THE USE OF SODIUM IODIDE FOR THE MANAGEMENT OF BOVINE RESPIRATORY DISEASE

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Master of Science

by
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MAY 2017
The undersigned, appointed by the dean of the Graduate School, have examined the thesis entitled

THE USE OF SODIUM IODIDE FOR THE MANAGEMENT OF BOVINE RESPIRATORY DISEASE

presented by Brian McMillan Shoemake,

a candidate for the degree of master of science,

and hereby certify that, in their opinion, it is worthy of acceptance.

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Dr. Brian Vander Ley

______________________________________________
Dr. Dusty Nagy

______________________________________________
Dr. Allison Meyer
DEDICATION

Love. This word takes on many meanings and varies in the intent of its use. Some use it to describe and define the profound emotion and sentiment shared between two people for one another. Others may use it indiscriminately to describe a passing fad or trend, only to reflect a lack of understanding of the depth of meaning in the four letters. The Bible describes love many times and in many ways. Ultimately, love is personified in the agape love of Jesus the Christ. This work is dedicated to those that have loved, in the deepest and richest meaning of the word, me through my life, making this achievement possible.

Catherine, I LOVE YOU! My amazing & wonderful wife, you have supported me throughout this entire endeavor. Even when I doubted me, you never wavered in your belief of me or that I could accomplish this task. You have taught me to trust deeper in God’s providence and love. Every day I look forward to dancing in the minefields with you!

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Who I am is deeply rooted with an unwavering strength and trust in Jesus the Christ. My unspoken mantra from the beginning of this chapter in life was, “I can do all things through Christ who strengthens me,” Philippians 4:13 (NIV). Not only through the
past two and a half years, encompassing this degree, but throughout life I have known an
unfathomable, enduring love and grace only possible through Jesus. Without His love, I
would be lost and nowhere near the person I am in Him.

*May I never boast except in the cross of our Lord Jesus Christ... – Galatians 6:14*
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADG</td>
<td>Average Daily Gain</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
</tr>
<tr>
<td>ASL</td>
<td>Airway Surface Liquid</td>
</tr>
<tr>
<td>BAV</td>
<td>Bovine Adenovirus</td>
</tr>
<tr>
<td>BCoV</td>
<td>Bovine Respiratory Coronavirus</td>
</tr>
<tr>
<td>BHV - 1</td>
<td>Bovine Herpesvirus type - 1</td>
</tr>
<tr>
<td>BRD</td>
<td>Bovine Respiratory Disease Complex</td>
</tr>
<tr>
<td>BRSV</td>
<td>Bovine Respiratory Syncytial Virus</td>
</tr>
<tr>
<td>BVDV</td>
<td>Bovine Viral Diarrhea Virus</td>
</tr>
<tr>
<td>D.A.R.T.</td>
<td>Depression, Appetite, Respiration, &amp; Temperature</td>
</tr>
<tr>
<td>DTT</td>
<td>Dithiothreitol</td>
</tr>
<tr>
<td>DUOX</td>
<td>Dual Oxidase Enzymes</td>
</tr>
<tr>
<td>EDDI</td>
<td>Ethylenediamine dihydroiodide</td>
</tr>
<tr>
<td>H$_2$O$_2$</td>
<td>Hydrogen Peroxide</td>
</tr>
<tr>
<td>HOI</td>
<td>Hypoiodous acid</td>
</tr>
<tr>
<td>I$^-$</td>
<td>Iodine</td>
</tr>
<tr>
<td>I$_2$</td>
<td>Iodide</td>
</tr>
<tr>
<td>IBR</td>
<td>Infectious Bovine Rhinotracheitis</td>
</tr>
<tr>
<td>IL$\alpha$D</td>
<td>Iodine - Lithium - $\alpha$ - dextrin</td>
</tr>
<tr>
<td>KI</td>
<td>Potassium Iodide</td>
</tr>
<tr>
<td>LDH</td>
<td>Lactate dehydrogenase</td>
</tr>
<tr>
<td>LPO</td>
<td>Lactoperoxidase</td>
</tr>
<tr>
<td>µg</td>
<td>micrograms</td>
</tr>
<tr>
<td>µM</td>
<td>micro Molar</td>
</tr>
<tr>
<td>NADPH</td>
<td>Nicotinamide Adenine Dinucleotide Phosphate</td>
</tr>
<tr>
<td>NAHMS</td>
<td>National Animal Health Monitoring System</td>
</tr>
<tr>
<td>NaI</td>
<td>Sodium Iodide</td>
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</table>
NSAID  Non-steroidal anti-inflammatory drug
O$_2^-$  Superoxide
OSCN$^-$  Hypothiocyanite
PI - 3  Bovine Parainfluenza Virus type - 3
PVP  Polyvinylpyrrolidone
PVP - I  Povidone - Iodine
RNA  Ribonucleic Acid
ROS  Reactive Oxygen Species
RT - PCR  Reverse Transcriptase – Polymerase Chain Reaction
SAS  Statistical Analysis System ®
SCN$^-$  Thiocyanate
T$_0$  Baseline data point
T$_{12}$  12 hour study time point
T$_{48}$  48 hour study time point
T$_{72}$  72 hour study time point
TSH  Thyroid Stimulating Hormone
CHAPTER 1: INTRODUCTION

Bovine Respiratory Disease Complex

Bovine Respiratory Disease Complex (BRD) is a leading cause of morbidity, mortality, and economic loss in beef production, of post weaning cattle in North America and across the world. The pathogenesis of BRD can be simplified into four simple steps. BRD begins with a stressful event causing the calf to become immunocompromised. Once the immune system is compromised, a viral infection of the upper respiratory tract becomes established. As the viral infection proliferates and stimulates the immune system, bacterial pathogens that are commensal organisms of the upper respiratory tract infect the lower respiratory tract. The bacterial colonization and suppression of natural immune defenses results in pneumonia and impedes normal respiratory function.

As reported in the most recent National Animal Health Monitoring System (NAHMS) data, BRD incidence increased from 10.3 per 1,000 head of cattle in 1994 to 16.0 per 1,000 head of cattle in 2011. Increasing disease severity and prevalence typically indicates a failure in ability to manage or control disease. A majority of calves are examined, diagnosed, and treated for BRD within the first 27 days of arrival at a feedlot. Despite scientific advances in understanding and control, BRD morbidity and mortality remains the most significant health concern of feedlot calves in the United States. 70-80% of feedlot morbidity and 40-50% of feedlot mortality is attributed to BRD. As the most prevalent feedlot disease, BRD constitutes the most financially straining disease in the North American beef cattle industry and is exceeded only by diarrheal disease in dairy calves. Treatment for BRD results in wide ranges of losses depending on as many factors as there are causes for the disease itself. Estimates of $23.23 - $151.18 in
lost production per morbid calf were reported in 2010. Individual per treatment analyses determined a single BRD treatment event cost $40.64, a second treatment resulted in $58.35 lost, and three or more treatments cost $291.93. Total industry lost potential in 2009 due to BRD was $800 million in North American markets. In 2010, BRD was estimated to cost more than $3 billion per year to the global market. BRD of beef cattle requires improvement, both for short and long-term health of animals, herds, and feedlots. Multiple options exist to aid in the prevention and treatment of BRD, yet a desirable management technique remains elusive and treatment options continue to evolve.

Risk factors for the development of BRD include: immune system status, nutrition, temperament, stress, marketing management, environment, concurrent diseases, and transportation. While BRD primarily affects the finishing phase of beef production, the care and husbandry of beef calves at the level of the cow-calf producer is crucial to long-term outcomes and ability to thrive in a feedlot.

Effective immunity for a calf begins with its dam and her immune system. Inadequate transfer of colostral immunoglobulin, or failure of passive transfer, to the calf can increase the incidence of early respiratory disease. Colostral immunoglobulin concentrations alone do not affect BRD incidence or overall health, but is a key early factor in disease prevention. Failure of passive transfer was previously reported to be a contributing factor of poor feedlot production and morbidity, specifically BRD. Ultimately, multiple early developmental interactions determine lifelong immunity. Nutritional management integrally affects calf health and feedlot performance. Grazing of endophyte infected fescue prior to feedlot entry potentially influences the initial arrival
period at the feedlot and can affect it for several days. Not only previous nutrition, but changing nutrition causes stress to calves upon arrival to the feedlot. Changing from a pasture based grazing to feedlot concentrate diets alters the calf’s rumen physiology and health status which integrates into the BRD pathogenesis. Calf temperament influences immunity and BRD susceptibility. Previous research demonstrates a correlation between highly-excitable cattle and poor immune response and lost performance. Clostridial vaccine trials investigated immune system function based on antibody response in calves based on exit velocity from a head gate, a measure used to quantify excitability. Calves with a calmer exit velocity had no reduction of antibody response compared to calves with a higher exit velocity had a 3 fold reduction of antibody response. Temperament also affects growth and gains in feedlot calves; calmer calves have an ADG of 0.14 kg/day more than temperamental calves. The correlation between stress and immunity has been well established: stress negatively influences the immune system. Cortisol levels increase and immunity declines when cattle experience physiologic or psychological stress. Stress also decreases feed intake resulting in nutrient intake decreases, and energy decreases, further exacerbating immune system compromise. Reducing stress greatly reduces the need for BRD treatment. Recognized conditions that are stressful include weaning, surgical procedures such as castration and dehorning, commingling at markets and during transportation, insufficient nutrition, severe changes in the weather, and overcrowding.

Marketing management includes all aspects of calf preparation and processing from the cow-calf producer to the feedlot buyer: cow-calf biosecurity and husbandry; preconditioning such as surgical procedures (castration and dehorning), growth implant
programs, vaccinations, feed bunk and water trough acclimation; commingling at auction markets; transportation to the feedlot; and environmental conditions at the feedlot. The husbandry applied in these early months of life dictate the calf’s future capacity to respond to diseases. As with husbandry, effective biosecurity also affects the calf’s future ability to handle disease. Castration and other surgical procedures affect immunity and BRD susceptibility. Repeated studies have implicated castration as a major, stressful event on intact bulls received at feed yards. One report noted morbidity of BRD in castrated - upon - arrival bull calves to be 92% greater than calves castrated prior to feedlot admission. The optimal time to castrate is not determined, but reports indicate that castration earlier in life results in less detrimental effects especially when not performed at weaning or feedlot arrival.

Environmental factors can be an uncontrollable aspect of a feedlot and BRD. These factors vary depending on the region of the country that the calf moves to and from as well as season of the year. Specifically, environmental changes that occur from the time of marketing to arrival at the feedlot can vary greatly; these weather and environment fluctuations can predispose calves to BRD. The feedlot environments often provide conducive conditions for respiratory disease and are in stark contrast to the open pastures to which a calf was previously habituated. Dust, wind, precipitation, mud, heat, cold, and sometimes minimal shade or shelter affect cattle and their ability to thrive, especially when aspects of the environment are novel. Mud alone can decrease feed and nutrient intake based on the depth of the mud. The National Research Council reports up to a 30 % reduction in feed consumption when mud is two feet deep. Calves received during extreme heat, humidity, or both heat and humidity that recently grazed endophyte
infected fescue may lack the ability to appropriately thermoregulate and subsequently be at increased risk for BRD or experience an increased mortality to BRD because of the stress incurred as a result of these environmental challenges.\textsuperscript{4}

Once the calf is stressed and the immune system is compromised, upper respiratory tract viral infections occur. The viruses associated with BRD considered significant include bovine herpesvirus - 1 (BHV - 1), parainfluenza - 3 virus (PI-3), bovine respiratory syncytial virus (BRSV), bovine viral diarrhea virus (BVDV), bovine corona virus (BCoV), and bovine adenovirus (BAV).\textsuperscript{1,3,4,6,12} The BRD viruses cause either a primary infection individually or in combination with other pathogens. BHV - 1 and BVDV can cause systemic disease in cattle; otherwise, the viral infections of BRD are localized infections of the respiratory tract. Younger animals are more susceptible to BRD infections; however, BRSV and BHV - 1 infections of adult cattle occur. Young animals become infected when they are highly susceptible early in the marketing process, especially calves from closed herds that are commingled with calves of varying herds and introduced for the first time to pathogens they have previously not been exposed to.

The most common bacterial pathogens of BRD are Mannhaemia haemolytica, \textit{Pasteurella multocida}, \textit{Histophilus somni}, \textit{Mycoplasma bovis}, and \textit{Trueperella pyogenes}. \textit{M. haemolytica, P. multocida, and H. somni} are gram negative aerobic bacteria. \textit{T. pyogenes} is a gram positive facultative anaerobe. \textit{M. bovis} is a pleomorphic bacteria without a cell wall. \textit{M. haemolytica} is identified in 25 – 30\% of necropsies of calves that die of pneumonia in feedlots. \textit{M. haemolytica} has 12 identified serotypes, some of which are nonpathogenic commensals of the nasopharynx. Serotypes A1 and A6 are the most commonly isolated pneumonic pathogens of cattle. \textit{M. haemolytica} is an opportunistic
pathogen that proliferates rapidly in the lungs. The virulence factors and toxins of *M. haemolytica* infections results in severe, fibrinous, lobar, necrotizing, pleuropneumonia. *M. haemolytica*’s major toxin, leukotoxin, is lethal to neutrophils, macrophages, lymphocytes, and platelets. *M. haemolytica* also releases endotoxin resulting in the activation of inflammatory cascades. *P. multocida* is also a commensal nasopharyngeal pathogen that results in bronchopneumonia after prolonged respiratory tract compromise. There are 5 serogroups based on capsule antigen differences. Like *M. haemolytica, P. multocida* releases endotoxin. The bacterial capsule also prevents phagocytosis. *H. somni* can be found on the upper respiratory tract and genital mucosa without causing disease. Other than pneumonia, *H. somni* can cause multiple other disease processes, including septicemia, abortion, polyarthritis, and thromboembolic meningoencephalitis. Between 25 – 100% of calves entering feedlots have been exposed to *H. somni*. *H. somni* is capable of evading the immune system as it can avoid opsonization and resist destruction once phagocytized. *H. somni* also secretes lipooligosaccharide, similar to lipopolysaccharide, which induces inflammation. *H. somni* is also capable of causing vasculitis by inducing vascular endothelial cell apoptosis. *H. somni* is also uniquely capable of inducing IgE production. IgE is a component of Type I hypersensitivity reactions; therefore, a second exposure to *H. somni* could result in an anaphylactic response. *M. bovis* commonly causes respiratory disease as well as arthritis and tenosynovitis. The exact mechanism of pathogenesis of *M. bovis* is not definitively known. The ability of *M. bovis* to attach to cells is important as the immune system is capable of producing antibodies to the variable surface proteins of *M. bovis* resulting in a partial ability to block bacterial attachment. Similar to *M. haemolytica* and *P. multocida*. 
*multocida’s* immune evasion strategies, *M. bovis* can impair neutrophil function and induce lymphocyte apoptosis. *M. bovis* can be cultured from normal cattle. It also spreads within groups of calves with relative speed. *T. pyogenes* infections result in pulmonary abscessation after chronic pneumonia. At a management and herd health perspective, *T. pyogenes* infections indicate that prevention and treatment efforts are deficient and need to improve.12

The manifestations of BRD range from subclinical (undetected) disease, overt moribund disease, or acute death. As such, early detection of disease is critical to successful treatment outcomes.13 Overt clinical signs and physical exam findings of BRD include lethargy, depression, serous or mucopurulent nasal discharge, ocular discharge, cough, dry muzzle, anorexia, increased respiratory rate and/or effort, dyspnea, dropped head, drooped ear(s), standing alone, recumbency, slow ambulation, and rough hair coat.2,5,7,8,12 Clinical signs usually develop within three to ten days after the stressful event.7 Physical examination findings are also widely variable. Rectal temperature greater than 104 °F (40 °C) and change in thoracic auscultation including bronchial tones, pleural friction rubs, wheezes, and/or decreased or absent lung sounds may also be found on physical examination leading to a diagnosis of BRD associated bronchopneumonia.2,7 Cattle naturally veil the clinical signs of illness, complicating detection of animals that need intervention. As a result, diagnosis of BRD is often a subjective, acquired skill, rather than an objective standard.2

Subclinical disease, pulmonary infection without overt clinical signs but results in pulmonary damage, causes a significant strain on animal health. The impact of subclinical disease can be quantified by lost gains; lung lesions alone decreased average
daily gains (ADG) of between 0.07 lbs./day/animal and 0.33 lbs./day/animal.²,¹³ Carcass quality also declines as a result of subclinical disease. It is well established that BRD lesions exist in cattle that were never suspected or treated for respiratory disease as supported by studies assessing lungs at slaughter plants and reviewing the animal’s treatment records.¹³ Varying estimates of subclinical disease exist, with 50 – 70% as a commonly reported prevalence.⁴,¹³ A significant portion of the feedlot population is affected by BRD that goes unrecognized.⁷

A uniformly accepted case definition of BRD remains undetermined, which exacerbates the inability to consistently identify, diagnose, and treat BRD.⁵,¹⁴ Numerous techniques exist to diagnose respiratory disease and attempt to alleviate the subjective aspect of diagnosis. Initial diagnosis currently relies on pen riders’ visual assessment of calves in feed pens for clinical signs and identification for further examination and evaluation. There is a significant bias in such a subjective system.⁴ This system places tremendous responsibility on feedlot caretakers to accurately assess and determine BRD amongst large groups of animals, ranging from hundreds to thousands of animals per feedlot. Some researchers originally diagnosed BRD solely based on presentation for treatment. The accuracy of the pen riders and animal caretakers can fluctuate and other diseases have some of the same clinical signs; therefore, diagnosis of BRD based on presentation for treatment is inherently risky and problematic. As such, multi-modal diagnostic techniques improve overall animal assessment and diagnosis.⁵ The D.A.R.T. system provides an easy way to recognize the four key clinical signs of respiratory disease: depression, appetite, respiration, and temperature.¹³ After visual appraisal, rectal temperature serves as a valuable determinant of disease, and in a feedlot population, an
animal with a fever greater than 104 °F without obvious signs of another disease process will be diagnosed and treated for BRD. Newer technologies include computerized, electronic stethoscopes that listen to and analyze lung sounds and assign a respiratory score to the calf and pen of calves. Previous authors developed a clinical scoring system to objectify BRD identification. Other methods of assessing body temperature may allow for improved detection of abnormalities. Infrared thermography and radiofrequency implants have both been investigated. Confirmatory ante-mortem laboratory tests can provide BRD verification, but the ideal diagnostic remains undetermined. Ancillary testing, field diagnostics, and metabolic analytes lack definitive diagnostic value and can be cost or time prohibitive. Cultures of nasal swabs are easily obtained and may provide diagnostic insight but do not sample the deep, pneumonic tissue of the respiratory tract. Measurement of acute phase proteins; C - reactive protein, α-1 acid glycoprotein, serum amyloid-A, lipopolysaccharide binding protein, ceruloplasmin, fibrinogen, haptoglobin, transferrin, and α-2 macroglobulin, have been measured with mixed results. Haptoglobin and lipopolysaccharide binding protein may prove useful in determining morbidity. Thus far, multiple ways to determine respiratory disease exist, but with so many options, one single methodology has yet to definitively diagnose disease.

Treatment and prevention of BRD cannot correct all of the pathology created during the infection. There are numerous treatments and therapies that have been applied and investigated to alleviate BRD. Antibiotic agents stand as the foremost treatment for BRD. As of the 2011 NAHMS, 16.2% of all cattle in feedlots received treatment for BRD. While antibiotics constitute a significant component of treatment, their use needs to
be judicious, based on scientific, epidemiologic principles and sensitive to changing bacterial populations. As with any disease, early treatment achieves greater success. When treated early in the disease course, clinical responses typically become evident within 24 to 36 hours if they will be successful. Failures continue to worsen and potentially become chronic or fatal pneumonias. If adequate improvement is not achieved by the first antibiotic administered, the second and/or third medication may be implemented.

Metaphylaxis, the timely mass medication of animals or groups of animals during the incubation period of disease to reduce or potentially eliminate the disease, remains a successful practice to manage BRD. Metaphylaxis antibiotic use helps alleviate disease but is increasingly concerning to consumers, producers, health officials, and veterinarians. The most common and effective use of metaphylactic protocols is in high risk calves. These calves are typically light-weight, young, and immunologically immature. Metaphylaxis of this particular calf group inhibits the bacterial pathogens, pre-emptively preserving animal health and wellbeing in a financially responsible and effective method. Metaphylactic antibiotic use has doubled in application since 2000. Advantages beyond reduction in morbidity and mortality include maintenance of normal feeding behavior post administration, increased ADG compared to untreated calves, and increased feed to gain performance. While metaphylaxis is useful and effective, it is likely that consumers will not support the practice in the future. In addition, veterinarians will have difficulty justifying metaphylactic antibiotic use if pathogen resistance develops or continues to develop. Other treatment modalities continue to be implemented. Anti-
inflammatories such as flunixin meglumine and meloxicam, have become used as ancillary treatments in BRD, but with mixed evidence for its use.\textsuperscript{1,20}

BRD will remain a disease requiring prevention and treatment. Methods to prevent BRD, effectively reduce the number of affected cattle, and the number of cattle requiring treatment are needed.\textsuperscript{7} Preconditioning programs remain an under-utilized opportunity to reduce BRD.\textsuperscript{1,4} One repeatedly documented preconditioning program, The Value Added Calf program, advocates and advises producers on the optimal timing for building calf immunity, when the immune system can focus almost entirely on immunity and not stress.\textsuperscript{2} Preconditioning programs provide an ancillary benefit to the feedlots of decreased morbidity.\textsuperscript{4} Initially, and maybe still today, the disease reduction and economic benefits of preconditioning may not be readily apparent.\textsuperscript{5} Recent evidence for preconditioning was recently provided: an eleven year study with an average return of $80.70 per head by preconditioning the calves for 63 days.\textsuperscript{1} The NAHMS of 2011 reported 81.5\% of feed lot operators regard certain pre-feedlot practices (preconditioning) beneficial to calf health in the feedlot, including: weaning four weeks or more prior to shipment, respiratory vaccination (specifically IBR, PI-3, BVD, BRSV, P. multocida, and \textit{M. haemolytica}), castration and dehorning four weeks or more prior to weaning, familiarity with feed bunks and waterers, and treatment for internal and external parasites.\textsuperscript{1,4,7} Preconditioning is not a guarantee of future health, but is a best management practice to provide the best health possible for calves. If the calf or group is presented with sufficient pathogenic load, the preconditioned calves can still succumb to BRD similarly to high risk calves that are not preconditioned. That stated, the value of preconditioning comes from improved animal welfare, more productive time on feed, and
less antibiotic use. Preconditioning programs are widely recommended and routinely demonstrate a benefit to both calf and feedlot by decreasing BRD morbidity and bolstering immunity. Initial processing at the feed yard to prevent disease fails to achieve the same reduction in morbidity as preconditioning; therefore, preconditioning should become the standard of practice as outlined in the Beef Quality Assurance guidelines.

Regardless of previous health history, feedlots still have to receive and process calves when they arrive. Timing of processing can help decrease BRD morbidity; however, the exact timing remains undetermined. Studies evaluating associations between the time of processing and vaccination at the feedlot regarding morbidity and mortality have varying results. Immediately on entry out to two weeks post entry have all been evaluated with inconsistent conclusions on morbidity and mortality. Vaccination upon arrival remains valuable in application but also remains fraught with complications as once at the feedlot, prevention of BRD may not be achievable. Nutritional management also influences health. Nutritional management at the feedlot has not achieved the ability to repeatedly improve or alter immune function to cause a decrease in BRD morbidity. The nutritional history of calves prior to feedlot placement may explain the variations observed in outcomes of trials, especially in regards to need for vaccinations, vitamins, protein, and minerals. Trace mineral injection during processing has yet to improve or decrease BRD incidence as measured by undifferentiated fever rate. Dietary mineral deficiency and supplementation have not been clearly associated with BRD development; however, chromium, copper, cobalt, selenium, vitamin A, vitamin E, and zinc all impact immune function.
While processing procedures can change and respond to advancing practices, certain aspects of feeding and finishing cattle cannot be controlled, such as the environment. Efforts to prevent against cold and heat stress help mitigate potential BRD caused by temperature derangements. Dust and mud also exacerbate BRD. Dusty conditions irritate and inflame the respiratory tract while mud decreases nutrition intake as discussed previously.²

BRD is a complex, multifactorial disease of numerous viral and bacterial pathogens, environmental conditions, and management practices with multiple interactions, complications, and outcomes.³⁴ Identifying specific risk factors, prudent preventative measures, and specifying individual importance of each is difficult due to the interactions and complexity of the disease.⁵ Collectively, the scientific community’s understanding of BRD continues to advance in areas of response to disease treatment and decreasing disease risk, as well as the epidemiologic triad of host, environment, and pathogen factors. Despite improvements, BRD incidence and severity continue to rise.¹⁴¹⁰

Iodine

The discovery of the essential trace halogen element iodine occurred in 1811 by Courtois. Ten years later, the Swiss physician Coindet began using tincture of iodine for the treatment of goiter (hypothyroidism) in his patients. In 1895, it was found that iodine was a requirement for normal thyroid gland function.²¹ Iodine is always found combined with other elements and does not occur in concentrations adequate enough to be found as an independent mineral. Various isotopes and compounds have medically valuable diagnostic and therapeutic applications. Compared to other halogen atoms, iodine is not
as strong an oxidizing agent, particularly compared to bromine, chlorine, and fluorine, but is a common antiseptic and disinfectant, primarily in a water and alcohol solution with potassium iodide. Other uses and applications exist for iodine, but are beyond the scope of this review.22

In the body, the thyroid gland requires iodine for the biosynthesis of thyroxine and triiodothyronine. Thyroxine and triiodothyronine serve to regulate basal metabolic rate and energy metabolism in the body.23-25 As a trace element, which cannot be produced by the body, iodine must be obtained primarily through dietary intake, such as in soils and forages.23 Soils and forages have variable iodine concentrations, though. In most areas of the world, iodine deficiency constitutes a common health concern.25 Commonly found or utilized inorganic iodine sources are potassium, sodium, and calcium iodide. Of these, potassium iodide easily oxidizes, becoming volatile prior to ingestion. Organic iodine, for example ethylenediamine dihydroiodide (EDDI) is biologically available but oxidizes less readily. Organic iodine is more tolerable when compared to inorganic iodine compounds in regard to iodine intoxication, but the biological efficacy of the two groups does not seem to differ.23,25

A dietary intake of 250 μg/kg of iodine in a dry diet is adequate for most livestock species.25 The National Resource Council estimates beef cattle diets with 0.5 mg I/kg to be suitable.26 In dairy cows, approximately 70 – 80% of the iodine ingested on a daily basis is absorbed in the rumen. The omasum absorbs approximately 10% of the ingested iodine; overall, 80 - 90% of the ingested iodine is absorbed.27 Throughout the gastrointestinal tract of ruminants, iodine is efficiently absorbed and secreted to help prevent iodine deficiency, as iodine is recycled within the gastrointestinal tract.27 Organic
iodine compounds such as pentacalcium orthoperiodate and EDDI remain more stable in the environment but less soluble compared to inorganic compounds. Because of these properties, mineral and salt supplements commonly include these organic compounds, especially when the supplement is exposed to the weather.\textsuperscript{25,27} Thyroid gland function and activity depends on circulating iodine concentration. The thyroid gland achieves a concentration gradient 20 to 40 times plasma concentration. This can increase another 20 fold when TSH stimulates the thyroid gland. In severely iodine deficient diets, 65\% of the available iodine becomes bound by a hyperplastic, goitrous, thyroid gland. With marginal dietary iodine intake, 30\% of the iodine becomes incorporated into the thyroid hormones. Diets with excess iodine result in less than 20\% of iodine utilization by the thyroid gland. Iodine not utilized by the thyroid gland is excreted primarily in urine (95\%) with small amounts excreted in milk and feces.\textsuperscript{25}

Iodine deficiency constitutes a global health concern. Iodine deficiency manifests as goiters, nodules of the thyroid gland, or severe deficiency results in hypothyroidism, cretinism, and mental retardation.\textsuperscript{28} These symptoms occur as a result of decreased thyroid hormone production, causing a slower rate of diffuse cellular oxidation and metabolism. Typically, the thyroid gland swells, creating a goiter in neonates as the first hallmark sign of iodine deficiency. Newborns may also lack hair, be weak, or be dead upon birth. Often, the dams of the affected newborns appear clinically normal. Adult animals commonly become unthrifty or infertile as a result of iodine deficiency.\textsuperscript{25} Iodine deficiency may also inhibit or reduce immunity. Iodine deficiency and decreased immunity, specifically in regards to pneumonia, cannot be directly associated as
pneumonia in iodine deficient ruminants is not common; therefore, iodine deficiency remains a minor component of respiratory defenses.³

Iodine intoxication in ruminants less commonly causes clinical complications because of the high doses required to achieve toxicity. However, iodine supplementation may exceed daily nutrient requirements. Iodine compounds have been used as feed additives to prevent and treat infertility, mastitis, infectious pododermatitis, and respiratory diseases. Iodine toxicity can manifest when dietary iodine intake per animal reaches 50 mg or more per day. Typically, symptoms in cattle include dry, scaly hair coats, decreased milk production, excessive coughing, salivation, lacrimation, and nasal discharge.²⁴,²⁵ Other clinical manifestations include hyperthermia, anorexia, depression, alopecia, and dermatitis.²³ Gross respiratory pathology due to iodine toxicity in cattle can include mediastinal lymph node enlargement with hyperemia, pleurisy, tracheitis, and bronchopneumonia. The lungs usually contain an exudative inflammation centralized around the affected region(s), bronchial mucosal membrane hypertrophy, bronchiole necrosis, and alveolar fibrous exudate. Severe to fatal intoxication occurs in calves when protracted doses of 10 mg/kg/day, approximately 500 times the daily recommended daily dose, are provided. Milder clinical signs occur at lower doses of 2.2 mg/kg/day. When iodine compounds were injected into mice in one study, intoxication resulted in short term injection site phlebitis, generalized weakness, and anorexia. Overall, the mice’s condition and body weight remained similar to the control group of mice and their own initial parameters.²⁹

Iodine can be used in multiple other applications in chemistry, manufacturing, and healthcare. Povidone – iodine (PVP-I) is an iodophore, an iodine compound in which the
iodine molecule is complexed with the solubilizing compound polyvinylpyrrolidone (PVP), which is water soluble. As a disinfectant, PVP-I has a broad-spectrum of activity as a microbicide and germicidal agent with the capacity to inactivate bacteria, spores, protozoa, fungi, and viruses. The spectrum of activity of PVP-I and elemental iodine are identical and resistance is not reported in most organisms. PVP-I antimicrobial activity begins with the dissociation of iodine from PVP. The iodine then quickly penetrates the cell membrane, in its free state, and interacts with the cell’s nucleotides, proteins, and fatty acids contained in the cytoplasmic membrane and cytoplasm. These cytoplasmic interactions quickly cause cell death. These interactions have not yet lead to microbial resistance, making iodine a potent microbicide that can be used repeatedly. Human and animal PVP-I topical applications exist currently for management of infectious diseases. An investigation into the viracidal activity of PVP-I determined that various dilutions achieved 99.99% inactivation of BVDV after 30 seconds in an organic environment. Two viruses with considerable resistance are poliovirus and adenovirus, proposedly due to their non-enveloped property. PVP-I non-selectively interacts with cells, thus mammalian cells can experience the cytotoxic effect. Potential future applications of a liposomal PVP-I complex could aid in the prevention or treatment of viral upper respiratory tract and ocular infections.

EDDI has been used in the treatment of diseases in cattle. Doses of 400 – 500 mg/animal/day administered for 14-21 days have been used to treat actinomycosis, foot rot, and respiratory diseases. Iodine compounds were used in animals with subacute to mild chronic respiratory tract diseases as an expectorant. Anecdotally, many producers and veterinarians suspected EDDL caused a worsened condition in the lungs. EDDL
resulted in respiratory tract inflammation and an increased susceptibility. Due to the release of ammonia from urea hydrolysis which upregulates EDDI breakdown causing ethlenediamine release. Ethlenediamine causes bronchodilation, which when in combination with intraluminal inflammation, fluid could accumulate within the bronchioles. Immune system alterations also occur when EDDI is administered continuously at 50 mg per animal per day, the common dose for infectious pododermatitis of cattle. Such alterations include neutrophilia, lymphopenia, depressed phagocytic ability, and reduced blastogenic response of lymphocytes to T and B cell mitogens. Ultimately, cellular and humoral immunity suppression occurs, potentially causing reduced acknowledgement of infectious agents by the host immune system. Clinical signs associated with EDDI toxicity match those previously described of I toxicity. Long-term use for 6 months resulted in resolution of all signs except a mucous nasal discharge. Dose dependent signs were noted in one study; calves given a lower iodine dose acclimated quicker as determined by resolution of signs of toxicity. The study concluded excessive, chronic, long-term iodine intake resulted in an increased susceptibility to respiratory disease, particularly the beginning portion of the study. Pathologic changes noted were presence of a tracheal mucosal exudate along with swelling and congestion of the mediastinal lymph nodes. Again, a dose dependent association was noted with frequency and severity of these lesions.

Another study investigated Iodine-Lithium-α-dextrin (ILαD) compound in rats. ILαD was well tolerated, and did not cause detrimental effects on animal behavior, body temperature, body weight, hematologic, morphologic, histopathologic, or biochemical alterations. ILαD is a powerful, safe antibacterial agent with the potential to reduce the
growth of bacteria in both the blood and organs, including the lungs, in rats. This is thought to be possible by the production of hypohalous acids and taurine haloamines that aid in the inflammatory response regulation and bacterial killing by neutrophils. The investigators found that when in the presence of sodium thiosulphite, ILαD up regulated oxidative burst of human neutrophils. This study determined that ILαD, at the maximally tolerated dose, was too low to independently be bactericidal, but did increase intracellular bacterial killing through production of hypoiodous acid via myeloperoxidase mediated iodine oxidation in neutrophils.\textsuperscript{39}

Sodium iodide (NaI) is an important antimicrobial to the animal health industry. It’s primary use is as an intravenously administered treatment for actinobacillosis and actinomycosis in cattle.\textsuperscript{32} Iodides can have a broad spectrum of activity though against bacteria, viruses, protozoa, yeasts, and fungal infections. The mechanism of action of iodide compounds as an antimicrobial primarily depends on the concentration of molecular iodine. Molecular iodine exerts its effects on microbial agents in multiple simultaneous methods. Iodine binds to proteins causing denaturation by oxidation of several amino acid and hydrogen binding sites. The denaturation of these proteins results in changes of both the structure and function of cellular proteins and enzymes. These changes therefore alter cellular function and capabilities. Molecular iodine also results in changes to cell wall structures, specifically fatty acids and hydrogen bonding in nucleic acids. Thus, the release of iodine from NaI to form molecular iodine (I\textsubscript{2}) results in a potent, multimodal microbe-cidal antimicrobial.\textsuperscript{33} NaI was previously used in many species as an expectorant; however, with little success. NaI was utilized as a supplement in iodine deficient regions as well. Toxicity to NaI is primarily due to the iodine
component of the compound. Specifically in ruminants, iodine toxicity can manifest as lacrimation, anorexia, nasal discharge, hyperthermia, exophthalmia, scaling of the skin/hair coat or dandruff (diffuse dermatitis), muscle fasciculations, decreased weight gain, diarrhea, and nonproductive coughing.\textsuperscript{32,34}

**Respiratory Defense**

The bovine respiratory system has multiple layers of defense, providing complementary and distinct layers of defense, to facilitate protection to the continuous exposure of antigens and debris.\textsuperscript{3,35,36} Anatomically, the upper respiratory structures filter and trap pathogens and foreign debris. Most of the bacterial pathogens of BRD are found as commensal organisms within these structures. The mucociliary apparatus of the trachea is significant to protecting the respiratory system. The mucus layer quality, the particulate matter deposited into the mucus, and ciliary function are all important factors of mucociliary function. The normal mucociliary apparatus is capable of clearing 90% of infectious particles within 4 hours of introduction. Various studies have investigated the function of the respiratory epithelium and demonstrated the importance of these cells. The viruses, bacteria, inflammatory mediators, clearance rate, and environmental conditions have all been investigated and proven to hinder the respiratory tract, specifically the ciliary action of the respiratory epithelium and the ability to resolve infections.\textsuperscript{3,37} An example of an environmental factor is that diesel exhaust particles detrimentally affect the clearance facilitated by the ciliated respiratory epithelial cells.\textsuperscript{38}

One of the recently investigated components of the respiratory immune system is the airway surface liquid (ASL). The ASL originates from the epithelial cells of the respiratory tract and provides a protective coating of fluid that contains macrophages,
plasma, lysozyme, lactoferrin, defensins, immunoglobulins, surfactants, complement proteins, lactoperoxidase, hypothiocyanate, and hypoiodious acid. The ASL is vital to protect the mucosa of the airways from exogenous pathogens.\textsuperscript{2,3,35,36,39} Multiple components of the ASL have been investigated. It has only been recently that an oxidative antimicrobial system of the respiratory epithelial cells has been reported.\textsuperscript{37}

With the advantages of the protective layers, the bovine respiratory system also has aspects that increase susceptibility to disease or potentiate disease processes. With the lack of Pores of Kohn, alveoli are compartmentalized and more likely to suffer from local hypoxia once occluded. The compartmentalization of the lungs by the interlobular septae also reduce the affected tissue’s ability to clear a pathogen and therefore further the pathologic process.\textsuperscript{17} The anatomical structures of cattle can promote pneumonia, but the pathogens can alter the host environment to perpetuate their infections. Viruses can not only overwhelm the immune system, but also promote bacterial proliferation and survival. Respiratory pathogens modulate the host immune response by stimulating or inhibiting inflammatory mediators. By altering the body’s response to the pathogen, the mechanisms of repair are also altered, resulting in defective healing.\textsuperscript{3} Metabolically, cattle require a higher basal oxygen supply than other species. This increased demand requires maximum utilization of available surface area for gas exchange even when healthy. Pathophysiologic processes such as pneumonia can diminish the available surface area for gas exchange causing decreased productivity and health as well as potentiate stress.\textsuperscript{3,36}

A recent advancement in the knowledge of the respiratory immune system is the recognition of a component of the ASL that is comprised of the dual oxidase enzymes
(DUOX), superoxides, and lactoperoxidase (LPO). The DUOX enzymes are NADPH oxidases that produce reactive oxygen species (ROS), which are present in animals and plants as part of the immune system. Previously, the actions of ROS were considered detrimental to respiratory tissues by causing oxidative damage. While in certain respiratory diseases this is true, ROS are required for normal cellular physiology, especially the respiratory burst of phagocytes.\textsuperscript{28,36,40} The DUOX enzymes reduce molecular oxygen extracellularly to form superoxide (O\textsubscript{2}^-) or hydrogen peroxide (H\textsubscript{2}O\textsubscript{2}) through transmembrane electron transport from intracellular NADPH.\textsuperscript{28} The DUOX system was originally recognized in the thyroid gland, as part of the oxidation of iodine when synthesizing thyroid hormone.\textsuperscript{36,40} DUOX enzymes have subsequently been identified in the salivary gland, rectum, trachea, bronchi, kidney, pancreas, brain, testis, heart, inner ear, and leukocytes.\textsuperscript{28,39,40} In the respiratory tract, DUOX expression has been recognized on the apical aspect of the respiratory ciliated epithelial cells.\textsuperscript{36} There are currently two recognized DUOX enzymes, DUOX1 and DUOX2. The expression of the two enzymes is dependent on multiple factors. DUOX1 is expressed through mature type II alveolar cells and non-ciliated cells throughout the trachea and bronchi. DUOX2 expression can occur in the tracheobronchial epithelial cells; however, DUOX1 expression is greater than that of DUOX2. Under pathologic disorders, the genetic expression to stimulate either DUOX1 or DUOX2 is regulated by cytokine secretion. Ultimately, DUOX1 and DUOX2 function similarly, with the only notable difference being the amount of H\textsubscript{2}O\textsubscript{2} produced. DUOX2 H\textsubscript{2}O\textsubscript{2} production is greater than that of DUOX1 H\textsubscript{2}O\textsubscript{2} production.\textsuperscript{28,35,36,40} When DUOX1 and DUOX2 expression are measured by RT-PCR, DUOX1 expression is approximately five times greater than that of
DUOX2, thus the actual H$_2$O$_2$ concentration generated from each DUOX may be equal.$^{36}$ A proposed difference between the two DUOX enzymes is that DUOX2 is more inducible, by approximately 20 fold increase, specifically by interferon gamma, and may be responsible for responding to inflammation or infection. DUOX1 has a more steady state of expression, induced mildly by interleukin 4 and 13, and therefore has a role in the defense of the normal airway, stabilization of the epithelial barrier, and production of mucus.$^{36,40}$ While the beneficial aspects of DUOX have recently been discovered, prolonged DUOX enzyme expression can result in increased inflammatory disease. Bacterial pathogens have recently been proven to induce DUOX2 and LPO, indicating a significant role of DUOX as a protectant of the respiratory epithelium. The role of DUOX as a supplier of ROS in the respiratory tract has changed the concept of H$_2$O$_2$ being detrimental to being beneficial when released in a regulated manner.$^{28,36,39,40}$

Release of H$_2$O$_2$ in large quantities can still cause significant damage to the pulmonary tissues. When regulated by DUOX though, H$_2$O$_2$ is considered a normal constituent of the respiratory tract that is continuously secreted by the respiratory epithelium. H$_2$O$_2$ has varied capabilities against infectious organisms. In vitro, H$_2$O$_2$ produced by DUOX on agar culture plates exerts a repellant effect against Salmonella. However, H$_2$O$_2$ alone cannot inactivate viral infections.$^{28,35,36}$ While H$_2$O$_2$ has antimicrobial properties, its effectiveness is increased when LPO catalyzes a reaction with H$_2$O$_2$.

The LPO system has been previously described and recognized as a potent immune defense mechanism. The antimicrobial properties of the LPO enzyme include both gram positive and negative bacteria, viruses, and fungi. LPO is found in tears,
airway secretions, saliva, and milk. Similar to DUOX, LPO also shares similarities with myeloperoxidase and eosinophil peroxidase. Throughout the body, each DUOX enzyme is co-expressed with an associated peroxidase, such as LPO, indicating the importance of DUOX providing \( \text{H}_2\text{O}_2 \) for the various peroxidases.\(^{28,37}\) In the respiratory system, LPO is found in the submucosal glands, specifically the serous acini, and goblet cells of the respiratory tract. Normally, LPO is found in high concentrations within the ASL. However, as a portion of the airway protein content, LPO constitutes approximately one percent of the soluble protein.\(^{35,36,40}\) Without LPO, normal bacterial clearance is reduced from the respiratory tract.\(^{40}\) LPO is one component of the respiratory immune system that functions with DUOX, \( \text{H}_2\text{O}_2 \), and thiocyanate (\( \text{SCN}^- \), secreted by the respiratory epithelia).\(^{35,36,40}\) When these components are combined, they produce hypothiocyanite (OSCN\(^-\)), an antibacterial compound to protect the mucosal surface of the respiratory epithelium.\(^{35-37,40}\) In the mammary gland, OSCN\(^-\) produced by LPO eliminates bacteria by damaging the bacterial inner membrane. The \( \text{H}_2\text{O}_2/\text{SCN}^-/LPO \) system can temporarily inhibit staphylococcus aureus organisms, coliforms, and streptococci.\(^{41}\) This antibacterial defense system requires all of the constituents to function, without \( \text{H}_2\text{O}_2 \) and \( \text{SCN}^- \), LPO cannot effectively function.\(^{39}\)

The summarized mechanism of the LPO/DUOX/\( \text{H}_2\text{O}_2/\text{SCN}^- \) system follows a simple progression and reaction. At the apical extracellular space, DUOX enzymes produce \( \text{H}_2\text{O}_2 \). \( \text{H}_2\text{O}_2 \) reacts with the \( \text{SCN}^- \) by a LPO – catalyzed reaction, resulting in the formation of OSCN\(^-\). The LPO enzymes are secreted specifically by the submucosal glands. It has been determined that humans and sheep have submucosal glands, rats have fewer submucosal glands than humans, and mice do not have submucosal glands. There
may be some evidence that adult animals have greater concentrations of DUOX1 and 2 and LPO based on studies performed in sheep. A recent discovery of LPO in sheep and humans is that it not only catalyzes thiocyanate to hypothiocyanite, but can also produce hypoiodous acid (HOI⁻) from iodine (I⁻). The formation of HOI⁻ does not naturally occur at potent concentrations though as serum SCN⁻ concentration is approximately 1,000 times greater than serum I⁻ concentration. Because of this, OSCN⁻ is preferentially formed by the respiratory epithelium. When I⁻ is supplemented as a single high dose bolus, I⁻ secretion in the respiratory tract increases. One concern of a high dose of I⁻ is that it would suppress thyroid function. This does not occur though because of the Wolf-Chaikoff effect that reduces the metabolism of I⁻ and prevents thyrotoxicosis. As I⁻ concentration increases in the ASL, SCN⁻ concentration decreases, indicating that I⁻ and SCN⁻ compete for secretion into the respiratory tract. Recent studies have investigated the antimicrobial properties of HOI⁻ and found it to have potent antimicrobial activity.

HOI⁻ is formed by the reaction of H₂O₂ and I⁻ (catalyzed by LPO oxidation), identical to that of OSCN⁻ and SCN⁻, with SCN⁻ replaced by I⁻. SCN⁻ and I⁻ secretion by the respiratory epithelium is thought to be facilitated via the sodium-iodide symporter found on the basolateral plasma membrane. Compared to OSCN⁻, HOI⁻ is considerably viracidal. Both respiratory syncytial virus and adenovirus, an encapsidated and enveloped virus, were rapidly inactivated in the presence of HOI⁻ in previous studies. The proposed mechanism of action of HOI⁻ is that HOI⁻ modifies the surface proteins of the virus. Oxidized halides such as HOI⁻ are capable of reacting with oxidizable groups: sulphydryl, iron-sulfur centers, and unsaturated double bonds of the bacterial cell surface. These
changes inhibit binding and/or entry of the virus into the host cells. Treatment with iodide (I$_2$) may also have prolonged affects in the respiratory epithelial cells. It has been hypothesized and investigated that I$_2$ administration may be able to damage or otherwise impair a virus for several replication cycles after initial viral inoculation in vivo. The authors stated that I$_2$ administration could be used as a prophylactic measure in the prevention of respiratory disease and potentially as a treatment for active infections.$^{37}$ A concern of any modified cellular process in animals is whether the new output or reaction will result in cytotoxicity to the cells or the animal. This was demonstrated by the application of LPO, sodium iodide (NaI), and H$_2$O$_2$ to well differentiated epithelial cells in vitro. By measuring lactate dehydrogenase (LDH) it has been determined that HOI is not cytotoxic as there was no increase in LDH to cells exposed to the LPO/H$_2$O$_2$/I$_2$. Based on these findings, HOI is a potent antimicrobial and is safe to be secreted by the respiratory epithelium.$^{35,37}$

The LPO/H$_2$O$_2$/I$_2$ system has been investigated and proven as a viable method to reduce the pathogen load of the respiratory system in sheep. In humans, a dose dependent response to the oral administration of oral KI was established. In an in vitro model, a 5 µM increase in I$^{-}$ concentration was enough to significantly decrease infectious pathogens. 500 µM I$^{-}$ resulted in a more significant reduction of viral pathogens. A human study investigated the administration of oral potassium iodide (KI) and ASL I$^{-}$ concentration. Prior to administration of the oral KI supplement, the ASL I$^{-}$ concentration was not detectable. After administration of the 130 mg KI, ASL I$^{-}$ concentration increased to a peak concentration of approximately 500 µM and exceeded serum I$^{-}$ concentrations throughout the 24 hour study period. The oral administration of KI was capable of
providing I in the ASL at concentrations high enough to achieve effective antimicrobial activity.\textsuperscript{35} In sheep, a similar project was undertaken with similar results. Lambs, newborn and three weeks old, were used as a model for human respiratory infections and physiology. After the oral administration of 5 mg of KI, nasal I secretion increased significantly and for a greater duration than compared to intravenous administration of NaI. Increased HOI production was found to occur in the upper respiratory tract, where submucosal glands are located, and not in the lower respiratory tract such as the alveoli. In the study described, weight gain, body temperature, and respiratory rate were all comparable among the lambs administered KI and those not given KI. Histopathologic analysis of three week old lamb lungs infected with respiratory syncytial virus and administered KI had similar lung lesions to lambs infected with respiratory syncytial virus and not administered KI. However, newborn lambs administered KI had significantly reduced gross pathologic lesions. Based on immunohistochemistry, the lambs that were infected with the virus and given KI had significantly decreased viral antigen concentration compared to virally infected lambs without KI. Overall, the authors concluded that oral KI reduced some of the clinical signs associated with respiratory syncytial virus. There were similar findings between the two age groups. A reduction of the expiratory effort was noted in the lambs administered KI compared to those that were not during days two through six post inoculation of respiratory syncytial virus. In summary, the impact of respiratory syncytial virus, both clinically and as measured quantitatively (RNA levels, antigen, and virus titer), were reduced by administration of KI as a result of the formation of HOI.\textsuperscript{37}
BRD is a significant, multifactorial disease process. It is a substantial health concern of the beef industry. Considerable effort has been invested in determining the pathophysiology of BRD. Likewise, considerable investigation into the prevention and treatment of BRD has also occurred. While these investments have increased animal welfare and knowledge of BRD, the incidence of disease and mortality due to BRD have not been adequately reduced. While iodide compounds have been previously used for the treatment and prevention of BRD, they were administered for multiple days in an organic formulation. By better understanding the effects of I\(^{-}\) on the body and the ASL, a single oral bolus of NaI may be useful in the mitigation and reduction of BRD.
CHAPTER 2: PILOT STUDY

Objective and Hypothesis
The objective of this study was to determine if the oral administration of NaI would result in the secretion of I\(^{-}\) in the upper respiratory tract of weaned beef calves. The experimental hypothesis was that the weaned beef calves administered a dose of NaI orally would secrete I\(^{-}\) in the upper respiratory tract secretions greater than the calves not administered NaI.

Material and Methods
Sixteen weaned commercial beef calves (average weight 270.5 kg ± 18.2 kg and age 291 ± 15.9 days) were selected from the University of Missouri, College of Veterinary Medicine teaching herd. The group consisted of four steers and twelve heifers. The cattle were housed at the College of Veterinary Medicine Middlebush Teaching Farm and sample collection occurred through standard cattle processing facilities on site. Each animal was uniquely identified by means of plastic ear tags, both farm assigned and project specific identification. The animals were fed, watered, and cared for in accordance to standard farm protocols. In addition, they were monitored for indications of iodine toxicity. Animal use and methods were approved by the University of Missouri Animal Care and Use Committee, protocol number 8207. Calves were divided into two groups of eight animals each, control and treatment, by random number generator\(^{a}\). The two groups were maintained in the same herd and pasture. Both primary investigators were blinded to treatment and control groups throughout the study period. The treatment group received a single dose of 70 mg/kg, 200 mg/ml (20\%) NaI\(^{b}\), by ororumen intubation. The control group received an equivalent volume of water.
Samples were collected immediately prior to administration of treatments, T<sub>0</sub>, then every 12 hours for 72 hours. Samples collected included blood and nasal secretions. Basic physical exams consisting of temperature, heart rate, respiratory rate, rumen auscultation, and general visual inspection of the cattle were performed at each sample time point. Nasal fluid was collected from all calves by use of a modified 1 mL serologic pipette<sup>c</sup> attached to a sample collection tube<sup>d</sup> and a vacuum pump. Samples were stored at -20 °C until final processing on all samples could be performed. Dithiothreitol, DTT<sup>e</sup>, was used to prepare nasal secretion samples for iodine quantification similar to the method described by Popov et al.<sup>45</sup> Blood samples were collected by jugular venipuncture into 10 mL serum separator vacutainer blood tubes<sup>d</sup>. Blood samples were centrifuged at 1,500 x g for 30 minutes at 4 °C. The serum sample was harvested and stored at -20 °C until analysis. The nasal secretions and serum were submitted to the Michigan State University Diagnostic Center for Population and Animal Health and analyzed by inductively coupled plasma – mass spectroscopy.

**Statistical Analysis**

Descriptive statistics of body weight and age were performed (previously reported) on the two groups. The levels of iodine measured in blood and nasal secretions were analyzed and graphed by SigmaPlot<sup>f</sup>. A Repeated Measures Analysis of Variance (ANOVA) on ranks was performed on all parameters of the study (iodine concentration, heart rate, rectal body temperature, and respiratory rate) in which the independent variable was treatment group and the dependent variable was parameter of interest; iodine concentration, heart rate, respiratory rate, or temperature. Tukey’s post hoc analysis was applied between groups and treatment time points.
Results

Both groups had no significant difference in serum I\(^-\) concentrations at T\(_0\), approximately 0.04 mg/L (0.3152 \(\mu\)M), \(p\) – value 0.999. After NaI administration, the serum I\(^-\) concentrations of the treatment group were significantly increased, \(p\) - value < 0.001, at each collection time point beginning with T\(_{12}\) through the final collection time point of T\(_{72}\) post NaI administration (Figure 1). The ANOVA model for serum I\(^-\) determined statistical significance of treatment groups, time point, and the interaction between group and time point, \(p\) – values < 0.001. The highest measured serum I\(^-\) concentration was 105.89 mg/L (834.4 \(\mu\)M); then, serum I\(^-\) concentration steadily declined during the remainder of the study period. During the 72 hour study period, at each collection time point, the control group did not have a significant change in serum I\(^-\) concentration. Both groups had no significant difference of I\(^-\) concentrations at T\(_0\) in nasal secretions: control 0.915 mg/L (7.21 \(\mu\)M) and treatment 0.529 mg/L (4.17 \(\mu\)M), \(p\) – value 0.968. The concentration of I\(^-\) in the nasal secretion was significantly increased, \(p\) < 0.001, after administration of a NaI oral bolus (Figure 2). The ANOVA model for nasal I\(^-\) determined a statistical significance of treatment groups, time point, and the interaction between group and time point, \(p\) – values < 0.001. At the T\(_{12}\) sample collection time point, the treatment group had a significantly higher I\(^-\) concentration of 180.743 mg/L (1,424.25 \(\mu\)M) in the nasal secretions that remained significantly different throughout the 72 hour study period of the treatment group. The I\(^-\) concentration of nasal secretions steadily declined during the study period. The control group nasal secretion I\(^-\) concentration did not change throughout the study period. There was not a significant difference in heart rate between the two groups, \(p\) – value 0.068 or group by time point interaction, \(p\) – value 0.123. Time point was statistically significant as there was a
statistically significant difference in heart rate at the $T_0$ and $T_{48}$ measurements, $p$ – value 0.022 and 0.01, with the control group greater than the treatment group (Table 1).

Physical exam findings for temperature and respiratory rates between the two study groups were not statistically different (Tables 2 & 3, respectively). The group by time interactions were not statistically different either, $p$ – value 0.229 for temperature and 0.915 for respiratory rate. A statistically significant difference was noted between time points for temperature, $p$ – value < 0.001. Similarly, a statistically significant difference was observed between time point in respiratory rate, $p$ – value 0.006. Throughout the study period, evidence of I\textsuperscript{3} toxicity was not observed during routine physical exams and sample collection. Herd caretakers did not report concerns of any health abnormalities during or immediately after the study period.
CHAPTER 3: FIELD TRIAL

Objective and Hypothesis
The objective of the field trial was to determine if the administration of a single bolus of oral NaI at the time of arrival and processing at a background feedlot operation would significantly reduce morbidity and mortality associated with bovine respiratory disease. The experimental hypothesis was that two hundred to three hundred pound calves administered NaI & meloxicam orally would have reduced morbidity and mortality compared to calves that received either NaI, meloxicam, or no treatment.

Material and Methods
Six hundred twenty-nine, 300 pound, auction market beef calves were purchased from Florida and received at a backgrounding operation in northeast Oklahoma on two different arrival dates. The calves were primarily bull and steer calves, transported approximately 40 hours, and considered ultra-high risk for BRD. All the calves were processed upon arrival. Processing included the following: vaccination either by subcutaneous and/or intranasal administration of a modified live pathogen 5-way vaccine consisting of M. haemolytica, BVD Type I & II, BHV – 1, PI – 3, BRSV, and Clostridium toxoid with tetanus. An injectable anthelmintic was administered subcutaneously. An ear notch was collected for BVD persistent infection testing. An estradiol growth implant was placed as described by the manufacturer. Bull calves were castrated by California bander technique. A factorial study design was implemented for the determination of the stated hypothesis. Four treatment groups consisted of a control group, an oral NaI group, an oral meloxicam group, and an oral NaI and meloxicam group.
Oral medications were dosed based on an average body weight for the group. Meloxicam\textsuperscript{h} was administered at a dose of 1 mg/kg. A 9 mg/mL suspension of meloxicam in a 1.5 % solution of carboxymethylcellulose was administered via oral dose syringe. NaI was administered at 70 mg/kg via oral dose syringe. The administration of NaI and Meloxicam orally to food producing animals is an extra-label use of these medications. Group assignments were generated by random number generator\textsuperscript{a} based on chute order for each arrival group. Farm personnel were blinded to treatment group assignments. The primary investigators were blinded to intervention and outcomes until the end of the study period.

At the backgrounding operation, morbidity and mortality were determined and assessed at least once a day. Calves refusing to eat at the time of feed delivery were pulled from the pastures for further assessment. Rectal temperature was obtained and animals were examined and assessed by farm personnel. Affected animals were treated based on clinical signs. Antibiotics are administered based on farm protocols and under the advisement of a veterinarian. The end of the study period was 90 days after the first group arrived.

**Statistical Analysis**

A logistic regression analysis was performed on the four study groups. Statistical analysis was based on frequency of mortality events. Significance of arrival date and gender at arrival were also analyzed. SAS\textsuperscript{h} was implemented to analyze the data of the study.
Results

All of the animals received were enrolled in the study. Of these 629 calves, 84 died during the study period. The significant variables in the model were treatment group, arrival date, and sex on arrival as described in Table 4. The gender composition of the group was 460 bull calves, 168 steers, and 1 heifer. Based on the output, each treatment group had an increased risk of mortality compared to the control group (Table 4). The combined Meloxicam and NaI group was 1.886 times more likely to experience a mortality event. The Meloxicam group was 1.365 times more likely to experience a mortality event compared to the control group. The NaI group was 1.815 times as likely to experience a mortality event compared to the control group. The first arrival group was 43.9% less likely to experience a mortality event compared to the second arrival group. Similarly, steer calves on arrival were 42.5% less likely to experience a mortality event compared to bulls that were castrated at processing.
CHAPTER 4: DISCUSSION

Pilot Study

The pilot study demonstrated that beef weanlings are capable of secreting I\(^-\) in the upper respiratory tract after a single bolus of oral NaI. The highest measured nasal I\(^-\) concentration was 180.743 mg/L (1,424.25 \(\mu\)M). These results are similar to those previously reported in both humans and sheep.\(^{35,37}\) In previous studies HOI\(^-\) was measured directly. In the presented study, the presence of I\(^-\) was measured as inorganic I\(^-\) as a proxy measurement of HOI\(^-\) in the nasal secretions of calves. This was done similar to previously reported methods.\(^{35}\) HOI\(^-\) is formed by the reaction of H\(_2\)O\(_2\) and I\(^-\) (catalyzed by LPO oxidation) identically to OSCN\(^-\) formation. Compared to OSCN\(^-\), HOI\(^-\) is considerably virucidal as well as antibacterial. In ovine models, both respiratory syncytial virus and adenovirus were rapidly inactivated by HOI\(^-\).\(^{37}\) The proposed mechanism of action of HOI\(^-\) is that it modifies the surface proteins of the virus.\(^{35}\) These changes can inhibit binding and/or entry of the virus into the host cells.\(^{43,44}\)

NaI has been used for the treatment of various infectious diseases in cattle since the beginning of the last century. Traditionally, NaI is administered as an intravenous bolus at a dose of 70 mg/kg. Signs of I\(^-\) toxicity can be observed at this dose, especially when multiple doses are administered for treatment. These symptoms include any degree or combination of the following: anorexia, salivation, diarrhea, excessive coughing, nasal discharge, pneumonia, lacrimation, epiphora, alopecia, dermatitis, scaly hair coats, and hyperthermia. I\(^-\) toxicity usually resolves when the I\(^-\) source is removed and clinical signs diminish over a period of two to three days without long term affects.\(^{23,25,32}\)

When considering an antimicrobial for administration in food animals, the effect on the animal and consumable product must be acknowledged. First and foremost is the
affect the treatment has on the animal’s health. In this study, there were no clinical signs or measurable abnormalities as a result of the administration of oral NaI at the dose administered. The only significant change between the two treatment groups were the heart rates at T₀ and T₄₈ when the treatment group heart rates were significantly lower than the control, 145 beats per minute (bpm) versus 166 bpm and 104 bpm versus 128 bpm, respectively. Both of these values are greater than the standard heart rates of cattle. These heart rates were taken immediately upon entry to the processing chute and are likely attributable to physiological responses associated with handling. While these were statistically significant, the biological significance is not yet determined. Secondly, there is concern as to the effect on the consumable tissues and potential harmful medication residues. I⁻ toxicity through food animal sources could present a potential risk to human health. Most of the soil throughout the world is considered I⁻ deficient. Currently, table salt is iodized to help prevent the occurrence of I⁻ deficiency in people. Recent investigations into the I⁻ content of food products determined that beef is not a significant source of I⁻ to humans (< 2% of requirements), even when the animal is fed chronic doses above natural homeostatic iodine requirements.

**Field Trial**

Many different interventions and processes have been implemented for arrival procedures to feedlots. In the field trial, four study groups were used. A control group that received the standard practices of arrival procedures. The remainder of the treatment groups received the same baseline treatment as the control group. The second group received NaI to determine its viability as a preventative for BRD. The third study group received meloxicam, a non-steroidal anti-inflammatory drug (NSAID), which is
becoming more widely used within the cattle industry for the alleviation of inflammation and pain. As pneumonia and castration both induce inflammation, the administration of meloxicam reduces the morbidity associated with the medical events. Both NaI and meloxicam were administered together to the fourth group to determine if a beneficial or detrimental interaction would occur with the co-administration of the two medications.

The backgrounding operation experienced unusually high morbidity in both arrival groups. Mortality reached a critical threshold within a couple of weeks of arrival that resulted in the administration of mass treatment of calves with antibiotics to mitigate disease. Because of this, the morbidity portion of the field trial was abandoned. The mortality events became the study variable of analysis.

Of the four study groups, the control group had the lowest frequency of mortality. The three treatment groups had similar odds ratios of mortality. While the exact cause of the relative increase in mortality may not be definitively known, there are possible explanations. One possibility is that the administration of NaI inhibited the production of a successful immune response to the vaccinations administered. A potential reason for this may be that the modified live viruses in the vaccines administered to the calves were inactivated by the formation of the HOI. A second possibility is that the oral dosing syringes served as a fomite among the calves. Since all of the calves that received a treatment had the dosing syringe placed in their mouth to deliver the medications, it is plausible that a pathogen was transmitted iatrogenically. Finally, the volume of NaI administered was 50 mL based on the calves’ average body weight. This volume may not have entirely gone into the gastrointestinal tract of the calves. Several calves immediately coughed a portion of the dose out upon administration. This resulted in a decreased
dosage for these individual calves. Thus, the potentially protective qualities of HOI would be diminished. This also indicates that some of the dose(s) may have been administered inadvertently into the respiratory tract which may have induced an inflammatory response or overwhelmed the respiratory defenses. Necropsy and histopathology were not recorded or performed. Post mortem examination may have yielded further explanation to the outcomes, similar to previous studies.\textsuperscript{37} Previous reports indicated similar clinical signs of respiratory disease such as coughing, sneezing, and nasal discharge between groups administered and not administered oral iodine. Interestingly, the histopathologic lesions were significantly reduced in number and severity in the group that received iodine compared to control calves. while our results are contrary to those reported, determining the differences would be beneficial to further investigating BRD and iodine’s affect in the bovine respiratory tract. In regards to the odds ratios of steers being less likely to experience a BRD event compared to bulls, this is currently the industry standard. As such, the standard of castration prior to marketing or feedlot arrival is based on similar observations. The significant differences between arrival dates could be due to variations in weather or the degree of fluctuation between weather extremes. The calves originated from Florida with an average temperature (min – max) in degrees Fahrenheit of 72 (63 – 81) and 72 (66 – 77) on the first and second arrival dates, respectively. The average temperature (min – max) in degrees Fahrenheit of the arrival facility in northeast Oklahoma was 71 (57 – 85) and 55 (42 – 67) for the first and second arrival dates, respectively. With such variation between environments, the stress encountered likely induced a weakened immune system that could not protect the calves against a BRD incident.
The pilot study indicated that I\(^-\) can be secreted by the upper respiratory tract. In vitro data indicates that HOI\(^-\) can inhibit some of the common pathogens of BRD, specifically BHV – 1, PI – 3, *M. haemolytica*, and *Bibersteinia trehalosi*.\(^{47,48}\) Potential remedies for the downfalls of this study observed in the field trial are to use oral NaI in conjunction with other antimicrobials or immune modulators as treatment for BRD. If NaI can be administered as a capsule or non-aqueous solution (in a granular form), there may be benefit as a preventative by reducing the volume delivered to oropharynx. This however would not remedy the inactivation of vaccines that are administered concurrently to oral NaI. Based on the results of this study, particularly the field trial, the use of oral NaI in a preventative manner on arrival to feedlots should not be implemented until further investigation and evaluation can be performed.
Figure 1: Iodine Concentration in Serum. The serum iodine concentration of treatment (NaI) and control (water) groups. At T₀, grouping markers overlap. The highest measured concentration of iodine was 105.89 mg/L (834 μM). Standard Error of the Mean bars graphed. * indicates a significant difference at p < 0.001 between control and treatment groups at individual time point.
Figure 2: Concentration of Iodine in Nasal Secretions. The concentration of iodine in nasal secretions of the treatment (NaI) and control (water) groups. At T₀, grouping markers overlapping. The highest measured concentration of iodine was 180.743 mg/L (1,424 μM). Standard Error of the Mean bars graphed. * indicates a significant difference at p < 0.001 between control and treatment groups at individual time point.
### Group vs. Time Point Heart Rate

<table>
<thead>
<tr>
<th>Time Point (hours)</th>
<th>Treatment Group</th>
<th>Control Group</th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average (bpm)</td>
<td>Average (bpm)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Confidence Interval</td>
<td>Confidence Interval</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>145 (135, 155)</td>
<td>166 (145, 187)</td>
<td>0.022</td>
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<tr>
<td>12</td>
<td>94 (81, 107)</td>
<td>105 (91, 118)</td>
<td>0.24</td>
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<tr>
<td>24</td>
<td>106 (90, 122)</td>
<td>112 (102, 121)</td>
<td>0.538</td>
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<tr>
<td>36</td>
<td>96 (87, 105)</td>
<td>103 (93, 113)</td>
<td>0.576</td>
</tr>
<tr>
<td>48</td>
<td>104 (91, 117)</td>
<td>128 (109, 148)</td>
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</tr>
<tr>
<td>60</td>
<td>82 (57, 108)</td>
<td>74 (62, 85)</td>
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</tr>
<tr>
<td>72</td>
<td>69 (50, 89)</td>
<td>70 (61, 78)</td>
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</tr>
</tbody>
</table>

Table 1: Pilot Study Repeated Measures Analysis of Variance Group versus Time Point with heart rate as dependent variable. Average beats per minute (bpm) with associated 95% confidence intervals presented. p – values considered significant at p < 0.05.
**Table 2: Pilot Study Repeated Measures Analysis of Variance Group versus Time Point with respiratory rate as dependent variable. Average breaths per minute (bpm) with associated 95% confidence intervals presented. p – values considered significant at p < 0.05.**

<table>
<thead>
<tr>
<th>Time Point (hours)</th>
<th>Treatment Group</th>
<th>Control Group</th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average (bpm)</td>
<td>Confidence Interval</td>
<td>Average (bpm)</td>
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<td>(69, 87)</td>
<td>79</td>
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<tr>
<td>12</td>
<td>73</td>
<td>(65, 81)</td>
<td>68</td>
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<tr>
<td>24</td>
<td>62</td>
<td>(51, 73)</td>
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</tr>
<tr>
<td>36</td>
<td>80</td>
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<td>80</td>
</tr>
<tr>
<td>72</td>
<td>82</td>
<td>(61, 102)</td>
<td>78</td>
</tr>
<tr>
<td>Time Point (hours)</td>
<td>Treatment Group</td>
<td>Control Group</td>
<td>p - value</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------</td>
<td>---------------</td>
<td>-----------</td>
</tr>
<tr>
<td></td>
<td>Average (°F)</td>
<td>Confidence Interval</td>
<td>Average (°F)</td>
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<tr>
<td>0</td>
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<td>103.8</td>
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<tr>
<td>12</td>
<td>104.7</td>
<td>(103.9, 105.5)</td>
<td>105.3</td>
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<td>24</td>
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<tr>
<td>36</td>
<td>104.7</td>
<td>(104.1, 105.3)</td>
<td>104.6</td>
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<tr>
<td>48</td>
<td>103.4</td>
<td>(102.8, 103.9)</td>
<td>103.4</td>
</tr>
<tr>
<td>60</td>
<td>104.1</td>
<td>(103.6, 104.7)</td>
<td>103.9</td>
</tr>
<tr>
<td>72</td>
<td>102.7</td>
<td>(101.9, 103.5)</td>
<td>102.8</td>
</tr>
</tbody>
</table>

Table 3: Pilot Study Repeated Measures Analysis of Variance Group versus Time Point with temperature as dependent variable. Average temperature in degrees Fahrenheit with associated 95% confidence intervals presented. p – values considered significant at p < 0.05.
<table>
<thead>
<tr>
<th>Effect</th>
<th>Point Estimate</th>
<th>95% Wald Confidence Limits</th>
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<tbody>
<tr>
<td>Treatment: Meloxicam &amp; Iodine vs Control</td>
<td>1.886</td>
<td>0.943</td>
</tr>
<tr>
<td>Treatment: Meloxicam vs Control</td>
<td>1.365</td>
<td>0.665</td>
</tr>
<tr>
<td>Treatment: Iodine vs Control</td>
<td>1.815</td>
<td>0.903</td>
</tr>
<tr>
<td>Arrival Date: 1&lt;sup&gt;st&lt;/sup&gt; Arrival vs 2&lt;sup&gt;nd&lt;/sup&gt; Arrival</td>
<td>0.439</td>
<td>0.269</td>
</tr>
<tr>
<td>Sex: Steer vs Bull</td>
<td>0.425</td>
<td>0.223</td>
</tr>
</tbody>
</table>

Table 4: Field Trial Odds Ratios of Statistical Model
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