal antibodies is halved (Smith, 2021). A calf retains less than 2% of the antibodies it absorbed from the colostrum by 96-120 days of age (Smith, 2021). At birth the immune system is functional but unprimed. Prior to 5-8 months of age, the immune response of calves is slow, weak, and easy to overcome. Even in the absence of stressors, calves 3-5 months of age may be particularly susceptible to pneumonia as well as other pathogens in the BRD complex (Smith, 2021). Age-related susceptibility due to loss of maternal antibody immunity may explain sudden outbreaks of pre-weaning BRD. Sex of calves was found to affect their risk of BRD with males at a greater risk than females. Also, calves born to 2-year-old dams were more likely to become sick at an earlier age, leading to conclusion that age of the dam may correlated with colostrum absorption by the calf. Calves born to a young dam may have delayed colostrum absorption due to dystocia or poor mothering skills. Young dam colostrum also may not contain as many antibodies in quantity and range of protection as older dams. Further research is needed to confirm these hypotheses.

The BRD complex is often caused by infectious agents, particularly by a combination of bacteria and viruses. Infectious agents refers or pathogens must be present to cause disease. Viruses usually cause initial BRD infection and predispose the animal to subsequent bacterial infections. Viruses responsible for BRD include bovine herpes virus (IBR), bovine parainfluenza virus (PI-3), bovine respiratory syncytial virus (BRSV), bovine viral diarrhea virus (BVDV) and bovine corona virus (BCV). Several viruses in the BRD complex can also cause reproductive (BVD, IBR) or diarrhea (BVD, BCV) challenges. The most common bacteria isolated from cattle with respiratory signs are *Pasteurella multocida, Mannhemia haemolytica*, *Histophilus somni* and *Mycoplasma bovis.* The most common form of severe BRD is a bacterial bronchopneumonia involving one or more of the bacterial agents. The viruses are thought to be initial infective agents that act to compromise the respiratory defense mechanisms and allow the bacteria to penetrate the lower airways and alveoli causing more severe disease.

The remainder of this section will describe many of the viruses and bacteria involved in the BRD complex more specifically.

Bovine herpes virus

Bovine herpes virus (IBR) type 1 is a DNA virus that is the known etiological agent for infectious bovine rhinotracheitis. It is believed to have been first isolated from German cattle with venereal disease in the nineteenth century, then later associated with a 1954 respiratory outbreak in California (Gaudino, 2022). Bovine herpes virus is divided into two circulating subtypes that are characterized by acute inflammation of the upper respiratory tract. Bovine herpes virus can also sporadically cause abortion in cattle, as well as conjunctivitis, vaginitis and enteritis (Gaudino, 2022). Respiratory signs associated include mucopurulent nasal discharge, sometimes accompanied by ulcers in the mouth and nose, conjunctivitis, coughing, sneezing, and difficult breathing. Bovine herpes virus is characterized by lifelong latent infection with sporadic viral reactivation and shedding when immune defenses are compromised. In various European countries, commercial vaccines are broadly used to prevent IBR associated syndrome leading to progressive eradication of the disease as a part of a monitoring program (Gaudino, 2022).

Bovine parainfluenza virus

Bovine parainfluenza virus (PI-3) is a single-stranded RNA virus that was first isolated in 1959 from cattle with shipping fever. Bovine parainfluenza virus is now endemic, with three circulating genetic groups worldwide named A, B, and C. Infection of PI-3 generally leads to mild respiratory signs such as fever, dry cough, nasal and ocular discharge, increased respiratory rate and dyspnea. Upper respiratory infection can also lead to transient immunosuppression, creating an opportunity for secondary bacterial infections. There are several commercially available vaccines, often in association with bovine respiratory syncytial virus (BRSV).

Bovine respiratory syncytial virus

Bovine respiratory syncytial virus (BRSV) is one of the most important viral pathogens involved in BRD. It is a single stranded RNA virus that has only been diagnosed in cattle as well as wild and domesticated small ruminants. The first report of BRSV dates to 1967 in Geneva, Switzerland, after which it spread to other countries. Clinical signs range from mild-moderate to subclinical because BRSV has the highest pathogenic potential out of all circulating viruses. Bovine respiratory syncytial virus infection can progress quickly and up to 80% morbidity and 20% mortality is reported (Gaudino, 2022). At necropsy, emphysematous and hemorrhagic lung lesions accompanied with necrotizing bronchiolitis and interstitial pneumonia, especially in the cranial lobes, are characteristics of BRSV infections. Several vaccines are on the market to prevent BRSV infection.

Bovine viral diarrhea virus

First discovered in North America in the 40's and later isolated in 1957, bovine viral diarrhea virus (BVDV) is a single stranded RNA virus (Gaudino, 2022). There are currently two different species in circulation, pestivirus A (formerly known as BVDV-1) and pestivirus B (formerly known as BVDV-2). Infection often manifests as respiratory and gastrointestinal diseases, the latter being associated with diarrhea and mucosal disease, especially when a persistently infected animal is involved. Lesions of mucosal and lymphoid tissues that can result in acute diarrhea, thrombocytopenia and respiratory signs. During BRD infections, like all other viruses mentioned, BVDV is immunosuppressive paving the way for subsequent superinfections by other viral or bacterial pathogens. Vaccination via maternally derived antibodies has been shown to be effective at protective cows and newborn calves, but efforts are still being made to eradicate the disease as vaccinations are helpful, but infections even after vaccination can still happen.

Bovine corona virus

First isolated in 1972 from diarrheic calves and in 1982 from BRD calves, Bovine corona virus (BCV) is a single stranded RNS virus belonging to the *Coronaviridae* family. Endemic in cattle worldwide, it is known for causing enteric disease and pneumonia outbreaks. In research, BCV inoculation develops cough, nasal discharge, respiratory distress and diarrhea in colostrum deprived calves. Treatment for the diarrhea is limited to supportive care. There are several vaccines on the market to protect from the enteric form of BCV, but vaccines protecting against respiratory disease are still missing.

Pasteurella multocida

Pasteurella multocida is a Gram-negative bacteria that can infect a wide range of mammals and domestic birds (Gaudino, 2022). *Pasteurella multocida* was first discovered by Louis Pasteur around 1881 during the investigation on the etiological agent of fowl cholera. The same bacteria can produce disease in different animal species and because of this, scientists proposed to classify all bacterial strains under the same genus and species in 1939 named *Pasteurella multocida* (Gaudino, 2022). Currently it is classified into five capsular groups (named from A to E) and 16 somatic serotypes (1 to 16). *Pasteurella multocida* A:3 is the most common serotype isolated from animal displaying BRD and its pathogenicity had been confirmed in experimental studies. Serotypes B, E and F can also be pathogenic in cattle. Infection in cattle can cause different types of bronchopneumonia, ranging from subacute to chronic fibrinopurulent, but also fibrinous and fibro-necrotizing. It can be accompanied by a variable amount of intra-alveolar haemorrhage with moderate to severe neutrophils and macrophages infiltration in bronchi and bronchioles (Gaudino, 2022). Bacterin containing vaccines are available on the market to prevent infection with *Pasteurella multocida*.

Mannheimia haemolytica

Mannheimia haemolytica is another Gram-negative bacterium involved in pneumonia. Formerly known as "*Pasterurella haemolytica*," some studies prior to 1999 still contain this older nomenclature. There are currently 12 capsular serotypes of *M. haemolytica*, and the serotypes associated with respiratory disease in cattle are prevalently A1 and A6. Principal cause of death with *M. haemolytica* is acute fibrinous pleuropneumonia due to obstruction of bronchioles and alveoli with fibrinous exudate (Gaudino, 2022). *Mannheimia haemolytica* serotype 1 is the bacterial pathogen most frequently isolated from lungs of cattle with BRD in dairy, beef or veal calves with pneumonia (Campbell, 2023). Vaccines have been demonstrated to be efficacious for disease prevention and may decrease morbidity in high-risk feedlot calves given one dose of vaccine on arrival by as much as 25%; however, trials have not been consistent in all risk categories of feedlot cattle (Campbell, 2023).

Histophilus somni

Histophilus somni is another Gram-negative bacterium that mainly affects cattle but can also affect small ruminants. *Histophilus somni* is not currently classified into specific serotypes. In 1956 it was first isolated from cattle with meningitis. Recently, it was shown that weaned calves seem to be at higher risk, but animals of all ages can be affected (Gaudino, 2022). Like other mentioned bacteria, *H. somni* can be found in nasal secretions, but different strains have been isolated from urogenital secretions, which can be responsible for venereal spread. After colonizing in the lung, the spread of *H. somni* can move beyond the respiratory tract causing systemic disease. Encephalitis, myocarditis, and sudden death due to acute septicemia can also be caused. Similar to *M. haemolytica*, bacterin based vaccines are currently available although they have failed to demonstrate effective protection in vaccinated animals (Gaudino, 2022).

Mycoplasma bovis

Mycoplasma bovis is a type of bacteria that greatly differs from those previously described and represents one of the most challenging bacterial BRD pathogens. *Mycoplasma bovis* was first isolated in 1961 and causes pneumonia outbreaks in calves and young cattle but also mastitis in dairy cows as well as otitis and abortion. It is the smallest known bacteria and it lacks a cell wall making it naturally resistant to several classes of antibiotics. Clinical signs involve fever, depression, nasal discharge, shallow breathing, and cough. *Mycoplasma bovis* can also affect joints and result in profound lameness, reluctance to move, poor appetite and poor or prolonged response to treatment. Post-mortem findings include bronchopneumonia with caseous necrotic lesions and fibrinosuppurative bronchopneumonia. After *M. bovis* is introduced to a farm, it typically remains persistent at that location due to strong environmental resistance of the bacteria and widespread transmission among herds through direct contact (Gaudino, 2022). In North America, there are few bacterin vaccines currently marketed to prevent *M. bovis* and those available have only shown limited protection.

Fungal and parasitic causes of bovine respiratory disease

Some fungi belonging to the *Aspergillus* genus and parasites, commonly known as lungworms, can also trigger respiratory disease. Lungworm is a parasitic infection of the respiratory tract that causes coughing and respiratory distress. Heavy infestations can cause death, but other signs can also include weight loss and reduced milk yield in dairy cows. Young cattle in their first grazing season are most likely affected through eating grass contaminated with infective larvae passed out of the dung of infected animals. Mild, damp conditions provide optimal conditions for larvae survival on the pasture (*Lungworm in Cattle*, 2020).

Environmental and animal management causes of bovine respiratory disease

Environmental or animal management factors may increase risk factors for disease. Common beef systems and corresponding sale of cattle typically begins with a farm of origin (where the animal was born), after or at the time of weaning, animals are transported and sold to a cattle feeding operation (stocker or feedlot operation). Each stage in this system can contribute additional risk factors for disease infection. For example, animals in overcrowded conditions, poor air quality or ventilation, sourced from auction markets or stressed by transport, comingling, temperature fluctuations, etc. can increase susceptibility to disease. Small farms of origin operations frequently lack natural, human, or capital resources, to provide an optimal health program. For example, the farm may lack the facilities, manpower or knowledge to dehorn, castrate, or vaccinate calves prior to weaning. Weaning often occurs the same day the cattle are marketed, resulting in an important, abrupt, stress event prior to the stocker or feedlot operation. Common management practices of marketing calves contribute to additional stressors to the auction market calf. Limited access to feed or water to and from the auction market, different tanks or feed bunks than their farm of origin, may cause calves additional stress during transportation. Comingling of calves from different sources is common at auction. After long distance transportation, calves may spend several days at an order-buyer facility as other calves are purchased to fulfil an order. During this marketing period, calves are exposed to different pathogens and may lose weight from not eating or dehydration. By the time calves have moved through these marketing channels, they are challenged by a variety of social and physical stressors which lower the ability of their immune response to fight any incubating respiratory infection. Most BRD morbidity occurs in the first 21 days after arrival in the stocker or feedlot operation (Smith, 2021).

Clinical signs of bovine respiratory disease

Behavioral indicators of sickness provide a pilar for early recognition of disease. The first clinical signs of BRD usually involve a reduction in appetite, lethargy, becoming slow to move, and separated from the herd. Depression, drooped head and ears, nasal and ocular discharge, head tilt, sanding with an arched back, gauntness, unwillingness to eat at all, coughing and labored breathing are also commonly observed signs with BRD. The described clinical signs can be applied across all classes of beef and dairy cattle. Abortion may be an easily overlooked sign that BRD pathogens are circulating in the cow herd. This is particularly true if the BRD complex includes IBR and BVDV, which can cause abortion in unvaccinated females. In feedlot cattle, peak incidence of BRD, often associated with *Mannheimia haemolytica*, generally occurs within two weeks of arrival. Symptoms 30-40 days after arrival typically involves *Mycoplasma bovis*. *Mycoplasma* can also affect the joints of ill animals, causing lameness, reluctance to move, poor appetite and a poor and prolonged response to treatment. Cattle are a prey species and tend to hide early sickness and behavioral signs. Therefore, it is important to have skilled, well-trained personnel who know what clinical signs to look for.

There are several BRD scoring systems that can be used to score and determine if an animal should be more closely examined for disease. Systems include the DART (Depression, Appetite, Respiration, Temperature) method, clinical illness scores for calves, the UC Davis bovine respiratory disease scoring system app for pre-weaned dairy calves, and the respiratory app from University of Wisconsin-Madison. Assessments to detect BRD including scoring rubrics, ultrasonography and auscultation have been proposed (Neibergs, 2020). One common rubric is the Wisconsin calf health rubric that scores each of the BRD clinical signs with a value of zero to three and sums them together to reach a cumulative score (McGuirk, 2008; McGurik and Peek, 2014). Clinical scoring is based on rectal temperature, presence of spontaneous or induced cough, nasal discharge, and the heaviest weighted score is based on ocular discharge or head and ear position. Maximum cumulative score is 12 and the minimum score is zero, with a case being defined as animal scores greater or equal to 5. Buczinski et al. (2015) recently completed a validation of this clinical scoring method where sensitivity and specificity of identifying BRD calves were 62.4% and 74.1% respectively. The Wisconsin calf health rubric was also applied to cattle in feed yards to identify cattle with BRD (McGuirk, 2008; McGuik and Peek, 2014; Neupane et al., 2018). The Wisconsin calf health rubric performed better than lung auscultation, but not as well as thoracic ultrasound (Buczinski et al., 2015). Thoracic ultrasound increased sensitivity to 79.4% and specificity to 93.9%, but it's use and availability to producers is extremely limited (Buczinski et al., 2015).

Early detection and treatment are key to decrease the likelihood of chronic sickness and death within the herd. As the disease progresses, damage to the lungs and inflammation caused by secondary infection can progress beyond repair if unrecognized. With early recognition of disease, treatment can be initiated, and unnecessary suffering can be avoided.

Diagnostics

Diagnosis of BRD is made by clinical signs, history, and laboratory testing. Well-trained experienced personnel are essential to identify clinical signs of disease prior to permanent, irreversible damage is done to the respiratory tract of the animal. Diagnosis often requires chute-side evaluations consisting of rectal temperature assessment and auscultation of the lung fields. Rectal temperatures of animals with BRD are usually higher than 104°F, with the normal body temperature for cattle being 101-102°F. Environmental temperature and humidity must be taken into consideration when evaluating rectal temperatures. When auscultated, the lung fields may have crackles and wheezes in sick animals. For additional confirmation of diagnosis, samples can be taken from upper and lower respiratory systems then submitted for bacterial culture and molecular identification of viral infections.

It is imperative that diagnostic samples be taken early in the onset of clinical disease as viral shedding occurs in early disease stages. In later disease, it may be harder to obtain viral pathogen results. While necropsies are helpful to diagnose BRD, preference would be to identify the disease prior to any mortalities. If clinical signs are caught early, viral shedding may still be occurring, and virus causing the disease may still be present and able to be recovered. For isolation of the virus, deep nasal or pharyngeal swabs are samples or choice. Transtracheal wash and bronchoalveolar lavage can also be useful tools in diagnosing respiratory problem, but they are more invasive than deep nasal pharyngeal swabs. Virus isolation turn-around time can be up to 2 or 3 weeks. Polymerase chain reaction (PCR) can be used in place of viral isolation to detect a virus. The test can be performed within a matter of hours is still able to give a practicing veterinarian useful information when trying to fight an outbreak. Bacterial culture and sensitivity, mycoplasma culture and viral detection are common testing methods for anti-mortem sample submissions (Gorden, 2010). Serology is another testing method that can be valuable. Blood samples are taken at the onset of clinical illness with another sample 10 to 14 days later. A four-fold rise in antibody titer is a good indication of viral infection (Montgomery, 2009). With using serological techniques, the turnaround time for results is about 2 weeks. Even though virus isolation and serology require several days to process, the results may help producers and veterinarian make management decisions in the face of an outbreak and in future years.

Necropsy can be an important diagnostic tool, but too often the wrong calves are chosen to provide accurate diagnostic and therapeutic information. Necropsies should not be performed on animals who are chronic or poor doers. Necropsies on this group of animals may not represent the bacterial ecology of the initial pathogen but may result in the isolation of treatment resistant strains of bacteria. Acutely affected animals are the sample specimens of choice; however, this is not to suggest that necropsies should not be conducted if acutely-infected animals are not available for necropsy. Necropsies cannot be done on every calf that dies on a feedlot; therefore, it is important to choose right subjects for necropsy that represent the pen/lot of cattle on the yard. Results of these examinations can provide crucial information to determine deficiencies in management or nutritional insufficiency and are an important tool in client education.

Veterinary diagnostic laboratories (VDLs) are an important service providing essential diagnosis of this complex disease. Diagnostic labs serve key roles in disease monitoring and diagnosis as well as surveillance of diseases. The services VDLs provide for management of BRD include disease outbreak investigation, abnormal morbidity characterization, routine monitoring, and biosecurity screening for a variety of infectious agents. Additionally, methods such as necropsy and histopathology, bacterial culture, antimicrobial sensitivity testing, virus isolation and serological assays are a few of the services VDLs can provide. Necropsy and histopathology allow for the identification of gross and microscopic patterns of BRD pneumonia. Necropsy results help veterinarians to be better equipped to distinguish between viral, bacterial, and non-infectious types of pneumonia, interstitial versus bronchial patterns, and cases of infectious versus non-infectious and mixed causes (Helman, 2020). Advances in scientific methodology and instrumentation have allowed the industry to increase current understanding of the respiratory disease complex through the identification of new pathogens, interactions of previously known pathogens, and how they influence the gross and microscopic lesions of pneumonia.

Prevention

Respiratory disease in cow-calf operations is common, yet sporadic in occurrence and usually in low prevalence. Calves between the age of 1 month and weaning are generally diagnosed with nursing calf pneumonia or summer pneumonia for spring calving herds. Common risk factors associated with BRD in post-weaned calves such as transportation stress, comingling, etc., does not always apply to a cow-calf operation. These common risk factors can still be identified, but may not be of primary importance (Stokka, 2010). Identification of risk factors associated with calf pneumonia is an important step in preventing and managing disease.

The probability of disease in a cow- calf operation is directly related to the presence of one or more of the following risk factors:

1. Failure or partial failure of passive transfer
2. Comingling of different groups
3. Environmental risk, such as extreme cold or heat with the addition of moisture
4. Nutritional risk, i.e. change in diet, energy, or protein deficiency
5. Exposure to pathogens, both viral and/or bacterial
6. Trace mineral deficiency
7. Handling stress

Each risk factor, or a combination of several, can result in enough stress to allow for clinical disease to manifest (Stokka, 2010).

Disease management and control can be accomplished through biosecurity practices. As a more challenging form of disease control, biosecurity is used to reduce exposure of pathogens to susceptible cattle, which involves stringent management practices in the area of sanitation. Receiving and hospital pens, feed bunks, and water troughs should be frequently cleaned to reduce transmission of pathogens. Equipment used in manure management and dead animal removal should not be involved in handling of feed sources or health animal management and husbandry (Stokka, 2010).

Vaccination of young calves is an effective management strategy and management practice to prevent BRD. Vaccination primes an animal's immune system by introducing antigenic material via vaccination to stimulate the animal's immune system to be able to fight off the disease-causing organism that may infect the animal in the future. Vaccines are given to prevent clinical disease and pathogen transmission, but it is not possible to vaccinate against every pathogen known to cause respiratory disease. Modified-live (MLV) and killed virus (KV) or inactivated vaccines are currently commercially available. Modified life vaccines induce complete humoral and cell-mediated immune response. They provide long-lasting immunity and fewer doses are required to provide protection (Chamorro, 2020). Killed vaccines induce strong humoral response, but less robust cell-mediated immunity. At least 2 doses are required when vaccinating with a KV vaccine. Many studies have compared efficacy of MLV and KV vaccines, and among veterinarians, it is thought that MLV vaccines provide better clinical protection against BRD than the KV counterparts (Chamorro, 2020). Using combination vaccines, which combine several different antigens into a single vaccination, is a common practice among cattle producers. Combination vaccines can include both viral and bacterin-toxoid antigens.

Understanding cow-calf vaccination protocols and accurate timing of vaccination is imperative in preventing disease. Other factors that should be considered is the health of the cows and calves being vaccinated, pregnancy status, handling of the vaccines and the frequency of the vaccinations. Some MLVs have been shown to cause abortions when used in pregnant cows or calves suckling pregnant cows that have not previously been exposed to MLV vaccines (Allen and Llewellyn, 2013). Most vaccine companies recommend that the cow must be vaccinated with a MLV product prior to breeding to ensure vaccine related abortions do not happen. Typically, the first BRD preventative vaccines given to calves are administered prior to six months of age. Most vaccine manufacturers recommend that animals be re-vaccinated after 6 months of age for proper vaccine efficacy. It is shown that maternal antibodies that are provided to a calf through colostrum can last up to six months, causing this need for extra vaccination after 6 months of age. Maternal antibodies will often decrease the effectiveness of vaccine immune response (Allen and Llewellyn, 2013). Vaccination at the cow-calf operation is extremely valuable when preventing disease at stocker and feedlot operations, but vaccination may not be pursued at the cow-calf production stage due to lack of resources.

As cattle transition from a cow-calf operation to a cattle feeding operation, often the vaccination history of newly received cattle is unknown. Immunity takes 2 to 3 weeks to develop and may take multiple doses to obtain optimal immunity. Despite its unideal timing for immediate immunity protection, industry practice is typically to vaccinate cattle upon arrival to cattle feeding operations because of the lack of vaccination history. Despite customary procedures for vaccinating cattle upon arrival, research data supporting its use is limited (Edwards, 2010). Upon entering the feedlot, vaccination timing varies dependent on time in transit, health status upon arrival, distance traveled and body condition of animals.

In feedlots, the first 45 days on feed have been identified as the most critical time in the development of BRD. This identified time frame is related to stressors associated with weaning, shipping, nutritional changes, and handling before or shortly after arriving at the feedlot. The primary goal of a feedlot herd health program is to reduce the costs associated with morbidity and mortality from BRD and other diseases through prevention and control programs. Through these practices, feeding performance and carcass value is maximized (Edwards, 2010).

When considering preventative practices to combat BRD, animal husbandry is often overlooked. As discussed previously, stress has a negative impact on the defense mechanisms of the host. Increased stress means increased vulnerability to illness. During periods of stress, cortisol levels increase and immune function declines (Edwards, 2010). By recognizing how stressful events impact animal health and ultimately causing BRD, producers can employ better cattle handling techniques and improved facility designs. Improved facility designs and better handling technique improvements also help to address the growing concerns regarding animal welfare. By understanding cattle behavior, the industry can provide quieter environments and handling practices to prevent animals from becoming over stressed. Clean receiving pens should be located away from hospital pens to avoid pathogen exposure to new arrivals. Overcrowding should be avoided upon arrival and in feeding pens. By providing the best possible animal husbandry practices, animal welfare only improves throughout the production cycle and decreases the likelihood of stress induced disease.

Another technique commonly used in industry for BRD prevention is metaphylaxis. Metaphylaxis is defined as the mass medication of cattle at arrival with the goal of preventing and reducing the negative health and performance effects induced by BRD (Nickell, 2010). Metaphylactic antimicrobial therapy is considered prevention and curative treatment because arriving cattle not only are at risk of developing BRD but may already be fighting and experiencing various stages of disease. Subjective assessment of sick cattle is highly variable and is directly dependent on experience and skill level of the pen rider. Treatment of the population is often preferable to individual animal therapy due to variation in animal caretaker knowledge and experience. A recent meta-analysis of metaphylactic treatment versus individual animal treatment reported that injectable antibiotics reduce the risk of BRD morbidity 1.5-fold on average compared to the placebo (Nickell. 2021). The economic value to the producer was significant and it was recently estimated that the practice of BRD control generated a net return of at least $532 million dollars to the US beef industry (Nickell, 2021). However, antibiotic metaphylaxis is highly controversial due to the increased risk of antimicrobial resistance that occurs with any use of antibiotic treatments. Additionally, the practice receives scrutiny from the public as it only treats bacterial disease but has no impact on any viral components of the BRD complex. As described, diagnosis of BRD is highly subjective and often the difference between bacterial and viral infection is not determined prior to the application of antibiotics. Improper use of antibiotics to treat viral disease only results in frustration for producers, and does not eliminate risk of viral BRD complex pathogens.

Current treatment practices

Treating BRD can be costly. Understanding costs and different marketed treatment options are crucial to provide the best care for sick animals. Early detection relies on the ability and experience of the pen rider and is often a subjective method of disease identification. Cattle instinctively mask of hide the clinical signs of sickness as a means of self-preservation as a prey species (Edwards, 2010). Recognizing early disease signs and symptoms is a learned skill that is essential for the detection of BRD. After animals have been removed from their pen of origin and brought to working facilities by pen riders, clinical symptoms are affirmed by high temperatures and/or abnormal lung sounds. Antimicrobial therapy is then administered. The USDA’s National Animal Health Monitoring System (NAHMS) in the fall of 1999 conducted a study of feedlots with a 1,000 head or more capacity within the top 12 cattle feeding states. These feedlots represented 84.9% of US feedlots in 1999 with 1,000 head or more capacity. Nearly all, 99.8%, feedlots included an injectable antibiotic as part of the therapeutic regimen for BRD. The most common antimicrobials used by feedlots for the initial treatment were tilmicosin, florfenicol, and tetracyclines (USDA, 2001).

Antibiotics have revolutionized medicine and saved countless human and animal lives. However, there is growing public concern about antibiotic use in the cattle industry (O’Connor, 2020). Antibiotics are not used to treat viral infections associated with the BRD complex. Antibiotics are designed to destroy or inhibit the bacteria that can cause infection (Sears, 2018). Based on in vitro results, antibiotics can be classified as either bactericidal or bacteriostatic.

Bactericidal antibiotics kill the bacteria. Bacteriostatic antibiotics inhibit or slow the growth of bacteria, then require the immune system to take over and fight the bacteria. Bactericidal antibiotics include penicillin, cephalosporins, trimethoprims and fluoroquinolones. Bacteriostatic includes sulfonamides, tetracyclines, macrolides and phenicols. Antibiotics are an important tool to help reduce animal suffering and death.

In the study performed by the USDA's NAHMS, 25% of large feedlots used multiple different products to ease the burden of BRD. Non-steroidal anti-inflammatory drugs (NSAIDs), oral electrolytes fluids or drenches, or corticosteroids were also used (USDA, 2001). In roughly one-third of small feedlots, NSAIDs, probiotic paste, vitamin B injections, an antihistamine, respiratory vaccines, or an oral antimicrobial in additional to an injectable antimicrobial was used (USDA, 2001).

Chapter 2 - Outlining novel approaches

Antimicrobial usage in cattle may affect public health and has become an increasing concern. Reduction of BRD would significantly reduce the total use of antimicrobials in the cattle industry and, in turn, reduce the risk of antimicrobial resistance development. New and novel approaches need to be introduced to the industry to help to combat BRD by reducing morbidity and mortality caused by the disease in each sector of the production cycle. Reduction of the effects of the disease benefit producers by decreasing costs and allocating resources dedicated to combating the disease elsewhere. Three major alternative strategies for combating BRD will be discussed: genetic selection, environmental and animal management, and animal husbandry.

Genetics

Genetic variability in cattle affects an animal's susceptibility to the pathogens responsible for BRD (Neibergs, 2020). Work by Neibergs (2020) has shown that there is evidence that there are genetic differences in susceptibility to disease. An approach to reduce BRD in cattle is to breed cattle that are less susceptible to the disease through the identification and selection of cattle that are more resistant to BRD (Neibergs, 2020). According to Gershwin et al. (2015), not all cattle exposed to BRD pathogens respond with a similar morbidity and mortality rate. Cattle housed and cared for in feedlot setting are all managed the same way, so the difference in infection prevalence amongst animals indicates that some of the susceptibility to BRD is due to the differences in the cattle's genetic predisposition to the disease (Neibergs et al., 2014).

Currently, little is known about breeding strategies on genetic predisposition to BRD. Phenotypic expression for resistance or susceptibility to a complex disease is influenced by both genetic and environmental factors. A host's innate ability to resist a pathogen is challenged by the pathogen's genetically influenced virulence (Snowder, 2009). Molecular geneticists commonly use the term genotype when referring to the alleles or variants an individual carries in a particular gene or genetic location. In animal breeding, the definition of genotype varies and can be used to describe a particular strain of animals or animals of a given breed from a particular origin (Neibergs, 2020). Environmental factors such as climate, management, nutrition, and production system, may suppress the expression of the host's genes for resistance, thus permitting the pathogen to spread throughout the respiratory system. The phenotype is the set of observable characteristics of an animal resulting from the interaction of its genotype with the environment. Using simple terms for the scope of this paper, phenotype is the observed performance of an animal 'in the field' (i.e. in the presence of infection, risk factors, etc). The interaction between genetic and environmental factors often determines whether or not an animal is infected and expresses signs and symptoms of the disease. Multiple studies show that differences in morbidity and mortality found between cattle breeds and between sire family lines support that there is a genetic component to BRD (Muggli-Cockett et al., 1992; Snowder et al., 2005; Cusack et al., 2007; Herignstad et al., 2008; Neibergs et al., 2014, 2011). Identifying DNA regions that are associated with enhanced ability to resist BRD is important in genomic selection when breeding cattle that are more likely to stay healthy when faced with pathogen challenge.

Heritability estimates are low and range from 0.02 to 0.29 for BRD susceptibility in beef and dairy cattle (Lyons et al., 1991; Snowder et al., 2005; Heringstad et al., 2008; Taylor et al., 2010; Neibergs et al., 2014; Buchanan et al., 2016; Gonzalez-Pena et al., 2019). Heritability in fields of breeding is statistic and used as estimate of the degree of variation in a phenotypic trait in a population that is due to genetic variation between individuals in the population. It summarizes the differences among a cohort of animals. Heritability varies from 0 (not heritable) to 1 (fully heritable) (Neibergs, 2020). If the heritability is high, it is expected that a large proportion of the phenotypic differences of the parents could be passed to the progeny. Low heritability does not necessarily imply that there will be slow/no genetic progress. Conversely, high heritability does not necessarily imply rapid genetic progress (Neibergs, 2020). Genomic selection is a tool that uses genotypes to predict future performance of offspring to select animals that will be part of the breeding herd. While it is not possible to determine an animal’s true breeding value, it is possible to estimate it. An estimated breeding value (EBV) can be defined as the estimate of the genetic merit for an animal for a given trait or series of traits, based on an evaluation of all available data on the performance of an animal and close relatives. Prior research has shown that genomic selection can be used to improve health traits. Expression of health related traits of the animal has been correlated to an animal's susceptibility to a multitude of pathogens including disease caused by viral, bacterial and parasitic sources (Bischop et al., 2010). Relatively inexpensive high-density genotyping assays have paved the way for genome-enhanced selection. Genotyping assays also provide a platform to identify casual mutations that are involved in the regulation of gene expression or gene translation (Tam et al., 2019). Host susceptibility can be better understood with the identification of casual mutations.

For effective genomic-enhanced selection, the cattle industry needs to define and standardize the trait throughout the industry. For many years, diagnostic evaluation has provided phenotypic examples of what a sick animal looks like. By standardizing and selecting a BRD phenotype that can be genetically traced, producers are able to accurately diagnose disease. Currently a standardized phenotype for BRD susceptibility has not been adopted throughout the industry. This is presumed to be because of the variation in phenotypes that exist due to differences in diagnostic evaluation and changes in phenotype that occur with number of treatments animal has undergone for BRD symptoms.

There is growing interest in selective breeding of livestock for enhanced disease resistance as demonstrated by the dairy cattle selection programs that find advantages to understanding the genetic variability in mastitis resistance. The heritability of clinical mastitis is low, but mastitis resistance has a correlation with production traits (Rupp and Boichard, 2003). Another example of selective breeding is seen in the poultry industry as chicken breeders have used genetic selection to improve resistance to avian lymphoid leucosis complex and Marek's disease (Stear et al., 2011). For BRD, the heritability of disease resistance is typically low, but this is partially a result of suboptimal diagnosis of sick animals. In 2011, the USDA funded a 5-year grant proposal titled the "Integrated Program for Reducing Bovine Respiratory Disease

Complex (BRDC) in Beef and Dairy Cattle' Coordinated Agricultural Project. This effort, known as the BRD CAP, involved a multi-institutional team collaborating to reduce the prevalence of BRD in beef and dairy cattle through the identification of genetic loci associated with BRD susceptibility. Information collected was used to develop DNS-based selection tools (Eenennaam et al, 2014). During this study, two large genome wide association studies (GWAS) were conducted on pre-weaned Holstein dairy heifers and beef feedlot cattle. A health scoring system was used to identify BRD cases and controls. The heritability estimates for BRD susceptibility ranged from 19 to 21% in dairy calves to 29.2% in beef cattle when using numerical scores as a semi-quantitative definition of BRD (Eenennaam et al., 2014). The GWAS analysis conducted on diary calf data showed that single nucleotide polymorphism (SNP) effects explained 20% of the variation in BRD incidence and 17-20% of the variation in clinical signs. A SNP is a genomic variant at a single base position in the DNA (National Human Genome Research Institute, 2023). Identification of SNP association with BRD incidence variation plays a large role in the ongoing work to identify loci associated with BRD. Future work includes validation of the chromosomal regions and SNPs that have been identified as important for BRD susceptibility, fine mapping of chromosomes to identify casual SNPs, and integration of predictive markers into genetic tests and national cattle genetic evaluations (Eenennaam et al., 2014).

Environment and animal management

The lack of standardized management progresses to prevent and treat BRD demonstrates that there continues to be significant room for improvement in animal management and husbandry practices. Bovine respiratory disease is not attributable to a single cause. A perfect storm must happen between environmental factors, pathogen exposures, and other stress related factors that lower immune system strength. Louie et al. (2018) investigated the effect of the environment on the risk of BRD in preweaning dairy calves during summer months. Heat stress is known to adversely affect the physiology, passive immunity, and growth of pre-weaning dairy calves. All are factors that increase animal risk for respiratory disease (Stott et al., 1976; Carroll and Forsberg, 2007). In dairy calves, BRD prevention focuses on improving the calf's ability to respond to challenge through adequate transfer of passive immunity at birth using techniques such as good colostrum management and appropriate nutrition. These techniques also apply to beef calves. However, because dairy calves are raised in a more standardized manner than beef calves, producers have opportunity to mitigating disease exposure and transmission through housing and biosecurity management practices. Environmental factors are strongly associated with animal housing and factors such as ventilation, ambient temperature and humidity, and airborne irritant levels can affect a calf's risk of developing BRD (Lago et al., 2006). Calves exposed to high temperatures, even in low humidity regions, during the day may be experiencing significant heat stress that predisposes them to developing BRD (Louie et al., 2018). Louie et al. (2018) demonstrated that raising calves with consideration for minimizing overall heat stress in micro- and macroenvironments of dairy calves is important. The use of fans or cooling systems during high temperatures might be considered, with the additional benefit of improving calf comfort and improving feed conversion efficacy and growth due to the calf not having to expend additional energy to avoid overheating. Simple and cost-effective methods, such as elevating the back of plastic hutches may increase airflow and reduce cardon-dioxide levels, moderating temperature and humidity within hutches and respiratory rates in calves. Good ventilation is a critical aspect of animal management and can directly impact respiratory health for both calves and feedlot cattle. Ventilation decreases the airborne pathogen concentration, eliminates noxious gasses (ammonia, hydrogen sulfide, carbon dioxide, carbon monoxide, and methane) and decreases dust contamination and endotoxin levels. Ventilation also helps to maintain optimum ambient temperature and environmental humidity levels. Stagnant air and drafts can also be eliminated. All are factors that improve lung health in cattle, a critical health factor when combating BRD complex pathogens. Other environmental conditions that should be emphasized are ample shade, spacing, cleanliness, and dryness of the ground beneath the hutches (Louie et al., 2018). Proper cleaning and disinfection of feeding equipment should be performed. Prompt removal of dairy calves from the maternity pen environment can also decrease transmission of potential respiratory pathogens. Newborn calves should not have direct contact with older calves and adults. Control of environmental factors ensure sanitary environment with reduced opportunity for persistence of BRD complex pathogens in the animal's living environment. While measured values for decreasing in BRD incidence with management of environmental stressors do not exist, management practices are still widely accepted by the industry as a key component of combating BRD in cattle. Bovine respiratory disease is a struggle in both the beef and dairy industry, but more scientific experiments have focused primarily on assessing dairy calf environment. Dairy calves are raised in a standardized environment that is easier to study in scientific experiments and there is less variation in management compared to cow-calf producers.

Many cattle management systems provide opportunities for exchange of respiratory pathogens from animal to animals. The feedlot sector often assembles groups of beef cattle from different origins, causing crowding, stressful conditions, and the optimal place for pathogen exposure and transmission. Although quarantine may not be effective or realistic in some flows of production, it has been shown to substantially decrease the risk of spreading respiratory pathogens (Callan and Garry, 2002). In a national survey, more than 50% of dairy producers housed sick animals in a manner that allowed direct nose-to-nose contact with healthy herd mates (USDA, 1996). Less than 25% of producers who buy animals from other sources provide any quarantine time for the incoming animals. For producers who introduced 15% or more of their total animal inventory during an expansion, 16.6% reported an increase in respiratory disease occurrence during the year (USDA, 1996). Practical suggestions for limiting pathogen spread by contact include quarantine of incoming livestock, maintenance of hospital areas that do not allow contact with healthy animals, prevention of contact between different ages of cattle, minimizing the time animals send in the market channels and limiting the introduction of new animals to assembled herd or pens of cattle (Callan and Gary, 2002). One animal can expose an entire pen of animals by simple close contact, airborne transmission, or environmental transmission at common areas such as feed bunks and water troughs. By reducing group sizes, the number of animals exposed is lowered significantly (Callan and Gary, 2002). Such management and housing decisions must be made on a balance between the risks and cost of disease versus the availability of resources and cost of facilities and labor (Callan and Gary, 2002).

Biosecurity practices

Biosecurity is defined as a set of management and physical measures designated to reduce the risk of introduction, establishment and spread of animal diseases or infection from and within an animal population (Huber et al., 2022). Transmission of respiratory pathogens can occur by close nose-to nose contact, environmental or fomite exposure, and airborne exposure. Increased contact between individuals shedding pathogens and susceptible animals increases spread. Environmental exposure through common areas and equipment that involve oral and nasal contact such as feed bunks, water troughs, and salt blocks pose a greater risk of pathogen spread (Callan and Gary, 2002). In general, clinically ill animals shed greater numbers of pathogens than normal or asymptomatic animals; however, individuals can also shed pathogens without evidence of disease. Periodically, well-vaccinated animals may also shed pathogens and should not be necessarily considered completely safe from disease transmission (Callan and Gary, 2002). The key to creating effective biosecurity measures is understanding how practices can either reduce pathogen shedding or exposure. There is little information available to specifically evaluate the effect of individual biosecurity practices in prevention of BRD. In the swine and poultry industries, biosecurity practices are common practices to decrease the spread of disease. Management practices such as strategic vaccination, calf biosecurity, housing ventilation, commingling and animal contact are crucial in reducing the effects of BRD in the cattle industry. True biosecurity practices are challenging to implement in cattle industry setting because of the wide variation in management styles that exist and the outdoor nature of cattle housing operations. Due to wildlife contact, multiple cattle sources and animal comingling, and culture of the beef industry truly bio-secure facilities may not be a possibility for cattle producers. However, the described management practices that are part of biosecurity protocols may provide benefit to slowing the spread of BRD in the beef industry.

Although BRD pathogens are not considered zoonotic in nature, there can be benefits to combating the spread of BRD (especially farm to farm) if biosecurity practices are implemented by personnel working directly with cattle. Additional hygiene protocols could include dedicated coveralls to be used in the sick pens, the use of rubber over boots and disinfectant foot baths. Personnel should be encouraged to wash their hands before and after entering the sick pens and between caring for animals with dissimilar disease conditions.

Conclusions

Bovine respiratory disease remains a challenge for the cattle industry, even after 30 years of research and advances. Although prevention and treatment opportunities for BRD are presently available, the complexity of BRD and resilient ability of pathogens to evolve presents pressing need for continued research in this area. As concerns surrounding antimicrobial resistance grows, and agriculture is forced to further reduce antibiotic use. The cattle industry needs to be actively searching for new solutions to combating the disease. Through understanding and continuing investigation of genetic heritability of BRD resistant animals, the cattle industry will continue to learn and evolve its opportunity to utilize novel approaches for combating BRD. Although animal management and biosecurity practices play a role in minimizing respiratory disease in cattle, they must be used in combination with other strategies that address the many other risk factors. Biosecurity practices aimed at the complete elimination of exposure are currently impractical in the industry because the cattle industry consists of multiple separated production sectors. Bovine respiratory disease will continue to be a significant issue for all phases of the cattle industry, affecting the value of all animals marketed, profitability to the producers, and providing diagnostic challenges to veterinarians and producers who need to make accurate and timely diagnoses. Although novel approaches are not well publicized and have limited available research at this time, the need for innovative solutions related to BRD is clear as the public for the cattle industry. Continuing research on novel solutions and understanding the practicality of their implementation, will be a key step to future prevention and treatment programs implemented in both cow-calf and cattle feeding sectors of the industry.

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