New Approaches to Bovine Respiratory Disease Prevention, Management and Diagnosis

July 30-31, 2014
Denver, CO

PROCEEDINGS

Held in conjunction with the Academy of Veterinary Consultants Summer 2014 meeting
Bovine Respiratory Disease Symposium 2014:
New Approaches to Bovine Respiratory Disease Prevention,
Management and Diagnosis

July 30-31, 2014
Renaissance Denver Hotel
Denver, CO

PROCEEDINGS

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Welcome From the BRD Symposium 2014 Organizing Committee

Welcome to the Bovine Respiratory Disease Symposium 2014: New Approaches to Bovine Respiratory Disease Prevention, Management and Diagnosis! As those in attendance know well, bovine respiratory disease (BRD) exerts a major impact on the well-being and productivity of cattle. This year’s Symposium presents an important opportunity for veterinarians, scientists, educators, producers and policy makers to come together to review the state of the art in research and management related to this disease. It is our hope that the Symposium presentations and breakout sessions will illuminate how the latest BRD research findings and emerging management technologies can be translated into industry practice to improve the health of beef and dairy cattle. We are pleased to announce that the Symposium has been approved for 12 continuing education units (CEUs) for the American Registry of Professional Animal Scientists (ARPAS) and 12.5 CEUs for K-State College of Veterinary Medicine Veterinary Medical Continuing Education. Information about how to claim CEUs for this event can be found in your welcome packets.

The Symposium has been organized through the efforts of members of the USDA Multistate Research Project NC-1192, “An Integrated Approach to the Control of Bovine Respiratory Disease”, and the USDA NIFA AFRI “Integrated Program for Reducing Bovine Respiratory Disease Complex (BRDC) in Beef and Dairy Cattle” Coordinated Agricultural Project (BRDC-CAP). Thanks go to the Academy of Veterinary Consultants, whose leadership has been generous in sharing information and assistance during the planning of the Symposium. Many thanks to Linda Hoffner and the staff at Frosch, who have been tireless in their attention to details related to the organization of registration, travel and meeting logistics. Amy Young of the Department of Animal Science at UC Davis deserves special recognition for her astounding efficiency and competence in communicating with speakers, organizing conference calls, and dealing with innumerable issues related to Symposium planning. We would also like to acknowledge the USDA NIFA Agriculture and Food Research Initiative (AFRI) Competitive Grants Program, which provided support through a conference grant. Additional support was provided by the BRDC-CAP and the American Association of Bovine Practitioners. Thanks also to our generous sponsors who are listed on the next page.

And lastly, thanks to those of you in attendance. We are confident that BRD Symposium 2014 will provide a forum for a variety of fruitful interactions that positively impact bovine health and productivity. These interactions wouldn’t be possible without your participation.

Sincerely,
The BRD Symposium 2014 Organizing Committee
Sponsors

Platinum Level

Gold Level

Bronze Level

Friend Level

AABP Beef Health Management Committee

BRDS 2014 is presented with support from:

Multistate Research Project NC-1192, “An Integrated Approach to the Control of Bovine Respiratory Disease”
## Wednesday, July 30

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Thursday, July 31

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8:30 – 9:00 AM Pathogen Variation across Time and Space: Sequencing to Characterize *Mannheimia haemolytica* Diversity – Dr. Michael Clawson
9:00 – 9:30 AM Effect of Stress on Microbial Growth – Dr. Mark Lyte
9:30 – 10:00 AM Questions and Discussion – led by Dr. Brian Vander Ley
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F. LABORATORY DIAGNOSIS AND THERAPEUTIC CONSIDERATIONS – Moderator Dr. Carol Chitko-McKown
10:15 – 10:45 AM Strengths and Weaknesses of Current Approaches to Diagnostic Testing – Dr. Robert Sprowls
10:45 – 11:15 AM Prospects for Diagnosis by Sequencing – Dr. Andrew Benson
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G. MANAGEMENT/TRANSLATIONAL CONSIDERATIONS – Moderator: Dr. Dale Grotelueschen
1:30 – 2:00 PM Evidence-Based Approach to Improving Immunity to Manage Cattle Health – Dr. D.L. Step
2:00 – 2:30 PM Field Epidemiology to Manage BRD Risk in Beef Cattle Production Systems – Dr. David Smith
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Notes:
BRD in 2014 – Where have we been, where are we now, and where do we want to go?
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Abstract
Bovine respiratory disease (BRD) is a worldwide health concern and is the number one disease of stocker, backgrounder and feedlot cattle in North America. In feedlots in the United States, BRD accounts for 70-80% of all feedlot morbidity and 40-50% of all mortality. In 2011, the United States Department of Agriculture's National Animal Health Monitoring System (NAHMS) conducted a feedlot study that showed 16.2% of all feedlot cattle were treated for BRD. It is universally accepted that this number is distressingly high and that our industry has the tools available to reduce the incidence of BRD.

Bovine Respiratory Disease
BRD is a disease of the lower respiratory tract of cattle that is multifactorial in origin and results in bronchopneumonia. Typical viral pathogens are: Infectious Bovine Rhinotracheitis, Bovine Viral Diarrhea, Parainfluenza 3, and Bovine Respiratory Syncytial virus; while bacteria include: Mannheimia haemolytica, Pasteurella multocida, Histophilus somni, and Mycoplasma bovis. There may be other pathogens involved, but these are the most cited (Cusack, 2003).

Risk factors to BRD include: weaning, surgical procedures at or near weaning, lack of immunity via vaccine or natural exposure, changes in diet – especially abrupt changes to a high starch diet, pooling of cattle from many sources, continuous additions of cattle to the pen, purchasing from sale barns, transportation, dusty conditions, parasitism, concurrent diseases, and weather extremes (Taylor, 2010). Exposure to pathogens from other cattle is frequently mentioned as a risk factor and the viral pathogens listed above are highly contagious, but this is not true for all of the bacteria. Recent work by Timsit (Timsit et al, 2013) and Taylor (personal communication, 2014) indicate that during BRD episodes, disease due to Mannheimia haemolytica and Pasteurella multocida is not primarily due to the spread of a single virulent clone among cattle and highlights the importance of predisposing factors such as viral infections, shipping, comingling, etc. that enable the resident flora to overcome the cattle's immune system. In these studies, the bacteria recovered were for the most part resident flora of the calves retropharyngeal lymph node and tonsil.

When a calf succumbs to BRD it is most likely due to an accumulation of errors earlier in life. One or numerous “stressors” listed above results in a compromised immune system that may or may not have been adequately protected from viral and/or bacterial challenge with vaccine and/or natural challenge. The immune system is overwhelmed, the resident bacterial normal flora invades the lung and sickness occurs.
Programs such as the preconditioning of calves – weaning calves at the farm of origin and feeding for a minimum of 30 days (45 days or more is highly recommended), vaccinating against BRD pathogens, training calves to eat from a bunk and drink from a tank, deworming and performing all surgeries well ahead of weaning – have shown to dramatically decrease morbidity and mortality if calves are shipped to a feedlot that purchases most/all preconditioned calves (Taylor, 2010; Cravey, 1996). If a pen of preconditioned calves is placed in a feedlot filled with unweaned, unvaccinated, high-risk calves with other risk factors mentioned above, the chances are great that the preconditioned calves will have morbidity and mortality rates similar to the high-risk calves that are also in the environment. Contagious viral pathogens can overwhelm the preconditioned calf’s immune system and the cascade of events that initiated BRD in the high-risk calves can also distress the preconditioned calves.

The vaccines available to prevent BRD continue to improve. We now have viral vaccines with Type 2 BVD and Type 1b BVD, which is the most prevalent strain found in morbid North American feedlot cattle. Current bacterins to the most common BRD pathogens have evolved and improved over the years similar to our viral products. We have also added ancillary treatments such as flunixin meglumine to our protocols, (NAHMS, 2000), but the fact remains that we have a higher incidence of BRD in the feedlot than we had 20 years ago. NAHMS data from 1994, 1999 and 2011 shows BRD deaths increasing from 10.3 to 14.2 to 16.0 per 1000 head placed (Loneragan, 2001). In 2011, we fed 25,747,000 cattle in the US and 1.6% or 411,952 cattle died of BRD. Zero mortality is impossible, but what is a reasonable number? Surely we can do better than 1.6% mortality.

Edwards sums up the current state of affairs in his chapter on BRD in the 2010 *Vet Clinics of North America*: “Although there have been aggressive advances in the technology of vaccine, antimicrobial, and antiinflammatory agents, these products are merely tools intended to assist in the prevention and control of BRD. Despite these advances, morbidity and mortality rates among feedlots has not declined. We cannot overlook the affect that sound animal care and husbandry practices have on the health and performance of cattle. It is highly unlikely that control of BRD in the feedlot can be accomplished through an on-arrival vaccination program. Therefore, the initial effort for developing a competent immune system must be initiated at the cow-calf level and carried through each sector of the production chain.” (Edwards, 2010)

**Why Do We Have Increased BRD in the Feedlot?**
Just as BRD is a multifactorial disease, the answer to the above question has many facets. Our differential list of why BRD is increasing includes: younger cattle with less immunity being placed into the feedlot environment; increased viral exposure due to larger numbers of cattle in the pens; more cattle moving through multiple marketing channels and, due to extremely high prices, more unweaned, unvaccinated cattle being marketed.

**Prevention of BRD**
Metaphylaxis
Metaphylaxis or mass medication during the incubation period of the disease of feedlot cattle has been a well-documented way to decrease morbidity and mortality due to BRD in “high risk” cattle. The 2011 NAHMS feedlot survey estimated that 21.3% of all cattle entering the feedlot undergo metaphylaxis while in 2000 it was only 10.4% (NAHMS, 2000). While quite effective, is this the complete answer? Will this satisfy the consumer when we see that the number one concern of the 2011 beef audit is food safety (NCBA, 2012)? I think we need to do even better yet.

What if McDonald’s or Wal-Mart decides not to purchase cattle that were given antibiotics at feedlot entry instead of using best management practices before arrival? Who among us can defend the practice of taking unweaned, unvaccinated calves and hauling them sometimes hundreds of miles and placing them in a new environment with hundreds of other similarly naïve calves? Our cattle deserve better and we can surely provide better care.

In the US Department of Agriculture’s NAHMS 2011 Feedlot Study, feedlot operators were asked about the importance of pre-arrival management practices like weaning at least four weeks prior to shipment, use of respiratory vaccines before or at weaning, calves castrated and dehorned at least four weeks prior to weaning, introduction to feedbunk and calves treated for external and internal parasites prior to shipping on the effectiveness of reducing morbidity and mortality. An average of 81.5% answered that these practices were extremely or very effective in reducing sickness and death loss in feedlot cattle.

When asked about the importance of having pre-arrival processing information, 69.3% of feedlot managers said this was “very important”. However, when asked how often the feedlot receives this information, only 34.7% responded “always” while 56.2% responded “sometimes”. This is another area where we must do better (USDA, 2013).

**Preconditioning**

Why are we continuing to discuss a subject that has shown promise in preventing BRD for over 50 years? Some of the reason is due to initial studies that showed it was not cost-effective for the cow-calf producer to precondition calves before sale. Many of these studies had daily gain well below what cattle should gain on a preconditioning ration and some showed a much higher morbidity and mortality rate at the farm of origin (cow-calf herd) than was seen in later trials. Others only focused on the preconditioning “premium” and totally neglected the much larger profit made in the efficient weight gain of newly weaned calves (Cravey, 1996). Another reason not everyone is on board with preconditioning is that buyers of “cheap calves” can at times add tremendous value to these calves in the right circumstances. Of course, other times these high risk calves are the source of large financial losses.

In 2008 it was estimated that only 33.6% of all calves marketed were sold after being weaned for 32 or more days (USDA, 2010). If we as a profession want to encourage the production of more preconditioned calves, staging a boycott of purchasing high risk calves would probably not work on an industry-wide basis. We have all heard stories of feedlot clients that have made a large profit on a group of high risk cattle despite a high morbidity rate. A long-time cattle
feeder once told me that “bought right is half sold” and I have never forgotten that. Cheap calves can become highly profitable. Our goal should be to continue to show the value of preconditioning to our clients so they produce less and less “cheap calves”. In an 11-year study of a herd in Indiana, the owner returned $80.70/head to labor and management for preconditioning calves for 63 days with 63% of the added profit due to additional weight sold. In our study, the owner’s wage for his time spent with preconditioning/backgrounding was $54.74-130.22 per hour (Hilton, 2011). It is my opinion that instead of always discussing the buyer-dependent “preconditioning bonus”, we need to highlight the profit from additional pounds sold and profit per hour for the enterprise which is seller dependent.

**What do we need to do to decrease BRD incidence in cattle?**
I have broken down some ideas into three areas relating to the impact of significantly decreasing the incidence of BRD in North America.

**Questionable Impact**
- Develop new BRD vaccines and/or bacterins to give at feedlot entry
- Develop new and longer-acting antibiotics

**Potential Impact**
- Increased study on micronutrients that are important for immune function
- Improve preweaning nutrition of calves
- Discover new viral or bacterial pathogens that cause BRD
- Develop new BRD vaccines and/or bacterins to be given well before entering marketing channels
- Discover genetic components of BRD susceptibility

**Likely Impact**
- Improve immunity of calf before it arrives at feedlot
- Increase age of cattle at feedlot entry
- Feed more calves to slaughter at farm of origin eliminating co-mingling
- Decrease number of high-risk calves entering marketing channels
- Perform all surgeries at farm of origin
- Demand by retailers for beef from preconditioned calves based on enhanced animal welfare

**Summary**
Despite many advances in prevention and treatment of BRD, morbidity and mortality due to BRD have increased over the past 20 years. Our current antibiotics and vaccines are superior to those used many years ago, and the addition of ancillary therapies to the use of injectable antimicrobials for treatment of BRD seems equivocal at best. The many known risk factors, not therapeutic failure seem to be the most important reasons for explaining an increased incidence of BRD in the feedlot.
While we have seen some advances in prevention of BRD, we still have morbidity and mortality rates due to BRD that most experts would concur are too high. Prevention of BRD must begin at the cow-calf level and producers need to closely examine the benefits of programs like preconditioning. Selling calves at heavier weights where the additional pounds are added in a cost-effective manner can add significant income to the producer’s business. Benefits of feeding preconditioned calves in the feedlot include: decreased morbidity and mortality, improved animal welfare, decreased use of antimicrobials, and increased profitability for the feedlot.

References
The Impact of Bovine Respiratory Disease: the current feedlot experience  
Michael Engler, Ph.D.\textsuperscript{1,2}, Paul Defoor, Ph.D.\textsuperscript{3}, Carter King, DVM\textsuperscript{4}, Justin Gleghorn, Ph.D.\textsuperscript{5}  
Cactus Feeders, Inc.  
Amarillo, Texas

Abstract  
Mortality during the finishing phase in beef steers has increased over the last 13 years at a rate of 0.05% per year for cattle fed in Cactus Feeders’ operations. A change in the demographics of placements has also occurred; in that heavier weight cattle are being placed as compared to previous years. Morbidity rates are lower, but higher case fatality rates are observed when compared to years when lighter weight cattle were placed. More lung lesions of varying degree are documented at necropsy of new arrivals and there is greater perception of reduced response to therapy in animals identified with respiratory disease. As placement weights have increased, mortality in the early stages of the feeding period has decreased, resulting in a greater proportion of total death loss later in the period. This shift, in conjunction with an increasing long term trend of total death loss, can lead to the interpretation of higher “late day mortality”. Rather than relying solely on observation and distributions of the data, Cactus Feeders believes that the development of a predictive model is better suited to address the potential of ‘late day mortality’ in confined cattle feeding operations.

I. Survey of Mortality Trends over Time  
A. Recent Mortality Trends  
Cactus Feeders’ internal data from 2001 through 2013 indicates an upward mortality trend in three weight classes of cattle: 600-wt, 700-wt, and 800-wt steers (Figure 1). Similar levels and trends are reported by USDA (2011) and Benchmark\textsuperscript{\textregistered} (G Vogel 2014, pers. comm., 5 June). Regression analysis of Cactus Feeders’ internal data indicates that mortality is increasing at a rate of 0.10%, 0.06%, and 0.04% per year for 600-wt, 700-wt, and 800-wt steers; respectively.

While the increasing trend is evident, careful attention must be given to variability in mortality across years and weight class of cattle. Cactus Feeders’ data indicate that mortality was observed at the highest level in 2012 (within the 13 year summary) for all three weight classes of cattle; especially evident in the 600-wt steers. This phenomenon may be explained by many factors, including: drought related immunity, cow-calf nutrition and environmental conditions. The effects of that single year had implications on the analysis of the trend data. When 2012 was removed from the regression analysis, the rate of increase for mortality across year for all three weight classes of cattle was 0.04% to 0.05% per year (Figure 2). Moreover, there is no clear pattern of when mortality occurred during the feeding period across years. That is, mortality occurs throughout the feeding period and whether it occurs at the beginning, middle or end of the feeding period is variable across years and weight class of cattle.
B. Economic Impact of Mortality Trends
The dynamic economic impact of increasing mortality is important to understand. Analysis of closeout data (2012 through May 2014) indicates that a one percent increase in mortality has a
$20.07 per head negative effect on the head marketed. Approximately 67% of the negative economic impact is accounted for in the increase in animal cost per head marketed. The remaining economic impact is reflected in the increased animal cost accrued for feed and daily charges; such as yardage and interest. The impact reflected in the increased costs per head marketed has risen approximately 98% since 2001. That is, using market prices in place in 2001, the effect of a one percent increase in mortality would increase the animal cost by $6.00 per head marketed. Using more current market prices, this same one percent increase in mortality will increase animal cost by $11.90 per head marketed. As market price increases, the economic impact of mortality is more largely explained by changes in animal cost; when reported on a per-head-marketed basis. As previously discussed, mortality has increased at a rate of 0.05% per year. At this rate, this represents a 0.50% increase in mortality rate over 10 years, which would cost approximately $1.00 per-head per-year.

As death loss has increased, we should address overall productivity changes across time. Regression statistics indicate that hot carcass weight has increased 4.9 lbs per year from 2001 through 2013 (600-wt, 700-wt, 800-wt steers), with initial weight and days on feed held constant at 200 days, 160 days and 140 days for the 600-wt, 700-wt, and 800-wt steers; respectively.

Trend data indicate that mortality rates are increasing. Cactus Feeders’ data also show an increase in hot carcass weight across time. While the increase in mortality has increased costs for cattle marketed, overall increases in productivity have been observed. This has largely been driven by increased production of saleable carcass weight (initial weight and days on feed held constant within weight class). However, our industry is tasked with balancing both the economic benefits of productivity and the ethical considerations of animal husbandry, and therefore should strive to make improvements in both health and productivity.

II. The Nature of BRD Mortality at Cactus Feeders
Bovine Respiratory Disease (BRD) continues to have a significant economic impact during the finishing phase of feeder cattle. In 2013 input costs associated with BRD labeled death loss is estimated to be $9.1 million, irrespective of feed costs, performance losses, and cattle realized during the feeding period. These losses accrued during the feeding period vary with risk level and placement weights, in addition to environmental conditions while on feed. Historically, from 2001 through 2011 there was a high degree of variability in our cattle in terms of risk level and arrival weight. During these years, losses attributed to BRD ranged from 65 – 70% of the total dead population. Morbidity rates of placements specific to respiratory issues varied from 6 – 8% and case fatality rates were 8 – 10%. In 2012 we began more consistently placing heavier cattle that had more growing time outside of the feedyard, such as in a backgrounding facility. This is evidenced by the increase in shipment numbers for 2013 (Figure 3), and today our arrival population continues to reflect this heavier placed animal. In 2013, 1.15 million cattle were shipped and closed in our operations. Of these, 45,405 animals were identified in pen as needing therapy for respiratory disease and consequently moved to a hospital for treatment. This represents a BRD morbidity rate of 3.95% for this placement population which would be expected with this lower risk class of animals. Of these pulls, 14.7% died and were
classified as respiratory deads at necropsy. During this same time period, losses attributed to respiratory disease were 55.6% of the total death loss that occurred. Based on arrival weight and risk level, a lower than historical morbidity rate was experienced; however, case fatality rates were higher during the same time period. Also, during this time death loss trended later in the feeding period than what was experienced in years past when placement weights were lighter and BRD morbidity rates were higher.

![Head Shipped](image)

**Figure 3.**

Although year-to-year comparisons of death loss are difficult to evaluate, we are experiencing an upward trend for total death loss; regardless of weight class or risk in our operations. With heavier placements today these losses tend to be distributed later in the feeding period. Over the past 25 years we have seen advancements in technologies that have provided us with a wealth of improvements in BRD prevention, control, and treatment strategies; as well as animal handling practices and laboratory diagnostics. Greater emphasis on Beef Quality Assurance has created opportunities for improvements in many areas of the production cycle. Yet today we see an increase in lung lesions of varying degree at necropsy in new arrivals and a perception of reduced response to therapy in animals identified with respiratory disease. We also are experiencing death loss shifting to later in the feeding period and we struggle to identify specific areas to measure improvement in health parameters. The impact of long standing drought also has far reaching effects. Reduced nutrition in pregnant dams potentially creates more immune compromised animals which impacts all phases from grazing to finishing. Those animals may survive until late in the finishing phase only to succumb to new challenges, both infectious and environmental, prior to harvest. The increased number of days with high heat and dust levels in recent years also has a negative impact on convalescence from illness and the ability of cattle with longer days on feed to recover in the cooler overnight hours. The impact of these observations is difficult to analyze in the absence of appropriate controls when seeking answers for increased case fatality rates and later day mortalities in our current population.
III. Late Day Mortality
There has been a great deal of discussion and debate recently regarding what some term “late day mortality”. While progress in the area of BRD still suffers from challenges related to diagnosis; among other things, the state of the science is such that, in broad terms we understand enough of the etiology to know how to greatly reduce the incidence and severity of the complex; and generally speaking have the tools to do so. It seems much of the energy around BRD discussions is, and should be, centered on understanding failures with respect to what otherwise should have been a “non-event”; cases where our preparatory strategies didn’t work.

In contrast, the study of late day mortality is at a stage where it still suffers from a lack of definition, as well as a lack of credible diagnosis; and almost certainly a lack of independence from success in the earlier stages of the feeding period. In terms of the distribution of mortality across the feeding period, the name itself compels one to compare shifts in distributions of death over time. For instance one might consider steers fed in a feedyard for 160 days and make a simple query of which quartile of the feeding period does the mortality tend to occur, and has that distribution changed over time? A perfectly even distribution would show 25% of the total mortality occurring in each of the four quarters over time. While very informative and interesting for beginning a study of late day mortality, the approach suffers from a lack of independence from improvements in BRD mortality in the first quarter of the feeding period for example. Improvements in one phase will be interpreted as regress in another phase.

The alternative approach of studying absolute values of late day mortality over time (instead of distribution changes), are likely also affected by successes or failures in the other stages of the feeding period; not through mathematical truisms as in the distribution approach, but through complex biological and environmental relationships. Tremendous population data resources and computing power exist today for creating knowledge of both early and late day mortality; and certainly those must be used to do so. However, escaping the necessity of a control to avoid misattribution is extremely difficult. We contend that the only chance to accomplish this with utility is through the creation of the predictive model. A predictive model disciplines the scientist and brings the appropriate credibility as it displays the residual fraction of late day mortality in this case, that can’t be explained by any known X-variable.

References
The Impact of BRD: The Current Dairy Experience
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Abstract
The primary source of data on the prevalence of Bovine Respiratory Disease (BRD) in adult dairy cattle in the United States is producer surveys carried out in important dairy states. Estimated percentage of cattle affected was 2.4-2.9%, which appears low when compared to calculations based on limited data on the number of on-farm deaths due to BRD and the number of carcasses at slaughter where severe BRD is diagnosed. Those calculations estimate that about 3% of dairy cows die on farm or are seen at slaughter with severe respiratory disease. One would have to add to those the cows that are treated for BRD on farm and stay in the herd.

The primary manifestation of BRD on dairy farms is in young calves. BRD and digestive disease are the main diseases calf raisers deal with. In the author’s experience, BRD is the major cause of death or culling in heifers between weaning and calving.

Nationwide surveys have estimated that 12.4-16.4% of preweaned dairy heifer calves are affected, and 5.9-11% of calves after weaning. More detailed prevalence studies have generally been on a limited number of small farms near a university, and limited in the age range studied. All studies rely on producer or manager recording of disease. Prevalence in these studies ranges from 0 to 52%. Median ages at onset show that many cases of BRD occur before weaning. BRD was associated with increased death rates of calves.

BRD affects heifer growth. It appears to have a small effect on age at first calving (AFC) of heifers and some studies have shown small effects on performance and herd life after calving. First lactation performance of heifers depends on many factors that can obscure the effects of calfhood BRD.

Case Definition
Bovine Respiratory Disease (BRD) must be defined in order to determine its prevalence and economic importance in the US dairy industry. Although there are other respiratory diseases, such as acute bovine pulmonary edema and emphysema, allergic reactions, lungworm, atypical interstitial pneumonia and calf diphtheria, BRD is commonly taken to mean pneumonia caused by an infectious agent, with inflammation, consolidation, and potential abscessation and fibrosis of the lungs. It can be caused by a number of pathogens, many of which are normal residents of the bovine respiratory tract.

Flöck (2004) enumerates some of the characteristics of the bovine lung that make cattle more susceptible to respiratory disease than other farm animals. In general, cattle have less effective pulmonary clearance mechanisms. Cattle have smaller gaseous exchange capacity and lower alveolar oxygen levels during exposure to high altitudes or high metabolic activity. Low oxygen tension can slow macrophage activity and decrease clearance of debris and pathogens.
Compartmentalization of the bovine lung makes cattle more prone to regional hypoxia due to occluded airways, which also results in reduced phagocytic activity and gives pathogens an opportunity to multiply.

In adult dairy cows, a diagnosis of pneumonia is often made when an animal looks sick, has a fever, and shows signs of labored respiration. She might cough and have a nasal discharge. Any cause of fever will generally cause a cow to breathe faster than normal. Many sick cows will stop licking their nose and show an accumulation of mucus in the nostrils. Cows pant and may have elevated body temperature in hot weather. Bovine lung sounds are hard to interpret and faster breathing generally increases the volume of lung sounds. Auscultation is often done in a noisy environment on the farm. True crackles and rhonchi are not heard very often in cattle; “harsh” lung sounds may just be the result of tachypnea. So cows with fever that does not have another obvious cause will often be treated and recorded as pneumonia. Cows with emphysema will present with respiratory distress, especially in hot weather, but may not have a BRD infection. Necropsy or carcass inspection at slaughter would give a definitive answer on whether there was inflammation of the lungs, but most dead cows do not get necropsied and slaughter lesions are rarely reported back to the farm.

Calf raisers know that respiratory disease is one of the main disease entities they deal with. But there is a similar problem of case definition. On many large calf-raising operations, the treatment crew is trained to respond to illness quickly and decisively. They do not have much incentive to save money on medicine, but they do have a strong incentive to save lives. So it is common that any calf that is off feed, depressed, or breathing hard that does not obviously have diarrhea will be treated for pneumonia. Many of them probably have pneumonia, but there is not a lot of rigor to the diagnosis. The McGuirk score has given calf raisers a useful tool for standardizing the diagnosis, but some would still treat calves with a low score because they have learned that early and aggressive treatment is preferable to waiting too long for a confirmed diagnosis.

Few reports say how recurrent cases or recurrent treatments were reported. These can be counted as a separate case or as part of the same case, depending on how much time between treatments is needed to count as a new case.

Septicemia caused by *Salmonella* spp. can present in its early stages as a depressed, febrile calf that is breathing quickly. This will often be recorded as BRD and treated with an antibiotic. During an outbreak, which usually results from sanitation failures, the apparent BRD treatment rate can be very high. *Salmonella* can spread rapidly and mimic BRD.

Diagnostic ultrasound may be used to detect consolidation or changes in the pulmonary surface, and may allow more precise diagnosis and prognosis than temperature, clinical signs, and auscultation (Flöck, 2004)

**BRD in Adult Dairy Cattle**

There appear to be no comprehensive epidemiological studies of BRD in adult dairy cattle. The National Animal Health Monitoring System (NAHMS) 2002 and 2007 (USDA 2009 & 2002) surveys used producer interviews to report that 2.4% of cows in 2002 and 2.9% in 2007 were
diagnosed with respiratory disease. NAHMS 2007 reported that 11.3% of cow deaths were due to respiratory disease.

In my practice experience on large dairy farms in the Western and Midwestern United States, BRD or pneumonia was rarely diagnosed in adult cows. Cattle on these farms were housed either in open lots or in curtain-sided or open free stall barns with open ridges. It is likely that there is a higher risk of BRD in more traditional tie stall or stanchion barn housing where ventilation may be poor in winter.

McConnel, et al (2009) necropsied all the cows that died or were euthanized on a large Colorado dairy for a year. The risk of death was 6.4 per 100 cow years at risk and the risk of culling was 34.7 per 100 cow years at risk. Culling reasons were not reported in the paper. Comparison of the producer-given reasons for death with the necropsy results revealed that the producer was only accurate about 55% of the time. Of the deaths, about 7% were due to respiratory disease other than aspiration pneumonia.

Rezac, et al (2014) analyzed gross pathologic findings in dairy cows slaughtered over 3 days in a plant in the Upper Midwest of the United States. Eighty-seven percent of the 1,461 cows were classified as Holstein. Severe BRD was found in 10.3% of the cows.

The 10 year average number of dairy cows culled in the US through 2012 is 2,679,000. Based on Rezac’s number one could estimate that about 275,000 culled dairy cows a year suffer from severe BRD. If we apply McConnel’s numbers to estimate that 5-7% of the 9.2 million dairy cows in the US in 2013 die on the farm and 7% of those are for respiratory disease, 32,000-45,000 cows per year probably die on farm of respiratory disease. So roughly 300,000 dairy cows a year would be culled or die because of lung problems. Every $100 of lost cow value due to respiratory disease deaths and culling would represent a loss of $30,000,000 to the industry, in addition to treatment costs and lost milk production.

The NAHMS estimate of 2.4-2.9% of cows diagnosed with respiratory disease implies between 221,000 and 267,000 cows, based on the 2013 cow population. This number probably includes animals that remained in the herds and is less than our estimates of respiratory culls and deads. So NAHMS may underestimate the true prevalence of BRD.

The bacteria commonly implicated in BRD in adult dairy cattle are Pasteurella multocida, Mannheimia haemolytica, Histophilus somnus, Mycoplasma spp, and Trueperella pyogenes (Rebhun, 1995). These infections may be secondary to viral infections with Infectious Bovine Rhinotracheitis, (IBR), Bovine Syncitial Virus (BRSV), or Bovine Virus Diarrhea Virus (BVDV). On many farms dairy cows are vaccinated repeatedly with modified live virus vaccines (MLV). In my clinical experience symptoms of these viral diseases are rarely if ever seen in herds with consistent MLV vaccination programs.

Outbreaks of adult cow BRD investigated by the University of Wisconsin Veterinary School have generally been traced back to lapses in vaccination, the introduction of cattle from other herds
or from sales, weather or other stress, or overcrowding. (McGuirk, personal communication). Over-diagnosis is a factor in some perceived outbreaks. It is often difficult to reach conclusions from diagnostic serology because of the effect of vaccinations, insufficient control samples, and sampling cows too late in the progression of the disease.

**BRD in Dairy Calves**
Most of the data on the prevalence of BRD in dairy calves comes from studies on a limited number of farms near a university. Most of the herds in these studies have been small by modern dairy standards. Herds were usually not randomly selected, and most studies rely on owner/manager recording of cases, although some verified the diagnosis with visits from study personnel. In many cases the prevalence data comes from studies that were designed to study some other aspect of disease or growth in calves. Most studies appear to have been done on Holstein calves. Many concentrate on a specific age range and few contain data for heifers between weaning and breeding.

The National Animal Health Monitoring System (NAHMS 2007) (USDA 2009) surveyed dairies in 17 states that represented about 80% of US dairy farms and cows and estimated that 12.4% of preweaned heifer calves had respiratory disease and that 11.4% were treated for BRD. 5.9% of weaned heifers were affected and 5.5% percent were treated. NAHMS 2011 (USDA 2012) surveyed heifer raisers with a one hour interview. It was estimated that 2.3% of preweaned heifers, 1.3% of weaned open heifers, and 0.2% of pregnant heifers died of pneumonia. 16.4% of preweaned heifers, 11% of weaned heifers, and 1.2% of pregnant heifers were treated for BRD.

The Gold Standard of the Dairy Calf and Heifer Association is less than 10% of heifer calves from 1-60 days of age, less than 15% from 61-120 days of age, and less than 2% from 121-180 days treated for BRD. If these are additive, the cumulative rate to meet the Gold Standard would be 27%.

In my clinical experience, there are times when BRD treatment rates on large calf raising operations with excellent colostrum programs are far higher, approaching 50% for certain periods. The effectiveness of colostrum delivery, weather events, and season affect the incidence of BRD. *Salmonella* outbreaks can cause perceived BRD rates to be very high. Some raisers practice metaphylactic treatment of all calves around weaning in order to reduce the incidence.

Waltner-Toews, *et al* (1986a) surveyed 104 randomly selected Holstein herds in Southwest Ontario and collected individual calf data on 35. They collected treatment and morbidity data based on owner data only up to weaning. Of 1968 calves born, 15% were treated for pneumonia. Heifers treated for pneumonia were 2.5 times more likely to die after 90d of age than those that weren’t (Waltner-Toews *et al*., 1986b). Windeyer, *et al*.* (2014) enrolled calves at 1-7d of age and followed them for about 3 months on 19 farms in Ontario and Minnesota. 22% were treated at least once for BRD. Median age at treatment was 30d. Failure of passive transfer of immunoglobulin (FPT) affected BRD incidence. Calves born in winter had 2.6 times
higher odds of contracting BRD than those born in summer, and 1.6x greater than those born in the fall.

Van Donkersgoed, et al (1993) collected data on calf health from every calf born in 17 herds around Saskatoon, Saskatchewan. Diagnoses were based either by the managers or by the study veterinarians on their weekly visits. Owners diagnosed pneumonia in 39% of calves, with a median age of 27 days and a recurrence rate of 56%. Veterinarians diagnosed BRD in 26% of calves, with a recurrence rate of 29% with a median age of 36d.

Curtis, et al (1988) studied 1171 calves on 26 herds near Cornell University, averaging 64 cows per herd. The study relied on farmer reporting but used symptoms, rather than treatment. The symptoms were those of scours, dullness, respiratory disease, and death. The prevalence of respiratory signs was 7.7% and that of dullness 7.4%. Outside this study, the dull calves might have been recorded as respiratory. The median age of onset of respiratory signs was 25 days. Season had no effect on respiratory disease prevalence. Calves were only studied for the first 90 days of life.

Stanton, et al. (2010) compared the effect of metaphylaxis with two antibiotics on BRD on a New York calf raising facility. Calves were enrolled and treated with antibiotics at weaning. 14.3% of calves were treated for BRD before enrollment. By 6 weeks after enrollment, 13.2-22.4% of calves had been diagnosed with BRD. BRD had a significant effect on weight and height gain for the 6 weeks after enrollment.

Lundborg, et al. (2005) studied risk factors for infectious diseases in calves up to 90d of age in one county in Sweden. 3081 females in 122 herds (28-94 cows) were enrolled. Farmer records were used; veterinarians visited every 2-3 months. Calves were indoors in either single pens, small group pens, or large groups with automatic feeders. The median percentage diagnosed with BRD on these farms was 3%, with a range from 0-52%. The 30th to 80th percentile of prevalence was 0-11.4%. The study looked at a wide range of risk factors for BRD and found that ammonia concentration in the air, BVDV infection in the herd, and drafts were the significant factors in their model. Paradoxically, lower ammonia levels were positively correlated with BRD rate.

Donovan, et al. (1998b) studied the association between passive immunity and health on two large dairies in Florida. The definition of pneumonia in this study included a minimum age of 29d. Twelve percent of the enrolled heifers died and 21% were diagnosed with pneumonia. Colostrum protected calves from BRD early in life but the effect disappeared as they got older. The case fatality rate for pneumonia was 13.8% and pneumonia caused 21.9% of all deaths. The number of days treated for BRD before 6 months of age decreased average daily weight gain from birth to 6 months by 10.5 gm/d, but not stature growth. BRD after 6 months of age did not affect weight or height gain in their model (Donovan et al., 1998a).

Sivula, et al. (1996) studied 845 heifer calves from birth to 16 weeks of age on 30 farms, ranging from 40-112 cows, in Southern Minnesota. 7.6% of calves got pneumonia, with a case fatality
rate of 9.4%. 36% of calves had FPT, but there was no significant difference in BRD rate between FPT and non-FPT calves. The BRD calves did not seroconvert to respiratory viruses. *Pasteurella multocida, Mannheimia haemolytica,* and *Mycoplasma spp.* but no respiratory viruses were isolated from calves that died of BRD. In another Minnesota study, Lago et al. (2006) studied BRD and pen microenvironments in 13 naturally ventilated calf barns. 12 calves per barn were selected and scored. 14.3% of the calves scored had BRD using the McGuirk score, with a range from 0-37%. Decreased air bacteria counts in the pen, solid barriers between pens, and the ability of calves to make a nest in deep bedding were associated with lower rates of BRD. The study suggested that providing deep bedding was a more effective preventive measure than enclosing the calf pen on all sides.

In sum, the studies on BRD incidence in dairy calves were mostly done in small herds, and show a range from 0 to 52%. The median ages at treatment in the studies show that preweaned calves, which are often housed individually, are at risk for BRD. No studies addressed the issue of management around weaning, but there is a broad agreement among clinicians that conditions at weaning and the first introduction of calves to group life can increase the risk of BRD. Exposure to coccidia in group pens may be a part of this increased risk, and in my observation coccidiosis and increased rates of BRD often go together. Empirically, mixing calves of different sizes at weaning increases the risk of BRD. It is best to wean into uniform small groups and to make sure that the calves learn where feed and water are.

**Effects of BRD on Heifer Performance**

One would expect that BRD in calves would have a significant effect on the performance of heifers after they calve. In my experience, most culling of poor-doing growing heifers appears to be due to chronic respiratory disease; at least many culls have a history of repeated treatment for BRD. However BRD mostly affects young heifers and it is difficult to separate the effect of early BRD from other factors that influence first lactation or later performance, such as age at first calving (AFC), size and weight at calving, dystocia, and season of calving. AFC in turn is strongly influenced by age at first insemination and breeding efficiency and is highly correlated with size and weight. The evidence in the literature is equivocal. Some of the effect of BRD may wash out in the cited studies because of the number of factors analyzed in the statistical models.

Some of the effects of BRD on growth in young calves have been cited. One might ask whether BRD impedes growth or whether slower growing or underfed calves are at higher risk of BRD.

Rossini (2004) examined records from 2556 cows in one herd in Virginia. Disease data was based on operator records. 48% of animals were treated for calfhood BRD. AFC was about 14d higher in heifers that had multiple bouts of BRD; those with only one bout calved 6d later. A higher percentage of heifers that had BRD calved after 25 months. There was no difference in 305 day milk yield, fat yield, or somatic cell count. Protein yield decreased by .05 kg/d in animals that had respiratory disease. Disease free calves had a 5% greater chance of staying in the herd through 305d and 8% greater chance of staying through 730d compared to calves with two or more disease occurrences.
Bach (2011) reviewed records and treatment records of 7,768 Holstein heifers that were raised on one heifer raising operation and returned to 133 herds in Spain. Heifers that had 4 or more bouts of BRD before first calving had 1.87 greater odds of not completing first lactation than those that no BRD. As the number of BRD increased, heifers had a decreased proportion of days of productive life as a percentage of days alive. There was also an 8d difference in average AFC between heifers with no BRD and those with 4 or more bouts.

Heinrichs (2011) used a linear mixed model to examine 10y of data from 795 calves from 21 farms in 2 counties in Pennsylvania. They did not differentiate between BRD and digestive disease. Days ill in the first 4 months of life decreased first lactation 305day Mature Equivalent (305ME) milk yield by 126 kg, protein yield by 4kg, and fat yield by 5kg. There was no effect on culling age, lifetime milk or component yield.


Stanton et al (2012) analyzed first lactation performance of the heifers in . Calves were all treated with an antibiotic at weaning and BRD recorded for 60d. 63-73% of heifers that had BRD survived to first lactation, compared to 84% of those that didn’t. Median AFC was 12 days longer for BRD heifers.

In sum, BRD in heifer calves appears to have a small but statistically significant effect on AFC and may affect herd life and milk and milk component yield. However all the effects are relatively small and may not be economically significant on the farm. All disease recording in these studies was by owners or managers.

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Summary of BRD data from the 2011 NAHMS Feedlot and Dairy Heifer Studies

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Abstract
The USDA:APHIS National Animal Health Monitoring System collects data on health and health management in livestock and poultry populations throughout the United States in order to provide stakeholders with population estimates to use as benchmarks for comparison, to guide policy development, and to identify research needs and prioritize education efforts. Recent studies of both the beef cattle feedlot industry and dairy heifer rearing operations provided information about BRD occurrence as well as information about prevention and treatment practices used on these operations. While a great deal of effort is dedicated to BRD prevention there are still opportunities to improve the strategies used. Despite efforts to prevent BRD continues to be widespread on both of these types of operations.

Introduction
Bovine respiratory disease (BRD) typically occurs as a result of the interaction of a variety of infectious and non-infectious factors. The occurrence of BRD exacts a major cost on the cattle industry including costs associated with prevention, lost production associated with morbidity and mortality, and treatment costs. Through a better understanding of the management of livestock operations and the occurrence of BRD on these operations cattle production can be improved. Furthermore, information gaps or needs for education can be highlighted in an effort to improve production efficiency and animal wellbeing. Characterization of management practices related to BRD prevention and treatment as well as describing the occurrence of BRD were objectives of two recent national studies conducted by the USDA:APHIS.
Data source and analysis
The NAHMS has been collecting health and management data in farm settings since the early 1990s. Each type of production stream (beef, milk, pork, etc.) is handled on a rotational basis, studying each type on a 5-8 year interval. The scale and scope of the studies along with the objectives are set with stakeholder input in order to assure the focus is on the most pressing information needs for the respective industries. In general the studies are meant to be national in scope and represent at least 70 percent of the operations engaged in the production stream and at least 70 percent of the animals of the respective production class. Selection of the operations to participate in the study is generally based on a stratified random sample of operations from a producer list in order to allow analysis and inference back to the source population. Data are collected through a series of interviews (in person or telephone) with the selected producers who provide responses to a structured questionnaire focused on key management factors and health parameters for the animals of interest on the operation.

Feedlot 2011
In 2011 a study of beef cattle feedlots was conducted. The study was comprised of two parts, each focusing on a separate segment of the cattle feeding industry. One part of the study was directed at operations with at least 1000 head one-time capacity located in the 12 major cattle feeding states. The other part of the study was directed at operations with less than 1000 head capacity and focused on operations in 13 states, 5 of which overlapped with the other part of study. Data from the larger feedlots were collected through two in-person interviews with the feedlot operator. Data from the smaller feedlots were collected during a single telephone interview.

In each part of the study questions were formulated to meet 5 key objectives:

1. Describe changes in management practices and animal health in feedlots.
2. Describe the management practices in feedlots that impact product quality.
3. Identify factors associated with fecal shedding of potential foodborne pathogens or commensal organisms by feedlot cattle.
4. Describe antimicrobial usage in feedlots.
5. Describe biosecurity practices and capabilities in feedlots.

Because bovine respiratory disease (BRD) is recognized as an important disease entity in feedlots and extensive efforts are expended to prevent or control BRD in feedlots many questions dealt with these components.

Dairy Heifer Raiser 2011
In 2011 NAHMS conducted a study of dairy heifer raisers in 21 states. Individual operations eligible to participate in the study were identified through a number of methods including
membership list for the Dairy Calf and Heifer Association (DCHA) as well as through referrals to operations known to be engaged in dairy heifer raising. All identified eligible operations were contacted to participate and data were collected by administration of a structured questionnaire during an in-person interview.

Results

Feedlot 2011

Health Management

Concern for the occurrence of BRD in feedlots results in many feedlots adopting management strategies directed at preventing, detecting, or treating BRD in groups of cattle placed. These management strategies include such practices as pre-arrival processing, arrival processing, vaccination, metaphylaxis, pen walking or riding to identify animals with clinical disease and treatments based on clinical syndromes. For example, on most feedlots (69.3%) with at least 1000 head capacity, operators believe that pre-arrival processing was very important to assure health of animals entering the feedlot. However, feedlot operators reported that such information is often not available. Nearly all larger feedlots processed cattle placed into the feedlots. Vaccination to prevent/control respiratory disease was the most commonly cited component of the arrival processing procedure (96.0% of those processing arriving cattle). Approximately half (50.4%) of feedlots incorporated an injectable antimicrobial into the arrival processing for at least some cattle presumably to avert an outbreak of respiratory disease. Fewer feedlots with less than 1000 head capacity (40%) process arriving cattle. When arriving cattle are processed at smaller feedlots most (92.6%) receive a vaccination for respiratory disease and 31.0 % receive an injectable antimicrobial.

BRD Occurrence and Treatment

For feedlots with at least 1000 head capacity, 16.2% of placed cattle reportedly develop respiratory disease such as shipping fever. Approximately 2.8% develop atypical interstitial pneumonia. Virtually all cattle with respiratory disease are treated with an injectable antimicrobial. Secondary treatments include administration of a vaccine intended to control respiratory disease (48.5% of affected cattle), administration of a vitamin C injection (34.1%) and use of nonsteroidal anti-inflammatory drug(s) (19.6%).

Dairy Heifer Raiser 2011

Health Management

Some dairy heifer raiser operations used vaccinations to control bovine respiratory disease pathogens. Most commonly operators vaccinated preweaned heifers to control Infectious Bovine Rhinotracheitis virus (45.3% of operations) followed by Parainfluenza type 3 virus (41.3%) and Bovine Respiratory Syncytial virus (307%). This practice resulted in 35.5%, 32.5%
and 23.5% of preweaned heifers being vaccinated to control these agents respectively. Some operations also vaccinated pregnant heifers to control respiratory disease agents. Approximately 1 in 3 operations vaccinated pregnant heifers for Bovine Viral Diarrhea virus, Infectious Bovine Rhinotracheitis virus and Parainfluenza type 3 virus. A variety of other biosecurity practices were also used on operations including method of housing, managing contacts with other animals or people and feeding procedures to mitigate the occurrence of various diseases.

**BRD Occurrence**
Overall, 18.1% of preweaned heifers experienced respiratory disease. For weaned heifers, 11.2% experienced respiratory disease. Only 1.2% of pregnant heifers were affected with respiratory disease. The percentage of heifers that died with respiratory disease was 2.3%, 1.3% and 0.2% for preweaned, weaned and pregnant heifers respectively.

**Conclusions**
Prevention and control of respiratory disease is a major focus in both cattle feedlots and dairy heifer raising operations. Still, bovine respiratory disease occurs frequently and has an impact on the health and production of cattle in feedlots and dairy heifer raising operations. Opportunities exist to enhance the use of existing tools to control bovine respiratory disease. Further research into the epidemiology of bovine respiratory disease and additional technologies for prevention and treatment could help to improve animal health and wellbeing as well as food production.

**References**
Feedlot 2011
The Clinical Syndrome of BRD: what it is and what it isn’t
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Abstract
The clinical syndrome of bovine respiratory disease (BRD) continues to be a major challenge in bovine production systems. We are challenged with our predictive abilities for morbidity in groups of cattle, our ability to accurately diagnose and provide a prognosis for individual cases, and our ability to evaluate the results of preventive and therapeutic interventions in the field when production system data are the sole basis for analysis. However, we are fortunate to have perhaps the highest quantity and quality of negative-controlled, prospective, randomized, and masked clinical trial data for any disease in veterinary medicine; understanding that case definitions in these studies may not be consistent or necessarily externally relevant, and that production data in these studies are often missing.

Introduction
The clinical syndrome of bovine respiratory disease (BRD) continues to be a major challenge in bovine production systems. We are challenged with our predictive abilities for morbidity in groups of cattle, our ability to accurately diagnose and provide a prognosis for individual cases, and our ability to evaluate the results of preventive and therapeutic interventions in the field.

We can agree that BRD is a complex disease, but after that the complexities of the disease syndrome make agreement on specifics more difficult.

As usual, we are frustrated by knowing that a lot of work is done in private systems and is not available in the literature; these may include equivocal or negative studies which are not made available to balance the positive bias in the literature. This paper is not intended as an exhaustive review of the literature for each of the categories, but rather points to recent publications as a means of highlighting our continued efforts to better understand this disease.

BRD is not a disease with well-defined prognostic indicators
There are multiple definitions of high and low risk cattle, with some managers also inserting a medium risk category in the mix. These systems are used to make decisions such as purchase price differentiation, whether to treat for control of BRD, nutritional management options, and inclusions in the processing protocol. While many may feel they have these categories nailed down, going to the literature gives us less confidence in our consistent prognostic ability on a specific group or individual animal basis.

Risk factors for BRD in calves still on the cow have been characterized by surveys of cow/calf producers (Woolums, Berghaus et al. 2013) (Hanzlicek, Renter et al. 2013). There are general
trends as to what predisposes cattle on a herd basis, but not really consistent approaches to identifying cattle within the herd.

A review of predisposing factors for BRD in feedlot cattle concluded that the complexity of BRD makes it difficult to specifically characterize the involvement of individual factors (Taylor, Fulton et al. 2010). The authors cited specific risk factors such as purchasing from sale barns and commingling, but the impact of shipping, weather, arrival weight, gender, castration and dehorning are less consistent when the whole of the literature is examined.

**Bovine respiratory disease is not easily and consistently diagnosed**

Put another way, diagnosis is easy if one is not going to be checked for accuracy. However, when diagnosis of BRD is checked against measurable outcomes, accuracy of diagnosis is usually revealed as marginal at best. What we are really talking about are the attempts to validate a case definition for BRD; this would let us evaluate true morbidity as well as an accurate case fatality rate.

Recent attempts at improving diagnostic precision in feedlot cattle have included lung biopsy (Burgess, Hendrick et al. 2013), ultrasound (Abutarbush, Pollock et al. 2012), RFID-associated thermography (Schaefer, Cook et al. 2012), breath biomarkers and serum haptoglobin (Burciaga-Robles, Holland et al. 2009), and rumen temperature boluses (Rose-Dye, Burciaga-Robles et al. 2011). Pulmonary auscultation and rectal temperature have been demonstrated to have a correlation with clinical outcome in feedlot cattle (DeDonder K 2010).

In neonatal cattle, evaluation of multiple scoring systems (Love, Lehenbauer et al. 2014), and evaluation of scoring systems in relation to ultrasonography and auscultation (Buczinski, Forte et al. 2014) have recently been published.

The treatment response to initial therapy (% treated that require no further treatment) and case fatality rate (% of those treated that die) can be too “good”. One interpretation of exceptionally high first treat response rates and low case fatality rates may be that a significant proportion of cattle are being treated which are not truly ill. This determination is dependent on the accuracy of our case definition for BRD.

It is hard to communicate to the public that we may have a target of losing a few as a balance point to not treating a high number of cattle that did not need treatment, but this is exactly the balance that is necessary. In fact, I think it would be rare to encounter a food animal veterinarian who is confident that with the proper application of chemical management we are able to avoid all death loss. In other words, to avoid putting antimicrobials in a large population that does not need them, perhaps we must accept that we get antimicrobials in a small population of animals at a time which is further into the disease process than we would like. This balance is elusive, and sure to bring about heated arguments involving the cost of treatment, conservation of animal resources, animal welfare, labor, and antimicrobial exposure in a population.
Bovine Respiratory Disease does have a wide array of negative-control treatment data available for high-risk feedlot cattle

With all the caveats about prognosis and accuracy of the case definition, BRD is still the disease with arguably the most negative-control treatment outcome data of any veterinary disease, perhaps any disease in both veterinary and human medicine. Therefore, in high-risk cattle (granted, begging a consistent definition for this term), we have an idea of treatment response rates and case fatality based on the case definitions for BRD used in these studies.

A good statistic for evaluating drug effects in a population is the Number Needed to Treat (NNT). This is the number of animals which need to be treated with the drug to make a clinical outcome difference in one animal. It is calculated using the Attributable Reduction in Risk (ARR). For example, in a trial where 25% of the untreated controls were classified as treatment successes, and 75% of the treated group was classified as treatment successes, the ARR is 50% (75% – 25%). If the only two outcome options are success or failure it doesn’t matter how you subtract, the difference is the same whether for the difference in successes or the difference in failures.

The NNT in this example would be 100%/50%, or 2, indicating that you need to treat 2 animals to make a difference in 1. Another way of looking at the example is that in every 4 treated animals there would be one response regardless of treatment (the 25% of untreated controls which are successes), one failure regardless of the treatment (the 25% of treated animals which were treatment failures), and 2 successes in the treated group which would have been failures in the control group (the ARR). Therefore, we made a difference in 2 out of 4, or 1 out or 2. We have to treat 2 to make a difference in 1, an NNT of 2.

The NNT therefore evaluates the effect of the drug in the context of a disease in a target population. The “response rate” observed in production data is a combination of spontaneous recovery and the effect of the drug. Negative-control clinical trials allow separation of these two components of treatment response, isolating the effect of the drug in the population according to the success/failure case definitions used in the studies. The higher the response (“cure”) rate in the control population, the less room there is for a treatment to make a difference.

Detailed tables of the available data on negative controlled, prospective, randomized, masked clinical studies for BRD have been published in the American Association of Bovine Practitioners Proceedings (Apley 2013).

With few exceptions, these studies are pivotal dose finding and clinical efficacy approval studies conducted under good clinical practices (GCP) guidelines and accepted in the approval process by the Food and Drug Administration Center for Veterinary Medicine (FDA/CVM). These studies would predominantly represent high-risk calves. In my experience, the success/failure criteria used by the FDA/CVM result in a lower apparent clinical success rate than would be observed in typical feedlot practice. However, the mortalities have a fairly constant definition, which even veterinarians might have a tough time arguing about. The extrapolation of these results to low risk cattle would likely overestimate the effect of the antimicrobials due to an expected higher response rate in the untreated controls.
Granted, these studies do not take into account the potential improved production performance of the successful cases in the treated group as opposed to the successful cases in the control group, but some type of clinical response is the basis for your clinical experience as far as drug effect, correct? In feedlot practice it is typical to evaluate treatment outcomes and to use these data to constantly monitor therapeutic “efficacy”. How much of the monitored clinical outcomes are actually due to the drug?

The median NNT in 30 studies evaluating treatment of BRD with commercially available antimicrobials is 2; for every 2 animals treated for BRD in the overall population of high-risk cattle, one animal became a treatment success which would have otherwise been a failure. Treatment success rates in untreated cattle in these studies ranged from 0% to 57%, with a median of 23.9%. This means that in these 30 studies, a median percentage of approximately 24% of the cattle meeting BRD case definitions were classified as treatment successes at the end of the placebo treatment regimen, and did not require treatment again during the study (these studies were not to closeout). In contrast, treated success rates in the treated cattle ranged from 51% to 92% with a median of 70.7%.

In 24 of these 30 trials, BRD mortality was also reported; this would be a case fatality rate since all cattle in the study were treated. In these studies, the median NNT for preventing a BRD mortality is 7; for every 7 animals treated for BRD in the overall population, one mortality was prevented in these study populations. The case fatality rates in the untreated controls fell in a range of 2.5% to 48% with a median of 17.0%. For treated cattle, the range was 0% to 23.0% with a median of 1.0%.

The authors of a meta-analysis of these and other treatment outcome data, as well as data related to antimicrobial comparison studies without negative controls, have classified antimicrobials used for BRD therapy as to their relative efficacy (O'Connor, Coetzee et al. 2013). Using 194 trial arms from 93 trials, the authors were able to rank antimicrobials for comparative efficacy across the trials.

**Conclusion**
While we struggle with accuracy of diagnosis and prognosis, there are still data to help us at least evaluate diagnostic and prognostic methods, as well as treatment outcomes in some classes of cattle. Our glass is definitely half-full, with promising research on the horizon to advance our understanding.

**References**


Buczinski, S., G. Forte, D. Francoz and A. M. Belanger (2014). "Comparison of thoracic auscultation, clinical score, and ultrasonography as indicators of bovine respiratory


The monster we don’t see: sub-clinical BRD in beef cattle.
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Abstract
Bovine Respiratory Disease (BRD) is the most expensive disease of cattle in the U.S. Recently weaned calves are the focus for prevention and treatment research. Identifying BRD affected cattle early in the course of BRD is difficult. Intervention during BRD early stages improves treatment outcomes, however cattle as prey animals are excellent at hiding signs of disease from caregivers, especially if the caregiver has not gained their trust. Depression, appetite loss and respiratory character are the principle signs used to assess BRD. Rectal temperatures from cattle pulled for treatment are used as a final measure of evaluation. Cattle suffering from subclinical BRD frequently escape identification and treatment. Observations of lungs at packing plants for anterior ventral (AV) lesions frequently documents higher BRD incidence rate than was observed pre-harvest suggesting subclinical BRD is common. Data from numerous studies document lower average daily gains (ADG) from cattle with AV lung lesions at packing plants that were not treated for BRD compared to cattle with normal lungs. Scoring lung lesions at packers can be a useful tool for gaining insight into BRD incidence. Data indicates ADG is lowered on average ~0.20 lbs. and the USDA Quality Grade is lowered by 50 marbling points.

It has become cliché to note “Bovine Respiratory Disease (BRD) is the most expensive disease of cattle in the United States (US)”. Estimates always include the cost of sickness treatments, deaths and loss of performance (Epperson 1999, Irsik 2010, Leach 2013 and Smith 1998). Almost all discussion and estimates of loss revolve around calves, especially stressed calves immediately post weaning.

In calves affected with BRD during the first four weeks post weaning, the relationship between their BRD clinical signs and treatment outcomes is disappointing. While dozens of descriptors have been and continue to be used to characterize BRD clinical signs, three characteristics have become the principle targets for identifying clinical BRD. The key clinical characteristics are: scaling levels of attitudinal depression; loss of appetite as judged by rumen fill; and abnormal respiration (rate and character). Finding cattle affected with BRD during the early stages of the disease is generally considered the most critical key to successful intervention (Smith 1998). When cattle are identified as “sick” and are “pulled” from their group for individual treatment, rectal temperature becomes the most common scale used to estimate the severity of their illness. The acronym formed from the first letter of the four key signs; depression, appetite, respiration and temperature is D.A.R.T. and has gained wide acceptance as a training tool for helping caregivers learn to identify cattle during the early stages of BRD.

Regressing the rectal temperatures of “sick” cattle against BRD relapse events and BRD deaths in over 30,000 BRD feeders indicate temperatures less than 104.0°F have an R² less than 0.5.
Regression against 105.0°F had an $R^2$ of over 0.67 (Anonymous 1982-1985). While selecting higher rectal temperatures will improve its statistical relationship to BRD deaths and relapse and therefore better “prove” the suspect animal was suffering from BRD, a higher cut-off rectal temperature will increase the number of BRD affected cattle not being treated. It is reasonable to consider many of these that have a rectal temperature below the veterinarian’s cut-off for BRD treatment would be “subclinical” BRD cases. Higher rectal temperature cut-offs lower the total expense of initial treatment costs. While treatment costs are saved, the loss of growth performance of “subclinical” BRD not treated may offset the treatment cost saving.

Until three decades ago, the magnitude of BRD subclinical lesions had not been characterized. Griffin’s observations of packing plant offal from known sets of finish fed cattle indicated BRD lesions could be very prevalent in groups of cattle that had experienced little clinical BRD during their stay in a feedyard. And conversely, found BRD scaring at rates less in some groups than the observed sickness rates suggesting not all cattle exhibiting BRD signs and confirmed by high rectal temperatures are true cases of BRD. “Don’t let a thermometer do you thinking” or “Thermometers lie” can be an interpretation of these packing plant observations. However, observations at the packing plant of cattle with severe BRD adhesive lesions involving over 50% of the lung would have hot carcass weights 10 to 15% lighter than carcasses from cattle in the same group with grossly appearing normal lungs. It was not uncommon to observe a third or more of the lung adhering so tightly that it would be torn away as the pluck (heart, lungs and trachea) was removed (Anonymous 1982-1985).

BRD was not the only cause of adhesive pulmonary events observed in the packing plant. Lung adhesions were observed occasionally in association with the inflammatory response across the diaphragm to severe liver abscesses or severe liver flukes infestations (Anonymous 1982-1985).

BRD has been documented to be associated with other non-infectious etiologies such as 3-methylindole (Bingham 2000), nutritional interactions and deficiencies (Galyean 1999), productions management tools such as hormonal implanting (Munson 2012), sourcing and prior or preweaning management (Reinhardt 2009, Renter 2013 and Smith 1998) and genetics (McAllister 2010). A tremendous amount of work has investigated pathogen interactions as related to both clinical and subclinical BRD. The most notable is the relationship between the development of BRD and normal cattle’s exposure to cattle persistently infected with Bovine Virus Diarrhea (BVD-PI). The clinical BRD incidence is magnified by the presence of other cattle that are persistently infected carriers and shedders of BVD virus (Loneragan 2005). When BRD is considered as a whole the term complex is frequently added (BRDC), because epidemiologic studies demonstrate complex interactions individual bovine and its environmental history, past and present (Renter 2013 and Taylor 2010).

Griffin and Perino outlined a protocol in the early 90’ to evaluate health and growth performance differences between newly weaned feeder cattle that were randomly selected to be treated with oxytetracycline for their BRD signs or denied antibiotic therapy. At the end of the study there were no differences in the BRD relapse rate or the BRD death rate. When the lungs were observed on the offal line at the packers. Just over a third of the weaned calves
were observed to have BRD signs prior to harvest. However over 70% of the cattle had BRD lesions grossly observable at the packer’s offal line. Only a quarter of the cattle with lesions had been treated for BRD prior to harvest (Anonymous 1993). Similar finding were made by Wittum, et al (Wittum 1996) studying weaned calves over three calving seasons from a biosecure closed herd. They found gross lung lesions at the packing plant, the majority of which were adhesive in over 70% of cattle and less than 40% of the cattle had been observe to have BRD signs during their life. Of those observed with BRD there was less than an 80% agreement between the BRD signs and the presence of gross lung lesions from lungs collected from the packing plant. Bottom line is the ability of spot cattle with BRD signs is not consistently accurate. Besides lung scaring associated with BRD, Wittum, et al (Wittum, 1996) documented a 6% (0.16 lbs.) reduction in average daily gain (ADG) association with the presence of a lung lesion observable at the packing plant.

Bryant was the first to develop a lung scoring system (Bryant, 1995). His work documented that as little as a tenth of the anterior ventral (AV) lung with adhesive BRD lesions was associated with a lowering of ADG (Bryant, 1998). Dr. Bryant’s observations suggested there were three important classifications of grossly observable lung lesions that could be made at the packer’s offal line at chain speed (one lung observation every 10 seconds). The classifications were: 1) collapsed consolidated lung parenchyma; 2) adhesions of the lung to itself or to the thoracic pleura; and 3) acutely reactive tracheobronchial lymph nodes. The majority of the AV lung involvement was less than 5% of the total lung but even this small amount of lung involvement could be associated with decreased cattle ADG. Lungs with AV lesions in less than 5% of the lung became his severity involvement score of “1”. The statistical variability in ADG impact rapidly increased when more than 15% of the AV lung was involved. This led to an AV involvement of greater than 15% being a maximal score of “3”. AV lung involvement between 5 and 15% became a lung involvement score of “2” (Figure 1). The significance of the involvement score was factored against the impact of the type AV lung lesion (collapse consolidated being the least impactful, adhesions the next most impactful and the presence of acutely reactive tracheobronchial lymph nodes the most impactful (Bryant, 1997 and Gardner, 1999).

Since the initial observations linking AV lung lesions at packing plants to cattle that had never been observed to exhibit signs of BRD, there has been a continual flow of work published that documented similar findings (Busby 2014, Leach 2013, Rezac 2014, Schneider 2009 and Thompson 2006). The impact of BRD on growth has been variable but the range published by these researchers has been a decrease in ADG between 0.10 lbs. per day or over 1 lb. per day. These researchers reported cattle subclinically affected with BRD as cattle that had never been observed as showing clinical signs of BRD and yet were found to have lesions in the AV lung lobes at the packing plant consistent with previous BRD. In their reports, cattle with subclinical BRD had decreased ADG during finish feeding of between 0.07 lbs. to 0.33 lbs. Additionally, some of the reports included lowering of carcass values associated with lowering of USDA Quality Grade and increased carcass trim loss. On average the loss in Quality Grade was 50 marbling points.
Financially, what does this mean? As an example, if the price differential was $10 per CWT between carcasses with a Select Quality Grade and carcasses with a Choice Quality Grade, a 900 lb. carcass from an animal affected with BRD would have 50 fewer marbling points which is half the marbling required to move a carcass from “Select” to “Choice”. The 50 marbling point decrease across a group of cattle would be $45 less for cattle affected with BRD compared to the carcass value from non-BRD affected cattle. If the AV lung adhesive rate from cattle never observed with BRD signs (subclinical) is 20% of a group of 100 finish fed cattle, the loss in carcass value alone would be $900 in the group of cattle. If the average ADG decrease for cattle with AV lung lesions is 0.2 lbs. and if these 100 cattle had been on feed for 180 days, there would be 720 lbs. less weight to market. If the live bid is $1.45 per lb., the gross dollar return would be an additional $1,044. In a nutshell, in this financial example, a 20% subclinical BRD rate cost every finish fed animal $19.44 from lowered weight gain and lowered carcass value.

Cattle feeding is two distinct businesses. Ownership and management of a feedyard is an “asset” business. Ownership and management of cattle in a feedyard is an “equity” business. By that I mean, you can own cattle in a feedyard by providing sufficient equity to insure the banker from whom you borrow money they you will be able to repay the loan. Seldom is the risk of loss greater than $200 per head, therefore a cattle feeder need not have more than $200 per head on feed. The $19.44 loss associated with subclinical BRD in the example represents approximately a 10% loss in equity. To view it a different way, if the subclinical BRD had been prevented, the cattle feeder would have realized an additional 10% return on their equity during the 180 days the animal was being finish fed. This equals a 20% return on equity on a yearly basis. The impact of subclinical BRD is enormous.
Table 1.

<table>
<thead>
<tr>
<th>LUNG SCORING CODES EXPLAINED</th>
</tr>
</thead>
<tbody>
<tr>
<td>AV right side evaluation</td>
</tr>
<tr>
<td>0 Normal / Negative (includes depressed healed areas), ½ = half views BUT evaluated AV right side</td>
</tr>
<tr>
<td>1 5% or less of lung affected with a granular, dark purplish &amp; meaty: collapsed/consolidated – Mycoplasma like (Bronchiectasis - AV Broncho-Pneumonia), and/or minor adhesions / pleuritis (fibrin tags) OR</td>
</tr>
<tr>
<td>2 Numerous adhesions (fibrin tags) affecting more than one A.V lobe (&gt;5% lung volume) and/or small missing piece of lung ... and/or ... &gt;10% affected with Mycoplasma like lesions (dark depressed purple areas) including Bronchiectasis - AV Broncho-Pneumonia</td>
</tr>
<tr>
<td>3 FUBAR (Fouled Up Beyond All Recognition): Large amount of missing lung tissue. Caused by pleuritis &amp;/or adhesions greater than 15% of the total lung volume and/or Active (inflamed tracheobronchial &amp; mediastinal lymph node (LN), may see acute to chronic inflammation ... swollen tissue, new adhesions. Note: look for purple ink … inspectors usually condemn these lungs … do not confuse with contamination, condemnation or heart condemnation.</td>
</tr>
</tbody>
</table>

References
77:3168-3175.


Field Results from Whisper® Stethoscope Studies
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Dr. Kurt Brattain, kbrattain@geisslercorp.com
Dr. Greg Quakenbush, gquakenbush@geisslercorp.com
Garrett Taylor, gtaylor@geisslercorp.com

Introduction
There are plenty of challenges in the feedlot industry, but our #1 health problem remains and is still in first place after more than a 100-year reign. That health problem is of course bovine respiratory disease or BRD. Morbidity rates vary between respective feed yards but BRD likely remains the #1 cause of illness and death.

One area on the BRD battlefield where we have been historically weak is in the area of “case definition” or diagnosis. Numerous research findings demonstrate a weak correlation between lung lesions at harvest and treatment histories at the feedlot. “Our current methods of disease diagnosis are not adequate for evaluating management changes or product efficacy if we are interested in understanding the cost effectiveness of our decisions.” (Bryant, Perino, 1999).

The industry has a poor track record in regards to correctly diagnosing BRD in part because we have lacked specific chute side diagnostic tools. In most feedlot hospitals or processing barns one will find a thermometer and nothing else. With no disrespect to the thermometer, it is not a specific diagnostic tool. The presence of a fever does not diagnose BRD. Analysis of hospital records measuring correlations between rectal temperatures and case fatality rates suggest that obtaining a rectal temperature may not constitute a thorough physical exam.

Methods
To analyze the effectiveness of current diagnostic tools (temperature, manual lung scores, and Whisper® lung scores), two data sets were collected. The first focused on discovering the correlation between rectal temperature, manual lung scores, and case fatality rate. The second data set focused on the improvement that Whisper® scores and rectal temperature could provide over either tool alone.

For the first, data were collected from a single feedlot source and analyzed on 3,063 head for “at-pull rectal temperature” and case fatality outcomes on health records that had temperatures recorded at greater than 100°F and less than 109°F. From the same feedlot source, 3,112 head were analyzed for lung scores (on a 10 point scale) and case fatality outcomes. Pearson correlation statistics were generated using Fisher’s z transformation and weighted by within temperature or within lung score categories by frequency count. Alpha levels at 0.05 were imposed to interpret the results testing for a null hypothesis of a zero correlation. Analysis was done using SAS 9.4 CORR module.

For the second, predictive analysis was performed using a stepwise logistic regression approach (SAS 9.4 LOGISTIC module). 15,411 head were analyzed from health records on BRD first time pulls across eight feedlots. There were 1,339 (8.68%) post treatment deads and 14,072
survivors. To preserve clinical relevance and align established treatment protocols with temperature, cases were categorized into two groups: Fever group (temperature at 104.5°F or greater) and No Fever group (temperature less than 104.5°F). To preserve consistency across feedlots, lung scores were assessed with Whisper® stethoscopes and software rendering a 5 point lung score scale. ROC curves and $R^2$ estimates were used to assess model performances at each step. Wald confidence intervals on odds ratio estimated were calculated to interpret results. At each step, false-negatives (those deads not classified as a positive diagnosis for a given diagnostic technique) were assessed and used to compare model performance and ultimately clinical usefulness of diagnostic technique.

**Results**

The first data set and analysis provided the motivation for the development of the lung scoring technique. Table 1 describes the population analyzed. Temperature correlated to case fatality rate at $r = 0.060$ (95% CI 0.024 – 0.095). Fisher’s $z$ was 0.0601, $p = .0009$. (see table 2.)

This lack of correlation between temperature and mortality inspired veterinarians to teach caregivers to use conventional stethoscopes to assign lung scores to pulled cattle. These manual lung scores were used to predict prognosis, select anti-infectives (AIF), assess pen rider skill, and assess disease severity in priority pens.

Table 3 gives a summary of the population where manual lung scores were collected. Lung score correlated to case fatality rate at $r = 0.799$ (95% CI 0.785 – 0.811). Fisher’s $z$ was 1.0956, $p < .0001$ (see table 4.) Both analyses indicated a Fisher’s $z$ statistic significant at an alpha level of $< 0.05$ with no overlap in 95% confidence intervals.

The primary issue with manual lung scores is ensuring consistent scores across caregivers and locations. This lack of consistency motivated the use of Whisper® to evaluate just how much utilizing both tools can improve the ability to reduce unexpected mortality.

The logistic model with intercept was significant; Wald chi-square = 3137.529, $p < 0.0001$. Stepwise regression analysis included Whisper® lung score at the first step. ROC curve went from 0.5000 to 0.6434 and residual chi-square was 199.8060, $p < 0.0001$. At the second and final step Fever was enter into the model. ROC curve went from 0.6434 to 0.6869 with Type 3 Analysis of effects showing Fever Chi-square = 192.1828, $p<0.0001$ and Whisper® lung score Chi-square = 294.8952, $p <0.0001$. Odds ratios for Fever were 2.274 (95% CI 2.025 – 2.555). Whisper® lung score odds ratios were: 1 vs. 5 (0.151, 0.119-0.191) 2 vs. 5 (0.306, 0.247-0.379), 3 vs. 5 (0.444, 0.357-0.554), 4 vs. 5 (0.561, 0.415-0.755). Parameter estimate for the intercept was -2.0693 (95% CI -2.1425 to -1.9976). The number of false negatives with Fever as a diagnostic test predictor (i.e. those that died and did not have a fever) was 608 head. The number of false negatives with Whisper® lung score of ‘1’as a diagnostic test predictor (i.e. those that died and scored a ‘1’ on lung score) was 398 less than Fever at 210 head. The number of false negatives with a combined Fever and Whisper® lung score diagnostic test predictor was 102 head or 506 less head than Fever alone as diagnostic test predictor and 108 less head than Whisper® lung score as a diagnostic test predictor of fatality. (see table 5.)
Data analysis indicates that the use of lung score data is more likely to predict treatment outcomes than a thermometer and that the incorporation of lung score and fever presence together most accurately explains mortality.

Making a proper diagnosis remains a challenge in many feedlots. Caregivers select cattle to undergo hospital evaluation based on pen observations that include clinical depression, anorexia, exercise intolerance, and abnormal posture. BRD complex can contribute to these signs but so can dehydration, fatigue, lameness, and digestive disorders. A significant number of cattle taken to hospitals do not have BRD and do not deserve BRD treatments. More importantly, treatment success of cattle with BRD depends on an accurate diagnosis and severity. AIF response can vary by feedlot and lung score. Treatment protocols can be designed to fit BRD severity. Antibiotic response comparisons are more valid when stratified by lung score severity. Chute-side lung score data provides information that refines pen rider activities, guides hospital management decisions, and identifies priority pens with BRD epidemics.

Table 1.
Table 2.

<table>
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<tr>
<th>Number of Head</th>
<th>Correlation</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,063</td>
<td>6.0%</td>
<td>2.5%</td>
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<td></td>
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<td>9.5%</td>
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* Pearson Correlation Fisher’s Z Transformation : p = .0009

Table 3.

<table>
<thead>
<tr>
<th>Lung Score</th>
<th>Case Fatality Rate</th>
<th># of Dead</th>
<th>Total Head</th>
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<tr>
<td>1</td>
<td>8.6%</td>
<td>12</td>
<td>139</td>
</tr>
<tr>
<td>2</td>
<td>4.6%</td>
<td>9</td>
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<tr>
<td>3</td>
<td>4.3%</td>
<td>21</td>
<td>488</td>
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<td>4</td>
<td>5.0%</td>
<td>42</td>
<td>837</td>
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<td>5</td>
<td>8.9%</td>
<td>57</td>
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<td>6</td>
<td>9.4%</td>
<td>33</td>
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<td>13.4%</td>
<td>26</td>
<td>194</td>
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<td>14.1%</td>
<td>28</td>
<td>198</td>
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<td>9</td>
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<td>31</td>
</tr>
<tr>
<td>10</td>
<td>32.3%</td>
<td>21</td>
<td>62</td>
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<tr>
<td>Overall</td>
<td>8.4%</td>
<td>260</td>
<td>3,112</td>
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Table 4.

<table>
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<th>Correlation</th>
<th>Confidence Interval</th>
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<tbody>
<tr>
<td>3,112</td>
<td>79.8%</td>
<td>78.5%</td>
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<td></td>
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<td>81.1%</td>
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* Pearson Correlation Fisher’s Z Transformation : p < .0001
Table 5.

<p>| BRD Severity Diagnostic Methods : 15,853 First Pulled Animals and Case Fatality Outcomes By Diagnostic Results |
|--------------------------------------------------|--------------------------------------------------|
| <strong>Diagnostic Result</strong> | <strong>Results of Diagnostic Techniques</strong> |</p>
<table>
<thead>
<tr>
<th></th>
<th># Deads</th>
<th>% of Total Deads</th>
<th>% Reduction Over No Fever</th>
<th>% Reduction Over Whisper Lung Score 1</th>
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</thead>
<tbody>
<tr>
<td>No Fever</td>
<td>608</td>
<td>43.5%</td>
<td>-</td>
<td>-190%</td>
</tr>
<tr>
<td>Whisper Lung Score of 1</td>
<td>210</td>
<td>15.0%</td>
<td>65%</td>
<td>-</td>
</tr>
<tr>
<td>Whisper Lung Score of 1 and No Fever</td>
<td>102</td>
<td>7.3%</td>
<td>83%</td>
<td>51%</td>
</tr>
</tbody>
</table>

**Conclusion**

Imagine we had two human medical clinics staffed by two different doctors. At medical clinic “A” the doctor spends little time with each patient and routinely provides a script for antibiotics. At clinic “B” the doctor takes a bit more time and typically gets a good history, does an exam, requests blood work, X-rays, or etc. to obtain a diagnosis. After each doctor has seen 1000 patients, which clinic would you expect to have the highest success rate and possibly the lowest mortality rate? Which doctor would you want to have for your physician?

The above example is a bit extreme, but the point is that the feedlot industry has tremendous opportunity to improve animal care, treatment success, lower mortality rates, and improve antibiotic stewardship. It all starts with understanding and embracing the opportunity provided by new diagnostic tools such as that provided by Whisper®.

Production animal medicine has plenty of obstacles, nuances, and challenges that are not to be found in human medicine. When used in a production animal setting, Whisper® is neither perfect nor infallible. However, the utilization of auscultation via Whisper® has resulted in better case definition, improved risk assessment, stratification of cattle by lung score, and targeted antibiotic treatments.

**References**

Timely Diagnosis of Dairy Calf Respiratory Disease
Using a Standardized Scoring System
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Abstract
Respiratory disease of young dairy calves is a significant cause of morbidity, mortality, economic loss and animal welfare concern but there is no gold standard diagnostic test that identifies affected live animals. Clinical signs typically used to make a diagnosis of respiratory disease of calves are fever, cough, ocular or nasal discharge, abnormal breathing, and auscultation of abnormal lung sounds. Unfortunately, routine screening of calves for respiratory disease on the farm is rarely performed and until more comprehensive, practical and affordable respiratory disease screening tools like accelerometers, pedometers, appetite monitors, feed consumption detection systems, remote temperature recording devices, radiant heat detectors, electronic stethoscopes, and thoracic ultrasound are validated, timely diagnosis of respiratory disease can be facilitated using a standardized scoring system. We have developed a scoring system that attributes severity scores to each of 4 clinical parameters; rectal temperature, cough, nasal discharge, ocular discharge or ear position. A total respiratory score of 5 points or higher (provided that at least 2 abnormal parameters are observed) can be used to distinguish affected from unaffected calves. This can be applied as a screening tool twice-weekly to identify preweaned calves with respiratory disease thereby facilitating early detection. Coupled with effective treatment protocols this scoring system will reduce post weaning pneumonia, chronic pneumonia and otitis media.

Introduction
As reported by producers in the most recent dairy study, respiratory disease was responsible for antibiotic treatment of 12.4% of preweaned dairy calves and 22.5% of the preweaned dairy calf deaths (USDA, 2008; USDA 2009). In dairy calves examined by a veterinarian, the reported incidence and prevalence of preweaned dairy calf respiratory disease are even higher at 25.6% (Virtala, 1996) and 14.3% (Lago, 2006), respectively.

The economic costs attributed to respiratory disease of calves including treatment expense, mortality, premature culling, reduced growth, impaired fertility, and reduced milk production in the first lactation on a typical Dutch farm ranges from $21.37 to $66.32 (median: $36.19) (van der Fels-Klerx, 2001). An earlier US study (Kaneene, 1990) reported the total cost, including prevention, of preweaned respiratory disease to be $14.71 per calf.
Despite the prevalence and importance of respiratory disease in preweaned calves, the diagnosis is problematic and delayed diagnosis may result in prolonged use of antibiotics, a high recurrence rate, and the development of refractory sequelae such as chronic lung injury, pulmonary abscession, ear infections and endemic herd respiratory disease. The potential reasons for poor farm detection of dairy calf pneumonia are numerous and include lack of veterinary input and training, poor knowledge of clinical signs of respiratory disease by farm staff, inaccurate detection methods, inappropriate timing of respiratory disease screening, lack of time, personnel limitations, poor equipment, limited animal contact and other social pressures.

Regular on-farm screening for disease in preweaned dairy calves is rare. Instead, appetite-based observations or other empiric measurements all too frequently serve as the basis for identifying sick calves. Without regular screening for respiratory disease, dairy calf respiratory disease detection on farms is poor (McGuirk, unpublished data). Although the correlation between clinical signs of respiratory disease and lung lesions at slaughter in young dairy calves may depend on severity of disease, timing of screening and duration of disease (Leruste, 2012), an on-farm screening procedure performed on a regular basis by individuals trained to recognize and grade selective clinical signs associated with respiratory disease may help identify previously unrecognized respiratory problems. Early recognition by a respiratory scoring system can prompt further diagnostic testing (ultrasound, other imaging, airway sampling, blood testing) or treatment, depending on farm protocol.

**Respiratory Scoring System**

The basis of the clinical signs-based respiratory scoring system described here is that when 2 or more examination parameters are moderate or severely abnormal, respiratory disease is present. The examination parameters and graded scale evaluation criteria are summarized in Table 1 and available at: [http://www.vetmed.wisc.edu/dms/fapm/fapmtools/8calf/calf_respiratory_scoring_chart.pdf](http://www.vetmed.wisc.edu/dms/fapm/fapmtools/8calf/calf_respiratory_scoring_chart.pdf).

As characterized in Table 1, points range from 0 to 3 as clinical signs progress from normal (0), to mildly abnormal (1), to moderately abnormal (2) to severely abnormal (3). Calves with a total respiratory score ≥ 5 or that have 2 or more clinical parameters with score 2 or 3 are considered to have respiratory disease. For calves in group pens, the respiratory screening process can be modified: [http://www.vetmed.wisc.edu/dms/fapm/fapmtools/8calf/group_pen_respiratory_scoring_chart.pdf](http://www.vetmed.wisc.edu/dms/fapm/fapmtools/8calf/group_pen_respiratory_scoring_chart.pdf).

The respiratory scoring system becomes one of the tools used in a farm’s calf health screening program. A successful screening program has three components: 1) daily observations; 2) twice weekly screening tests; and 3) a defined exam process. Respiratory scoring is part of the twice-weekly health screening program but it is also used when workers doing daily observations have marked an individual calf as needing a more detailed examination. Calves selected for daily examination may be high risk calves (assisted delivery, poor calf vigor score, failure of passive transfer), recheck calves, calves found standing when 90% are sleeping, calves slow to
stand at feed delivery, calves with diarrhea, calves with sunken eyes, calves with abnormal posture, calves that are coughing or breathing abnormally or calves that have blood visible externally (nose, mouth, skin, or feces). Respiratory disease prevalence increases with age in preweaned calves (Lago, 2006) so strategic use of a standardized respiratory screening procedure to identify and treat affected calves just prior to weaning can positively impact the common occurrence of post weaning pneumonia.

Table 1. Clinical parameters and point scale used for respiratory clinical scoring.

<table>
<thead>
<tr>
<th>Clinical Parameter</th>
<th>Points and Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal temperature (°F)</td>
<td>0</td>
</tr>
<tr>
<td>100-100.9</td>
<td>101-101.9</td>
</tr>
<tr>
<td>Cough score</td>
<td>No cough</td>
</tr>
<tr>
<td>Nasal discharge score</td>
<td>Normal, serous discharge</td>
</tr>
<tr>
<td>Eye or ear score</td>
<td>Normal eye and ear</td>
</tr>
</tbody>
</table>

With the regular implementation of a standardized scoring system to detect respiratory and other disease in preweaned calves, additional labor will be required. From a University of WI Extension study (http://eauclaire.uwex.edu/files/2013/07/ICPA-2013-PPT-Overview.pdf), it has been estimated that, on average, 1 full time equivalent (FTE) employee is needed for each 100 calves to perform the routine daily chores. We estimate that an additional 0.5 FTE is needed for every 100 calves to perform daily and weekly health screening procedures such as the standardized respiratory scoring system described here. Initially, farms can expect increases in number of calves treated, treatment costs, respiratory morbidity and calls to the veterinarian. At the same time, mortality rate from respiratory disease is expected to decrease. Over time, decreases in calf treatment rate, number of days of treatment, treatment relapses, treatment costs, and morbidity and mortality measures will all be appreciated. Long-range productivity and profitability of replacement heifers adds value and worker satisfaction with performance of the calves reduces employee turnover, improves motivation and job performance. Individual calf scoring results can be entered into a record system to track performance and cost, monitor disease incidence, analyze treatment efficacy or create valuable health reports. When a change in prevalence of respiratory disease is detected, appropriate diagnostic testing can be focused on the most recent, untreated diseased calves.
Summary and Conclusions
Individual respiratory screening exams performed twice weekly can improve respiratory disease detection in preweaned dairy calves. Early detection with appropriate diagnostic testing and effective treatments will minimize antibiotic use, disease recurrence, chronic respiratory disease cases and endemic dairy calf pneumonia.

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USDA–APHIS–VS, CEAH. Fort Collins, CO #N482.0908
USDA:APHIS:VS, CEAH. Fort Collins, CO #N494.0209
**Design and validation of an on-farm bovine respiratory disease scoring system for dairy calves**

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**Abstract**

We developed an on-farm scoring system for bovine respiratory disease (BRD3) comprised of 6 clinical signs classified as normal or abnormal. Cough, eye discharge, fever (≥ 39.2°C) and abnormal respiration were each assigned 2 points, nasal discharge was assigned 4 points and ear droop or head tilt were assigned 5 points. A score of 5 or higher was the optimal cut-off to classify BRD cases. The new scoring system’s sensitivity to detect pneumonia in calves was 57% and its specificity to classify calves without pneumonia was 90%. The simple design and reduced calf handling required by our BRD3 scoring system make it advantageous for on-farm use.

**Introduction**

Bovine respiratory disease (BRD) is an important disease of cattle that leads to reduced weight gain and productivity. Field diagnosis remains a challenge for control and treatment of BRD. Several clinical scoring systems have been proposed, including the Wisconsin (WI) system1 which uses five clinical signs, each partitioned into 4 levels of severity. The objectives of this study were to develop and validate an on-farm scoring system for BRD in preweaned dairy calves.

**Materials and Methods**

**Scoring system development.** A matched case-control study was performed on a large calf ranch in the San Joaquin Valley. Clinical signs observed included ocular and nasal discharge, cough, head tilt, ear position, rectal temperature, respiratory quality and effort, appetite, and stool quality. Viral PCR tests were performed to detect infectious bovine rhinotracheitis, bovine viral diarrhea virus, bovine respiratory syncytial virus, and bovine coronavirus. Swabs were also cultured for aerobic bacteria and mycoplasma. Cases were defined as calves that were clinically ill and culture- or PCR-positive for BRSV, unpigmented *Mycoplasma spp.*, *B. trelhalosi*, *H. somnus*, *M. haemolytica*, or *P. multocida*. Controls were clinically healthy and negative for all pathogens. Conditional logistic regression coefficients were used as the weights for each clinical sign.

**Scoring system validation.** Using a nested case-control study, hutch-raised calves were enrolled from 4 dairies and a calf ranch. Calves were scored using both systems and evaluated for
pneumonia using auscultation and thoracic ultrasound (TUS) that were interpreted in parallel to estimate the sensitivities and specificities of each scoring system.

**Results**

For the scoring system development, clinical signs and pharyngeal and nasal swabs were collected from 2030 Holstein calves in 2011 as part of the BRDC CAP consortium (www.brdcomplex.org). The developed system (BRD3) used 6 clinical signs each classified as normal or abnormal. Cough, eye discharge, fever (≥ 39.2°C) and abnormal respiration were each assigned 2 points, nasal discharge was assigned 4 points and ear droop or head tilt were assigned 5 points. A score of 5 or higher was determined to be the optimal cut-off to classify BRD cases. Hence, users would obtain a temperature only if a calf had nasal discharge, ear drop or head tilt.

For the validation study, 500 calves were enrolled and ranged from 15 to 137 days old. The BRD3 scoring system's sensitivity for pneumonia in calves was 57.0% and its specificity for calves without pneumonia was 89.9%. The WI scoring system sensitivity for pneumonia in calves was 56.1% and its specificity for calves without pneumonia was 93.1%. The sensitivities and specificities of the two systems were not significantly different.

**Significance**

The sensitivity of the WI score was similar to that reported by Buczinski et al, however, the specificity was higher (93.1% versus 58.0%). Such a difference may be attributed to the difference in case definitions between studies; specifically, only ultrasound was used to define BRD in the study by Buczinski et al., whereas both TUS and auscultation in the current study. The comparable sensitivity and specificity, simpler design and reduced calf handling required by the BRD3 system make it advantageous for on-farm use.

**Acknowledgements**

The scoring system was developed using case-control data that was collected as part of the Bovine Respiratory Disease Complex Coordinated Agricultural Project (BRDC CAP) funded by the USDA National Institute of Food and Agriculture (Grant #2011-68004-30367; J. E. Womack, PD). Developing the scoring system and its validation was funded by the University of California at Davis Division of Agriculture and Natural Resources (Grant #1753). The authors thank the study dairies and calf ranch owners for their participation, and Mr. Paul Rossitto and Dr. D. Williams for technical assistance.

**References**

Genetics of BRD in cattle: Can breeding programs reduce the problem?

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Abstract
Genetics is responsible for approximately half the observed change in performance internationally in well-structured cattle breeding programs. Almost all, if not all, individual characteristics, including animal health, have a genetic basis. Once genetic variation exists then breeding for improvement is possible. Although the heritability of most health traits are low to moderate, considerable (i.e., exploitable) genetic variation does exist. From the limited studies undertaken, and mostly from limited datasets, the direct heritability of susceptibility to BRD varied from 0.07 to 0.22 and the maternal heritability (where estimated) varied from 0.05 to 0.07. Nonetheless, considerable genetic variation clearly exists; the genetic standard deviation for the direct component (binary trait), although varying across populations, varied from 0.08 to 0.20 while the genetic standard deviation for the maternal component varied from 0.04 to 0.07. Little is known about the genetic correlation between genetic predisposition to BRD and animal performance; the estimation of these correlations should be prioritized. (Long-term) breeding strategies to reduce the incidence of BRD in cattle should be incorporated into national BRD eradication or control strategies.

Introduction
Genetics is responsible for approximately half the observed change in performance internationally in well-structured cattle breeding programs. Performance change here implies improvement (e.g., milk yield in dairy cows and growth rate in beef) but also deterioration (e.g., reproductive performance in dairy and beef cattle). The advantage of genetic selection is that it is cumulative and permanent; although most well-structured breeding programs achieve genetic gain of ~1% per annum, this equates to an annual 10% improvement by year 10, or cumulatively a 55% improvement over those 10 years. Therefore, although management has a considerable influence on the performance levels of an individual, genetics, and therefore genomics, should also be part of a (long-term) strategy for improvement. Genetics creates the potential for performance, management realizes that potential, but disease destroys the potential.

Technical terms
Many technical terms are used in animal breeding which are briefly described (Berry et al., 2011):

**Phenotype.** The phenotype is simply the observed performance of an animal “in the field” (e.g., the presence or absence of infection as measured by a positive or negative diagnostic test result).

**Genotype:** The definition of genotype varies. Animal breeders commonly use genotype to describe a particular strain of animals (e.g., animals of a given breed from a particular origin).
Molecular geneticists however commonly use genotype to describe the genetic variants (i.e., alleles) an individual possesses at a particular position in its DNA, also known as a locus.

**Genetic variation:** A measure of the variation or differences within a population that is due to the differences in genetic merit of the animals. More commonly, genetic variation is expressed as the genetic standard deviation (i.e., the square root of the genetic variance) within a population.

**Heritability:** Heritability summarizes the proportion of phenotypic variation, or differences among a cohort of animals, attributable to genetic variation between individuals. Animal breeders commonly cite the narrow sense heritability ($h^2$), which is the proportion of phenotypic variation attribute to additive genetic variation (i.e., allelic effects passed on from one generation to the next). Heritability varies from 0 (not heritable) to 1 (fully heritable). If the heritability is high, we can expect a large proportion of the phenotypic differences of the parents to be passed on to the progeny. Also, the larger the heritability, the greater the expressed phenotype resembles the underlying genetic merit of the animal. Low heritability does not necessarily imply slow/no genetic progress and conversely high heritability does not necessarily imply rapid genetic progress.

**Maternal heritability:** Maternal heritability is the proportion of phenotypic variation among offspring that is due to the genes expressed by the dam. A maternal heritability of calving difficulty is often quoted which encompasses for example, the pelvic size of the dam. The direct heritability for calving difficulty is the effect of the alleles of the dam (and sire) on, for example, the size of the calf. Maternal heritability estimates have also been reported for weaning weight which includes genetic characteristics of the dam such as her milk yield.

**Genetic correlation:** A genetic correlation describes the strength of the linear relationship between two traits due to the genetic influences on each trait. It varies from -1 (strong negative relationship) to 0 (no relationship) to +1 (strong positive relationship between two variables). Genetic correlations can be due to the same genomic mutation affecting both traits (termed pleiotropic effect) or different genomic mutations affecting both traits but tending to, on average, be inherited together (i.e., linked).

**Estimated breeding value (EBV):** Estimated breeding value is an 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. Using traditional methods of genetic evaluation, the true breeding value (or true genetic merit) is not known. The estimates of genetic merit are generally presented as the predicted transmitting ability (PTA) in dairy cattle or expected progeny difference (EPD) in beef cattle which are the EBV divided by two (i.e., an animal only passes half its genes to its progeny).

**Genetic improvement**

Annual genetic gain for a given trait may be described by the following equation (Rendel and Robertson, 1950):

$$
\Delta G = \frac{i \cdot r \cdot \sigma_g}{L}
$$
where $\Delta G$ is annual genetic gain; $i$ is the intensity of selection; $r$ is the accuracy with which you know the genetic merit of each animal, $\sigma$ is the genetic standard deviation (i.e., the square root of the genetic variance or simply just a measure of the genetic differences among animals), and $L$ is the generation interval. All else being equal, the greater the selection intensity (in other words, the smaller the proportion of extreme animals you select for a given trait), the greater will be the genetic gain for that trait. The accuracy of selection is affected by both the heritability of the trait and the information available on either the animal itself and its relatives. Figure 1 illustrates how the accuracy of selection, ignoring pedigree contributions, increases as the number of half-sib progeny with records increases for different heritability estimates. For a given number of progeny, the accuracy will be greater for higher heritability traits. However, accuracies of near unity are still achievable even for low heritability traits if sufficient information is available. Therefore, with the appropriate breeding program (i.e., large paternal half-sib groups) and infrastructure for the collection and storage of data, genetic gain in low heritability traits is certainly achievable if genetic variation is present. The accuracy of selection for a given trait may also be augmented by indirect selection for a correlated trait (Figure 1) or exploiting genomic information in the genetic evaluations. The genetic standard deviation is a measure of the variation present in the population and the generation interval is the average age of the parents when its progeny are born. The generation interval is approximately 6 years in dairy and beef cattle but is expected to reduce with the implementation of genomic selection.

Figure 1. Accuracy of selection across different number of half-sib progeny based on direct selection where the heritability of the trait is 0.03 (diamond with continuous line), 0.15 (triangle and continuous line), 0.35 (square with continuous line) and indirect selection where the goal trait is the 0.03 heritability trait and data is available on the 0.35 heritability trait alone (square with broken line) or also available on the 0.03 heritability trait (diamond with broken line), assuming a genetic correlation of 0.80 between both traits.
Lessons from the past

Most Holstein dairy populations worldwide are, on average, subfertile. This subfertility materialized from the now known antagonistic genetic correlation that exists between reproductive performance and milk production and the employed dairy breeding programs that aggressively selected for increased milk production alone. At the time, the antagonistic genetic correlation between milk production and reproductive performance was not known so therefore the repercussions of the implemented breeding programs were not established. The lack of knowledge of this correlation was due simply to a paucity of data on reproductive performance; the lack of data also hindered the ability to monitor reproductive performance over time which would also have alerted the deterioration in reproductive performance.

Nonetheless, once the issue was detected and the presence of genetic variance in reproductive performance quantified, reproductive performance was included in most international breeding goals (Miglior et al., 2005). Figure 2 illustrates the genetic trend in reproductive performance and milk production in the Irish dairy population; such trends are mirrored in almost all other international Holstein-Friesian populations. Moreover, the genetic trends are also reflected in phenotypic (i.e., field) trends. Thus, reproductive performance in Irish dairy cows (and most international Holstein-Friesian cow populations) is now improving due primarily to genetic selection for improved reproductive performance. Despite the antagonistic genetic correlation between milk production and reproductive performance, genetic merit for milk production is also increasing, albeit at a slower rate, to that prior to the inclusion of reproductive performance in the breeding goal.

Figure 2. Genetic trend for fat plus protein yield (■) and calving interval (▲) for Irish Holstein-Friesian dairy cows. (Source: http://www.icbf.com)
The impact of current breeding goals in dairy and beef cattle on susceptibility to BRD is not conclusively known. No large national datasets also exist for incidence of BRD with associated risk factors to evaluate whether any observed annual trends can be accredited to the prevailing breeding programs. Large scale collection of individual animal incidence of BRD and associated environmental risk factors is however probably prohibitive. Nonetheless, a lower cost option exists to evaluate the impact of current breeding strategies on genetic predisposition to BRD. A controlled experiment where animals genetically divergent for the breeding goal can be generated and the animals challenged with the pathogen. Results will indicate whether or not the genetically elite animals succumb more easily to the disease which will permit inferences to be made on the impact of the prevailing breeding strategies.

**Genetics of animal health**

Figure 3 summarizes the mean and variation in heritability estimates for a range of animal health and disease traits in both dairy and beef cattle. On average, the heritability of most health and disease traits is low and is consistent with the low heritability estimates of other viability and fitness traits like reproductive performance (Berry et al., 2014). Nonetheless, variation in heritability estimates exists among populations. Heritability (as described earlier) is a function of the additive genetic variance present in the sample population as well as the corresponding non-(additive) genetic variation; both components are likely to differ between populations. Genetic variance is a function of the DNA allele frequency, the degree of allelic segregation, the allele substitution effect and the mode of allele action; for example no genetic variation exists among a population of cloned individuals. Genetic variation is therefore affected by evolutionary forces like selection, migration, genetic drift, inbreeding and assortative mating. Genetic variation can also vary across time; for example genetically susceptible animals may die or be culled in the presence of a pathogen load and thus the genetic variation in the population of older animals may be less than in a population of younger animals. The estimated environmental variance can also vary across populations and will depend on, for example, factors such as the pathogen load present and even the complexity of the statistical model used in the analysis or the precision of the diagnostic test.

Although varying by health and disease trait, as well as population, there is a general tendency for an antagonistic genetic correlation to exist between animal health and performance (Berry et al., 2011); there is a paucity of large scale studies however in beef cattle necessary for more precise estimates of the genetic correlations. This is not however to say that both traits cannot be improved simultaneously as evidenced by the genetic trends for both milk production and fertility in Figure 2; both milk production and fertility are antagonistically correlated but once both are included in a breeding goal, the genetic merit for both attributes can improve simultaneously. This therefore implies, that breeding goals that select for improved performance (which all breeding goals do) should take cognizance of health traits either directly, through the use of health phenotypes, or indirectly through the use of correlated traits such as general immunity traits, body condition score or survival (and possibly also fertility given it is expected to be linked to animal health).
Figure 3. Mean (♦) and range (standard error bars) in documented heritability estimates for a range of diseases in cattle from 38 different populations.

Genetics of BRD

Few studies have attempted to quantify the genetics of susceptibility to BRD. Only three (relatively) large scale studies exist, including a study undertaken at the US Meat Animal research Center, Clay Center (Snowder et al., 2005; Muggli-Cockett et al., 1992; Schneider et al., 2010), the national Norwegian dairy calf population (Heringstad et al., 2008) and the Irish national dairy and beef population (Berry et al., 2014).

Schneider et al. (2010) reported a heritability for BRD of 0.11 (0.06) in a population of pre-weaned US calves and 0.07 (0.04) in a population of feedlot cattle. However, of arguably more importance, especially in the genomics era, is the extent of the genetic variation present. The genetic standard deviation (transformed to a binary scale) for incidence of BRD in preweaned calves and feedlot cattle was 0.094 and 0.076, respectively signifying considerable exploitable genetic variation was present. Snowder et al. (2005) reported a direct heritability estimates of 0.22 (0.01) and maternal heritability estimate of 0.07 (0.01) for BRD in pre-weaned beef calves at the US MARC research station from the years 1983 to 2000; the genetic standard deviation (transformed to a binary scale) was 0.13 and 0.07 for the direct and maternal component, respectively.

Heringstad et al. (2008) using data from >250,000 calves with a BRD incidence of 0.7% documented a heritability of 0.05 with a genetic standard deviation of 0.20 estimated using a threshold model. Norway is free from both IBR and BVD so therefore the most prevalent agents of BRD in this dataset were bovine respiratory syncytial virus (BRSV) and parinfluenza-3 virus (PI-3).
A compulsory national BVD eradication program was implemented in Ireland in 2012 (a voluntary scheme was implemented prior to 2012) for all cattle. An ear biopsy from all newborn calves is sent by each producer to a laboratory to quantify the presence of BVD virus. Therefore, for the analysis of BVD in Irish cattle almost 4 million calf BVD test results were available. The data were restricted to only calves born into a contemporary group of gestation, a maximum of 60 days apart, where at least one BVD positive calf was detected; this was undertaken to maximize, as far as possible, the equal likelihood of exposure of all animals to the virus. The final dataset consisted of 86,786 calves with an incidence of 9.75%; this does not reflect the national average incidence as it was a highly edited dataset. Primiparae and multiparae were considered separately (as they are managed separately on farm) and the incidence was slightly greater in primiparae.

The direct heritability of BVD was 0.16 (0.02) and the maternal heritability was 0.05 (0.02). The genetic standard deviation for the direct component was 0.08 and the genetic standard deviation for the maternal component was 0.04 implying considerable genetic variation present. The existence of genetic variation in the Irish dataset is exemplified in Figure 4 which presents a histogram of the mean incidence of BVD per paternal half-sib group for sires with >50 progeny in >10 herds. Considerable (exploitable) variation clearly exists. Figure 5 depicts the relationship between sire estimated breeding value for BVD and mean progeny prevalence for BVD. A clear relationship exists substantiating the potential of animal breeding programs to reduce the incidence of BVD/BRD.

![Figure 4. Mean prevalence per paternal half-sib group for dairy and beef sires with >50 progeny in >10 herds.](image-url)
Figure 5. Association between sire estimated breeding value for the direct genetic effect of BVD and sire mean progeny prevalence of BVD for dairy and beef sires with >50 progeny in >10 herds.

Data were also available from Ireland on IBR. Following edits 5,589 IBR records from 4,523 dairy animals (different ages) from 53 contemporary groups were available for analysis; all contemporary groups had at least 1 home-born animal positive for IBR antibodies. Of the 5,589 records 2,581 were IRBgB and 3230 were IRBgE; 236 animals had records for both IRBgB and IRBgE. The incidence of IRBgB and IRBgE positive records in the database was 28.5% and 35.8%, respectively. Heritability estimates for IRBgE (0.03 to 0.06; the lower estimate was not different from zero) was lower than observed for IRBgB (0.28 to 0.34). The repeatability estimates for both varied from 0.42 to 0.69. The genetic standard deviation for the binary trait of IBR status was 0.07 and 0.15 for IRBgE and IRBgB, respectively indicating considerable genetic variation present in these study herds.

The potential gains achievable in genetic merit for susceptibility to BRD is very much dependent on the breeding program implemented (i.e., phenotyping strategy), the genetic parameters for BRD (which we now know, albeit from limited populations) and the genetic correlations between BRD and other traits in the breeding goal (currently not known). With a good breeding program (i.e., high accuracy of selection either through a well-structured and large progeny test or through the exploitation of genomic information) a response of 0.22 genetic standard deviations annually is possible. The genetic standard deviation for BRD from the US and Irish data appear to be approximately 0.10. This however assumes no antagonistic genetic relationship exists between BRD and the entire breed goal. The presence of an antagonistic genetic correlation (which is very likely to exist) will reduce the response to selection.

Conclusions
Exploitable genetic variation in susceptibility to BRD exists among cattle with documented heritability estimates ranging from 0.07 to 0.22 for the direct component and from 0.05 to 0.07 for the maternal component. Little is known of the impact of current breeding strategies on
genetic predisposition to BRD. Including BRD in breeding strategies as a component of national strategies to reducing the financial implications of BRD seems sensible. Breeding strategies for a trait have traditionally been achieved by recording the trait (i.e., BRD) on large populations of animals; although phenotypic information is still required, the use of genomic information in national genetic evaluations is partly reducing the requirement for such phenotypic information on large populations of animals. For the doubters who suggest that genetics is not responsible for animal health and breeding strategies to improve animal health will be futile or too long-term, one only has to read the popular press (and some scientific articles) a decade ago where the same argument was made for reproductive performance. Recent breeding programs are now credited in most countries for the observed improvement in reproductive performance in dairy cows. The same can be achieved for animal health.

Acknowldgements
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References
Results of the BRD CAP project: Progress towards identifying genetic markers associated with BRD susceptibility
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Abstract
The BRD CAP is a 5-year USDA-funded Coordinated Agricultural Project to address the problem of BRD in dairy and beef cattle. An overriding objective of the project is to use the tools of modern genomics to identify cattle that are less susceptible to BRD. To do this two large genome wide association studies (GWAS) were conducted using a case:control design on preweaned Holstein dairy heifers; and Bos taurus beef feedlot cattle. A calf health scoring system was used to identify BRD cases and controls. Heritability estimates for BRD susceptibility ranged from 19-21% in dairy calves to 29.2% in beef cattle when using numerical scores as a semi-quantitative definition of BRD. A GWAS analysis conducted on the dairy calf data showed that SNP effects explained 20% of the variation in BRD incidence, and 17-20% of the variation in clinical signs. These results represent a preliminary analysis of 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 causal single nucleotide polymorphisms (SNPs), and integration of predictive markers for BRD susceptibility into genetic tests and national cattle genetic evaluations.

There is growing interest in the selective breeding of livestock for enhanced disease resistance. In dairy cattle, selection programs have been developed to take advantage of genetic variability in mastitis resistance, despite the fact that the heritability of clinical mastitis is low and mastitis resistance has an adverse correlation with production traits (Rupp and Boichard, 2003). Likewise chicken breeders have long used breeding to improve resistance to avian lymphoid leucosis complex and Marek’s disease (Stear et al., 2001).

The heritability of disease resistance is typically low, partly as a result of suboptimal diagnosis (i.e. not all sick animals are identified, healthy animals may be incorrectly diagnosed as ill, and some susceptible animals will appear resistant when in fact they have not been exposed). Obtaining predictive markers that track disease resistance loci relies on “linkage disequilibrium” (LD) between DNA markers and the causative loci, in this case those associated with BRD resistance. If host BRD resistance is a quantitative trait governed by the action of many genes, as might be expected for this complex trait, then a large dataset of case and control animals will be needed to identify and estimate the effect of all of the large and small causative loci contributing to susceptibility. As a general rule, increasing the accuracy of disease diagnosis
and the size of the case:control study population results in increased power to detect loci associated with disease. Studies involving several hundred to a thousand cases and matched control animals are recommended to achieve the statistical power required to reliably detect genetic variants with small effects on relative risk of disease (Allen et al., 2010).

In 2011, USDA AFRI funded a 5-year grant proposal entitled 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, involves a multi-institutional team led by Dr. James Womack at Texas A&M University, and involves research groups from Washington State University, University of Missouri, Colorado State University, New Mexico State University, USDA ARS, and the University of California, Davis. Coordinated Agricultural Projects are large-scale USDA National Research Initiative (NRI) awards intended to promote collaboration, open communication, exchange information, and coordinate activities among individuals, institutions, states, and regions. CAP participants serve as a team that conducts targeted research or a combination of research, education, and extension in response to emerging or priority area(s) of national need (Van Eenennaam, 2012).

Genome Wide Association Studies
One of the primary aims of the BRD CAP is to reduce the prevalence of BRD in beef and dairy cattle through the identification of genetic loci associated with BRD susceptibility, and to use this information to develop DNA-based selection tools. The foundations of this research effort are two large (2,000 animal) BRD case:control field studies. The first of these was carried out on a large commercial dairy calf ranch in 2011/2012 by researchers at the UC Davis School of Veterinary Medicine Teaching and Research Center in Tulare (T.W. Lehenbauer, S.S. Aly. J.H. Davis, P.V. Rossitto). Pre-weaned Holstein calves from California (CA) (n=2015) were scored using the McGuirk scoring system which evaluates rectal temperature, cough, nasal and eye discharges, and ear position or head tilt (McGuirk 2008). For each clinical sign, a numerical value of 0 to 3 was assigned based on the severity of the clinical signs. Cases were assigned as a score ≥5; controls were <5, typically 3 or less. In CA over 200,000 calves were screened to obtain 1,003 cases and 1,012 controls over 180 days (Neibergs et al., 2013). Each day after completion of respiratory scoring and identification of cases and matched controls, a veterinarian and trial personnel then returned to those animals to collect samples. All case and control calves had nasopharyngeal and pharyngeal recess swabs collected for qPCR diagnostics (B.M. Crossley) and a second pharyngeal recess swab collected for aerobic bacteria and mycoplasma respiratory pathogen culturing (P.C. Blanchard), and blood was taken for DNA extraction and genotyping using the Illumina BovineHD (~770K) BeadChip (H.L. Neibergs). A similar protocol was followed to obtain a validation population of pre-weaned dairy calves in New Mexico (NM) (n=763) (R. Hagevoort, E. Chavez).

An analogous study design was used to obtain 497 cases and 498 controls from a commercial feedlot in 2013 (H. L. Neibergs). All cases and controls were Bos taurus beef cattle. The mean clinical score for cases was 8.04 ± 1.23 and the mean score for controls was 2.06 ± 0.037 (Neibergs et al. 2014b). Collection of additional cases and controls for beef cattle is in progress.
Preliminary Results
Calves identified as BRD cases in the California dairy study using the criterion of a McGuirk score ≥5 were significantly associated with positive cultures of BRSV, Mannheimia haemolytica, Pasteurella multocida, Histophilus somni, and Mycoplasma spp. All 2,030 samples tested for BVDV were negative (Lehenbauer et al. 2013).

Heritability estimates for BRDC susceptibility in dairy calves were 19-21% for NM and CA as individual populations and 13% when combined (Neibergs et al., 2014a). In beef cattle the heritability estimates were 17.7% for the binary case-control phenotype, and 29.2% when using numerical values of the McGuirk system (that ranged from 0 to 12) as a semi-quantitative definition of BRDC (Neibergs et al., 2014b). These estimates are higher than a prior estimate of 0.18 that was obtained for beef feedlot animals, when adjusted to an underlying continuous scale (Snowder et al., 2005). The higher heritability estimate may be attributable to the use of the objective calf health scoring system to more precisely identify BRD cases and controls. Heritability is known to increase when the accuracy of the measured phenotype (i.e. correct assignment of calves to BRCD case or control group) improves (Neibergs et al., 2014b).

A case-control genome wide association study (GWAS) was conducted on the dairy calf data in the laboratories of H.L. Neibergs at Washington State University, C.M. Seabury at Texas A&M University, and J.F. Taylor at the University of Missouri, using four different analytical approaches (GBLUP, EMMAX, SNP and Variation Suite 7 and PLINK). The SNP effects explained 20% of the variation in BRD incidence (Neibergs et al., 2013), and 17-20% of the variation in clinical signs (Seabury et al., 2014). All analytical approaches identified concordant single SNP associations on bovine chromosomes 3, 15 and 23. Twelve additional chromosomes provided evidence for association with two or more approaches. When chromosomal regions (rather than single SNPs) were compared, 29 regions on 13 chromosomes were associated with BRD including those identified in the single SNP association comparison (Neibergs et al., 2013). These results represent a preliminary analysis of ongoing work to identify loci associated with BRD. Subsequent work will include fine mapping in regions associated with BRD (C. M. Seabury, TX) to attempt to identify the causal mutations that actually result in BRDC susceptibility rather than predictive markers that are located in linkage disequilibrium with these mutations. Additional analyses will look at the interaction between host genotype and the results from the diagnostic laboratory.

It should be noted that the GWAS studies detailed in this paper are just one component of the BRD CAP research being conducted to identify genomic regions associated with BRDC susceptibility. Other approaches include the identification of DNA structural variants (differences in the number of copies of a DNA region that alters gene expression) that have major effects on BRDC susceptibility (L. Skow, and S. Dindot, TX); gene expression (RNA-sequencing) studies from challenged animals to identify genes differentially expressed in cattle in response to a pathogen (L. Gershwin, CA and J. F. Taylor, MO); and pathway analysis to identify genes whose individual effects on BRDC susceptibility are small but whose effects on BRDC susceptibility are great when taken together with other genes present in a biological pathway (H. L. Neibergs, WA). It is envisaged that jointly these studies will result in the
information required to enable the much-needed development of DNA tests for the selection of animals that are less susceptible to BRDC.

A validation of the chromosomal regions and SNPs that have been identified as important for BRD susceptibility will be conducted by estimating the predicted transmitting abilities (PTA) of the sires of the CA and NM Holstein calves and evaluating whether their predicted PTA is confirmed by the prevalence of disease in their offspring. The development of genomic breeding values for Holstein sires that are less susceptible to BRDC is underway (C. Van Tassell, MD). Ultimately, the trait of BRD susceptibility will need to be included in the dairy industry economic selection index ($NetMerit). The appropriate selection emphasis for this trait will need to be weighted by its effect on profitability relative to other economically-important traits.

The translation of results to the beef industry presents a more challenging situation. It has been found that the accuracy of prediction equations developed in one breed of beef cattle have not proven to be useful in other breeds when using the more sparsely spaced 50K SNP chip (Van Eenennaam et al., 2014). The BRD CAP envisioned that by performing the GWAS with the Illumina BovineHD BeadChip using ~770K SNPs, predictive markers would be associated with many loci associated with BRD susceptibility and that such markers would be predictive across beef breeds. It is not yet known if this will in fact be the case. There are also developing efforts to whole genome sequence numerous prominent beef bulls throughout the world as a result of the ever decreasing cost of sequencing, and these efforts may further accelerate the identification of causal SNPs that directly affect susceptibility to BRDC.

To date the US beef industry has made little use of economic selection indexes (Garrick and Golden, 2009). Although there is undoubtedly huge value associated with selection against BRD susceptibility (Neibergs et al., 2014b; Van Eenennaam and MacNeil, 2012), to incentivize the inclusion of genomic BRD susceptibility criteria in breeding decisions, and to offset the concomitant decreased selection pressure on growth traits that return value directly to producers who do not retain ownership (i.e. sell on a weight basis prior to feeding), there would need to be some mechanism analogous to a backgrounding premium to transfer the value derived from delivering animals that are less susceptible to BRD to the feedlot back up the supply chain to the producers and breeders involved in making the selection and management decisions that ultimately impact the prevalence of BRD in the beef cattle industry.

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**References**


How Stress Alters Immune Responses During Respiratory Infection
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Abstract
Fall-weaned calves entering the feedlot experience a variety of psychological and physical
stressors, including maternal separation, transportation, social mixing, restraint, and dietary
changes. Mixing calves from multiple sources also exposes them to respiratory pathogens at a
time when maternal immunity has waned. Using an experimental bovine respiratory disease
(BRD) challenge, we analyzed the effects of specific stressors on clinical disease and immune
responses following bovine herpes virus (BHV-1/IBR) infection of naïve calves. Transportation
stress was compared to either abrupt weaning plus transportation or transportation following a
two-step weaning process. Transportation alone significantly (P < 0.05) increased BHV-1
shedding in nasal secretions despite elevated interferon-gamma production in the upper
respiratory tract. In contrast, abrupt weaning and transportation, significantly (P < 0.05)
increased serum haptoglobin on day 3 post-infection (PI) and blood leukocyte TNFα secretion on
day 5 PI. These systemic responses were reduced by instituting a two-step weaning process 4
days prior to transportation and BHV-1 infection. In conclusion, these observations are
consistent with earlier studies implicating weaning and transportation as stressors contributing
to BRD severity and mortality. Current studies also revealed that different stressors or
combination of stressors have distinct effects on host responses to viral infection in naïve
calves.

Introduction
Bovine respiratory disease (BRD) remains the primary cause of mortality in feedlot calves and is
the most costly health problem in these cattle with an estimated cost of $49.55 to $151.18
US/animal (Smith, 2009). Vaccines and antibiotics are the major tools used to control BRD, but
despite increasing use of these treatments, the first two weeks in a feedlot remains a high risk
period for calves to develop fatal respiratory disease (Duff and Galypean, 2007; Snowder et al.
2006). This risk is most pronounced in 400-600 lb beef calves which have no prior vaccinations
for respiratory pathogens, have been recently weaned, transported, and co-mingled with calves
from multiple sources (Ribble et al. 1995; Stanton, 2009).

Management of BRD has focused primarily on the many different viruses and bacteria that
cause respiratory infections in cattle. Vaccines and antibiotics have reduced the impact of these
infections but BRD still remains the primary health problem in the feedlot. This has led to the
suggestion that it may be more effective to focus on the host, rather than the pathogens, to
further reduce the economic cost of this disease (Miles, 2009). Epidemiological investigations
have identified host factors contributing to BRD morbidity and mortality and psychological and
Physical stressors have been identified as important contributing factors in high-risk calves. Psychological stressors include separation from the cow, transport, co-mingling, exposure to new environment, and restraint while calves are processed. Physical stressors include transport, limited access to feed and water, dietary change, and exposure to a variety of new pathogens.

It is difficult to measure and quantify stress responses and determine how much individual stressors or combined stressors contribute to the severity of BRD clinical disease and mortality. Using an experimental BRD challenge model, we demonstrated that combining abrupt weaning and transportation increased mortality from 40-50% to 80-90% (Hodgson et al. 2012). Furthermore, metabolomic analysis of serum samples revealed stress-induced metabolic responses that changed rapidly with time (Aich et al. 2009). We now present evidence that individual stressors, alone and in combination, have differing effects on immune responses following respiratory infection.

**Modeling Stress and BRD Infection**

Crossbred (Angus X Hereford), suckling calves of either sex were selected from a single herd (Gaffe Ranch, Swift Current, SK) where cows were vaccinated pre-breeding with a multivalent, modified-live viral vaccine. Calves were born in April and May and in August serum samples were collected from calves to screen calves for antibody titres to BHV-1. Forty seronegative calves (n = 8 calves/group) were randomly assigned to five experimental groups (Table 1) to determine the effects of transport stress, either alone or in combination with abrupt weaning on clinical disease and immune responses following BHV-1 infection. The effect of abrupt weaning was further investigated by including a group that was weaned using a two-step protocol, previously described by Haley et al (Haley et al. 2005). The day prior to BHV-1 challenge, calves were transported for 3.5 hours prior to being housed in a single pen at the research facility. The average weight of calves on arrival was 218 kg with body weights ranging between 174 and 242 kg. The day following transport, calves were aerosol challenged with a clinical BHV-1 isolate (Isolate 108; 5 X 10^7 PFU/animal) using a nebulizer (Babiuk et al. 1987).

**Monitoring Clinical and Immune Responses to Infection**

Body weight, rectal temperature, and virus shedding in nasal secretions were monitored daily by a clinical veterinarian blinded to treatment groups. Nasal secretions were analyzed for interferon-gamma (IFN-γ) levels on days 0, 3, 5 and 7 post-BHV-1 challenge by capture ELISA (Raggo et al. 2000). Systemic inflammatory responses following BHV-1 infection were monitored by quantifying the level of serum haptoglobin with a capture ELISA (Godson et al. 1995). TNF production by peripheral blood mononuclear cells (PBMCs) was assayed by plating 5 X 10^5 PBMC/well and stimulating cells with 100 ng/ml LPS. Culture supernatants were collected 24 h later and stored -80°C until TNF levels were assayed using a capture ELISA (Mookherjee et al. 2006). Statistical analyses were performed using GraphPad Prism Version 6.10 software (GraphPad Software, Inc., San Diego, CA). The Shapiro-Wilk normality test was performed to determine if data sets were normally distributed. When appropriate either an ANOVA or Kruskal-Wallis analyses were used with Dunn’s post-test for analyses of differences (daily body
temperatures, body weight, serum haptoglobin, IFN-γ and TNF secretion) among treatment groups.

Table 1. Summary of Stressors in Each Experimental Group

<table>
<thead>
<tr>
<th>Group</th>
<th>Transport Stress</th>
<th>Weaning Stress</th>
<th>BHV-1 Infection</th>
<th>Pre-Infection treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Adapt calves to weaning and transportation stress for 2 weeks at research facility</td>
</tr>
<tr>
<td>B</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Adapt calves to weaning stress for 2 weeks at ranch before transport to research facility</td>
</tr>
<tr>
<td>C</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Suckling calves removed from dams the day of transport to VIDO research facility</td>
</tr>
<tr>
<td>D</td>
<td>+</td>
<td>Modified</td>
<td>+</td>
<td>Nose paddles inserted into suckling calves 4 days prior to being transported to VIDO research facility</td>
</tr>
<tr>
<td>E</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Suckling calves removed from dams the day of transport to VIDO research facility</td>
</tr>
</tbody>
</table>

Results

Clinical Data
All BHV-1 infected calves displayed a marked decrease in body weight and similar increases in rectal temperature following BHV-1 infection (Figure 1). Calves undergoing two-step weaning (Group D) were the only group to display a significant difference in body weight during the first 24 h after BHV-1 infection and after day 4 post-infection (PI) all infected groups displayed similar reductions in weight relative to uninfected controls (Group E). Neither transportation alone or combined weaning and transportation altered fever responses following BHV-1 infection. In contrast, the stress of transportation and abrupt weaning significantly (P < 0.05) increased viral shedding relative to Group A, which was pre-adapted to these stressors for two weeks among experimental groups (Figure 1C). There was, however, no significant difference in the duration of virus shedding with fewer than 3 animals/group shedding low but detectable levels of BHV-1 on day 11 PI (Figure 1C).

Innate Immune Responses
BHV-1 infection is a potent inducer of IFN production (Hodgson et al. 2012) and transportation alone (Group B) resulted in significantly higher (P < 0.05) IFN-γ secretion on day 5 PI relative to calves acclimatized for two weeks (Group A). Combining abrupt weaning (Group C) or two-stage weaning (Group D) with transportation reduced IFN-γ secretion but these levels still exceeded Group A (Figure 2A). Serum haptoglobin provides a measure of inflammatory responses following infections, such as a BHV-1 respiratory infection (Hodgson et al. 2012). Combining
transportation and abrupt weaning (Group C) resulted in the highest serum haptoglobin concentration three days after BHV-1 infection (Figure 2B). Transportation alone (Group B) did not result in a similar elevation in haptoglobin and two-step weaning also resulted in a significantly (P < 0.05) lower inflammatory response. Serum haptoglobin levels were similar among Groups A, B and C on day 5 PI, indicating that abrupt weaning had a transient effect on the inflammatory response to BHV-1 infection. A remarkable observation was that modifying the stress of maternal separation, with two-step weaning, significantly reduced the inflammatory response on day 5 PI (Figure 2B). Tumor necrosis factor (TNF) α is a potent mediator of tissue damage and inflammation which contributes to lung pathology during bacterial infection. LPS stimulation of PBMCs prior to BHV-1 infection induced very low levels of TNFα secretion. On day 3 PI, however, TNFα secretion increased significantly (P < 0.05) in all BHV-1 infected animals but combining transportation and abrupt weaning (Group C) resulted in a significantly (P < 0.05) greater elevation of this response (Figure 3C). Transportation alone (Group B) did not enhance LPS responsiveness and using two-step weaning, to modify the stress of maternal separation, also reduced TNFα production.

Discussion

A variety of stressors have been associated with an increased risk of fatal secondary bacterial respiratory infections in humans (Graham et al. 1986) and animals (Hoerlein and Marsh, 1957; Jensen et al. 1957). There is, however, contradictory evidence regarding the contribution made by transportation stress to undifferentiated BRD in feedlot calves (Cole et al. 1988; Ribble et al. 1995), but weaning and maternal separation are highly correlated with an increased incidence of undifferentiated BRD (Step et al. 2008). We recently confirmed that maternal separation and weaning, in combination with transportation, doubled mortality and enhanced inflammatory responses when naïve calves were aerosol challenged with BHV-1 followed by a secondary bacterial infection with *Mannheimia haemolytica* (Hodgson et al. 2012). These studies did not, however, determine the contribution of transportation and maternal separation as individual or combined stressors to enhanced pro-inflammatory responses following BHV-1 infection.

Monitoring clinical responses, including body weight and temperature, confirmed that all calves, with or without stress, develop clinical signs typical of an acute primary BHV-1 infection (Figure 1). Divergent changes in body weight during the early PI period suggest, however, that stressors may induce significant physiological differences among treatment groups at the time of BHV-1 infection. This is consistent with transportation resulting in significantly (P < 0.05) higher virus shedding on day 3 and 5 PI (Figure 1). Serum from stressed calves enhanced BHV-1 replication *in vitro* (Blecha and Minocha, 1983) and stress plays an important role in the recrudescence of latent BHV-1 infections (Pastoret et al. 1985). Therefore, further investigation may be warranted to determine if transportation stress is a factor that influences the severity of a primary BHV-1 infection.

Daily handling of calves to collect samples and data, represents a potentially significant stressor in and of itself that may contribute to the values obtained, but all treatment groups were exposed to this same handling stressor. Nevertheless the stressors we intentionally manipulated had differential effects on a variety of innate immune responses (Figure 2). These differential effects on pro-inflammatory cytokines are of particular interest since our previous investigations revealed that increased inflammatory was significantly correlated with fatal
secondary *Mannheimia haemolytica* respiratory infections (Hodgson et al. 2012). Of particular interest, is that using two-step weaning to modifying the stress of maternal separation significantly (P < 0.05) reduced pro-inflammatory responses. These observations provide the first evidence that management procedures altering psychological stress may have a direct impact on immune responses following a respiratory infection.

Figure 1. Clinical response to BHV-1 infection was monitored daily by measuring changes in body weight (A), temperature (B) and virus shedding in nasal secretion (C). Calves in Groups A to D were infected with BHV-1 and Group E provided an uninfected control. Weight changes were normalized relative to Day 0 to eliminate variation in initial body weights among animals. The number of plaque forming units (PFU)/ml of culture medium was used to quantify infectious virus particles in nasal secretions. Data presented are mean values for each group (n = 8). Significant changes in BW relative to control Group E are indicated only for the first four days post-infection. Virus shedding, relative to Group A, was observed in Group B, C, and D on day 3 and Group B on day 7 post-infection. *P < 0.05
Figure 2. Immune responses following BHV-1 infection. (A) IFN-γ production in nasal secretions following BHV-1 infection. (B) Changes in serum haptoglobin levels following BHV-1 infection. Data presented are mean values for each group. (C) LPS-induced production of TNFα by PBMCs following LPS stimulation. (D) LPS-induced production of TNFα by PBMCs following LPS stimulation. * (P < 0.05)

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References


Review of BRD pathogenesis: the old and the new
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Abstract
The pathogenesis of bovine respiratory disease (BRD) is determined by a complex interaction of environmental, infectious, and host factors. Environment trends could impact feedlot cattle by increasing their level of stress. The polymicrobial nature of BRD produces synergies between infectious agents that can alter pathogenesis. However, the nature of the host response to these environmental and infectious challenges largely determines the characteristics of the progression and outcome of BRD.

The fundamental concept of the pathogenesis of bovine respiratory disease (BRD) in newly arrived feedlot cattle is relatively well defined. Stress and adverse environmental conditions predispose the animal to infection with a virus or other agent that damages respiratory mucosa and alters host immunity so that commensal bacteria become pathogens and produce fibrinopurulent bronchopneumonia. The purpose of this brief review is to highlight a few specific topics of current interest regarding the environment, infectious agents, and the host that are relevant to the pathogenesis of BRD.

Environment
Intensive management contributes to many of the stressors that predispose to BRD (e.g.: crowding, shipping, food and water access, and exposure to multiple pathogens). Feedlot capacity has progressively shifted towards larger feedlots (>31,999 head) compared to smaller feedlots (MacDonald and McBride, 2009). Concurrently, global consumption and demand for beef is projected to increase over the next 10 years (Westcott and Trostle, 2014). These trends suggest there will be continued pressures for intensive management, which will possibly increase exposure of cattle to known and unforeseen management stressors in the future.

Extreme weather (e.g.: very high temperatures, decreased or excessive rainfall, and severe storms) has increased during the past 10-30 years and is projected to continue to increase (Coumou and Rahmstorf, 2012). Extreme events could increase challenges to cattle due to heat stress, dust or mud, high or low humidity, changes in pest and disease distribution, and altered impacts on services that support the feedlot industry (e.g.: cattle inventories, and feed and water quality and supply) (Henry et al., 2012).

Regulatory issues related to climate change, environmental quality and antimicrobial use could also impact the feedlot environment. Livestock reportedly account for 18% of the total climate change-associated global anthropogenic greenhouse gas emissions and contribute substantially to air and water pollution, land degradation and water shortages, and loss of biodiversity (Steinfeld et al., 2006). Antimicrobial use in animal production is considered to contribute to
antimicrobial resistance of human pathogens (Anonymous, 2014). Regulations to reduce greenhouse gas emissions, or to reduce emergence of antimicrobial resistance could have substantial impacts on the characteristics of the feedlot industry and the stressors encountered by feedlot cattle.

Agents
“Stressed” cattle are more susceptible to the influence of contagious or commensal agents associated with BRD. Common viral components of BRD (eg: bovine herpesvirus-1 [BHV-1], bovine parainfluenza virus 3, bovine respiratory syncytial virus [BRSV], bovine virus diarrhea virus [BVDV], and possibly bovine coronavirus), typically contribute to pathogenesis by damaging respiratory mucosa and by modifying the host innate and adaptive immune responses (Hodgins et al., 2002). Many virus infections are self-limiting and predominately serve to promote secondary bacterial infection, but others may cause severe disease due to differences in host susceptibility and the heterogeneity that exists between strains of some BRD-associated viruses.

Common BRD-associated bacteria (e.g.: *Mannheimia haemolytica* [MH], *Pasteurella multocida*, *Histophilus somni* [HS], and *Mycoplasma bovis* [MB]) are commensals that most likely exist in healthy cattle as biofilms (Panciera and Confer, 2010). Some combinations of BRD-associated bacteria occur together in commensal polymicrobial biofilms, most notably HS and PM (Elswaifi et al., 2012). The cooperative community of the biofilm creates an environment in which the bacteria co-exist with the host and are protected against toxins, antimicrobials, and other adverse substances or agents (McDougald et al., 2012). Biofilm bacteria often downregulate virulence factor production, but alteration of the biofilm microenvironment (e.g.: changes in nutrient concentrations, hypoxia, high or low temperatures, and other stressors), can trigger dispersal of large numbers of planktonic (free-living) forms which quickly convert to a virulent phenotype (Landini et al., 2010; McDougald et al., 2012). Biofilm dispersal is one mechanism by which commensal BRD-associated bacteria could become pathogenic and colonize deeper portions of the lung. Colonization of the upper respiratory tract by HS is most efficient when phosphorylcholine is expressed on its surface lipooligosaccharides (LOS) (Elswaifi et al., 2012). However, when phase variable loss of phosphorylcholine expression occurs, the bacteria disperse from the biofilm and invade systemically. A similar situation may occur with capsular expression by MH. The capsular characteristics of typically non-virulent MH serotype 2 from the nasal cavity of normal calves may reflect a colonizing phenotype more likely to exist in a commensal biofilm. In contrast, the capsular characteristics of more virulent MH serotype 1 isolated from pneumonic lungs may represent a planktonic form dispersed from the biofilm.

Once established in the lung, bacteria are responsible for inflammation and bronchopneumonia associated with severe BRD. Bacteria associated with BRD damage the host by virtue of a variety of virulence factors and the host response to these factors (Panciera and Confer, 2010). Notable among the virulence factors are leukotoxin and lipopolysaccharide of MH (Singh et al., 2011), LOS and immunoglobulin binding protein A of HS (Agnes et al., 2013), and variable surface proteins of MB (Caswell et al., 2010). Similar to BRD-associated viruses, there is
considerable strain variation within these bacteria which is sometimes reflected in differences in disease severity.

The polymicrobial nature of BRD determines many events in the pathogenesis of pneumonia. Enhanced or altered pathogenesis can occur due to the synergistic effects of various combinations of BRD-associated agents to cause more severe disease than that caused by either agent alone. Some combinations of agents that result in enhanced disease include MH with MB, BHV-1 or BVDV (Leite et al., 2004; Ridpath, 2010; Caswell et al., 2010), HS and BRSV (Gershwin et al., 2005), and MB and BHV-1 (Prysliak et al., 2011). The various combinations of virulence factors can cause direct host injury, but these synergisms also alter host responses involved in pathogenesis (e.g.: enhancement or inhibition of cytokine production, alteration of cell surface receptors, activation or inhibition of neutrophil and macrophage functions, and immunosuppression and interference with immune functions (Srikumaran et al., 2008; Caswell, 2014).

Host
There are inherent anatomical, physiological and immunological features of the bovine that make it more prone to pneumonia, such as a large amount of respiratory dead space volume and poor collateral ventilation, pulmonary intravascular macrophages, and high numbers of circulating gamma-delta T cells (Ackermann et al., 2010). Within the lung, antimicrobial peptides, cytokines, activities of epithelial and inflammatory cells and other innate or acquired immune responses are the resources available to prevent BRD (Ackermann et al., 2010). However, these responses can fail or create adverse effects in response to a multitude of environmental and infectious pulmonary challenges (Caswell, 2014).

Innate responses are often considered an important source of damage to the lung during the pathogenesis of BRD. Most commonly incriminated is an excessive and poorly regulated pro-inflammatory response to BRD agents that can cause extensive cell and tissue injury. However, in some cases it may be the lack of an anti-inflammatory balance in the host response that enhances disease. In a mouse model of viral-bacterial synergism, viral involvement caused fatal disease even when the bacterial infection was controlled by the immune system, (Jamieson et al., 2013). Fatality and severe disease in this study was proposed to be due to an impaired ability to tolerate and manage tissue damage partially due to downregulation of genes involved in tissue protection and repair. In bovine bronchial epithelial cells co-infected with BHV-1 and MH, a gene involved in wound healing, fibrosis, and apoptotic functions of inflammatory cells (CYR61), was upregulated less than pro-inflammatory genes by the co-infection compared to either agent alone. The inhibition of pro-inflammatory NF-kappa B signaling and stimulation of secretion of anti-inflammatory substances by macrolide antibiotics is considered to be one reason for their effectiveness in treatment of BRD (Fischer et al., 2014). The complex interactions between the pro- and anti-inflammatory components of the host response are critical aspects of BRD pathogenesis. The optimal situation is to strike a balance between a pro-inflammatory host response that eliminates the agents of BRD, without causing excessive tissue injury that could overwhelm anti-inflammatory responses that are necessary for healing and repair of the damaged lung.
Multi-institutional and U.S.D.A. Agricultural Research Service projects using large numbers of cattle are underway to determine the genetics of resistance to BRD; the results of which could have major implications for improving host responses to BRD in the future. Observational phenotypes (e.g.: breed, treatment rates, lung lesions, and production parameters) are generally associated with low heritability for resistance to BRD (Snowder et al., 2005). However, more specific criteria based on host response or accurate estimates of disease incidence could be more powerful indicators of resistance. Loci on bovine chromosomes 2, 20 and 26 were linked with BRD, and these loci also had associations with incidence of other infectious diseases (Casas and Snowder, 2008; Neibergs et al., 2011). Immune responses to vaccination with viral and bacterial agents of BRD had moderately high heritability (Leach et al., 2013). These and other studies suggest that targeting animals with the best immunity could provide inherited resistance to BRD as well as other infectious diseases. Selection for other traits such as heat tolerance, and good temperament may also improve the ability of the host to respond to BRD challenges (Burdick et al., 2011).

Although the basic features of BRD pathogenesis are relatively well defined, the multiple factors involved create combinations and complex interactions between the environment, infectious agents and the host which will continue to provide challenges to our understanding and management of BRD.

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**Pathogen variation across time and space: sequencing to characterize *Mannheimia haemolytica* diversity**

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**Abstract**

Bovine Respiratory Disease Complex (BRDC) is a major animal health and economic issue that affects cattle industries worldwide. Within the United States, the beef cattle industry loses up to an estimated 1 billion dollars a year due to BRDC. There are many contributors to BRDC, including environmental stressors, viral, and/or bacterial infections. One species of bacteria in particular, *Mannheimia haemolytica*, is recognized as the major cause of severe fibrinonecrotic pneumonia in cattle. *M. haemolytica* is an opportunistic pathogen that normally populates the upper respiratory tract of cattle, and invades the lower respiratory tract in stressed and/or virally infected cattle by mechanisms not completely understood. However, not all *M. haemolytica* appear to be equally pathogenic to cattle. Thus, a test could be developed that could distinguish *M. haemolytica* genetic subtypes by their propensity to cause respiratory disease. To that end, the genomes of over 300 *M. haemolytica* strains are being sequenced.

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**Bovine Respiratory Disease Complex (BRDC)**

BRDC manifests from multiple causes and predisposing factors (Caswell, 2014, Taylor et al., 2010). Viruses including bovine corona virus (BCV), bovine herpesvirus 1 (BHV-1), bovine parainfluenza 3 virus (BPIV-3), bovine respiratory syncytial virus (BRSV), and bovine viral diarrhea virus (BVDV) cause or predispose cattle to BRDC (Caswell, 2014). Bacteria including *Bibersteinia trehalosi*, *Histophilus somni*, *M. haemolytica*, *Mycoplasma bovis* *Pasteurella multocida*, many of which are normal flora of the bovine upper respiratory tract, cause BRDC (Caswell, 2014). Additionally, a myriad of environmental factors contribute to BRDC, including transportation, sale barn auctions, and comingling (Cusak et al., 2003, Taylor et al., 2010). Thus, BRDC manifests from complicated interactions between and within individuals of a population, the stressors they are subjected to, and the microbes that they harbor, including those that act as opportunistic pathogens.

**Mannheimia haemolytica**

*M. haemolytica* is a primary agent of fibrinonecrotic pneumonia in cattle and a major bacterial component of BRDC (Rice et al., 2008). *M. haemolytica* places within the Pasteurellaceae family and is represented by distinct gram negative, nonmotile bacteria that may be either rods or coccobacilli, and that share a number of metabolic and/or biochemical phenotypes (Angen et al., 1999a, Mutters et al., 2005). When grown on blood agar plates, *M. haemolytica* colonies may be surrounded by a distinct zone of β-hemolysis, due to production of leukotoxin (LKT), which is a major virulence factor (Mutters et al., 2005, Singh et al., 2011). Importantly, *M. haemolytica* is a commensal organism of the bovine nasopharynx and tonsilar crypts (Shoo et
al., 1990, Radostits et al., 2000). However, when animals are environmentally stressed and/or immunocompromised by viral infections, *M. haemolytica* can invade the lungs, evade the host immune response, and cause pulmonary inflammation with leukocyte damage and apoptosis due to leukotoxin, lipopolysaccharide, and other virulence factors, and eventual death of the bovine host (Radostits et al., 2000).

Considerable evidence shows that *M. haemolytica* bacteria are genetically and phenotypically diverse, and that distinct subsets of *M. haemolytica* associate with disease whereas others do not (Quirie et al., 1986, Frank and Smith, 1983, Rice et al., 2008, Klima et al., 2014). *M. haemolytica* are typically encased in capsules, which are virulence factors that interfere with host cellular phagocytosis (Chae et al., 1990). There are 12 capsular serotypes for *M. haemolytica* (A1, A2, A5, A6, A7, A8, A9, A12, A13, A14, A16, A17), (Angen et al., 1999b). Isolates of serotypes A2 and A4 are commonly found in the upper respiratory tract of healthy cattle, and rarely in the lungs of diseased animals. Conversely, isolates of serotype A1 in particular, and also those of serotype A6, are predominantly over-represented in the lungs of diseased animals (see references (Rice et al., 2008) and (Singh et al., 2011) for reviews of serotype associations).

In addition to capsular serotyping, *M. haemolytica* diversity has been characterized using pulsed-field gel electrophoresis (PFGE) (Klima et al., 2011, Klima et al., 2014, Timsit et al., 2013). This is a technique that detects insertion and/or deletions, genome rearrangements, and, to a smaller extent, nucleotide polymorphisms within microbial genomes through restriction enzyme digests and electrophoretic banding profiles (Goering, 2010, Sabat et al., 2013, Foley et al., 2009, Kudva et al., 2002). *M. haemolytica* isolates originating from the lungs of diseased animals have been found to have pulsed-field gel electrophoresis (PFGE) banding profiles that suggest closer genetic similarity to one another then to isolates originating from the upper respiratory tract of non-diseased animals (Klima et al., 2014). Consequently, two very different techniques that assess microbial diversity, capsular serotyping and PFGE, both support the notion that *M. haemolytica* subtypes do not share an equal propensity for associating with, or causing respiratory disease in cattle. This also indicates that a potential approach to managing or preventing bovine respiratory disease attributable to *M. haemolytica*, could involve testing cattle for the subtypes they are harboring, and isolating and/or treating those that are harboring strains with an increased propensity to cause disease.

**Goals and approach:**
The goals of this ongoing project are to 1) identify fundamental genetic variation within *M. haemolytica* strains of North America, 2) develop a set of nucleotide polymorphisms to detect that variation, and 3) use the set to identify genetic determinants that influence *M. haemolytica* pathogenicity in cattle. This is being accomplished through whole genome sequencing of *M. haemolytica* strains that originated from either the upper or lower respiratory tract of cattle that were either 1) clinically ill or deceased, or 2) disease free. Two collections of *M. haemolytica* strains have been assembled that are comprised of strains isolated from the lungs of clinically ill or deceased cattle throughout North America (Portis et al., 2012). One collection is being used primarily for the discovery of genetic variation, including nucleotide
polymorphisms, and consists of 158 epidemiologically-unlinked strains originating from cattle within 35 U.S states, as well as the Canadian provinces of Alberta, British Columbia, Manitoba, Ontario, and Saskatchewan. The strains were isolated from beef or dairy cattle from 2002-2011, with a majority originating from beef animals. The second collection is being used primarily for validation of the discovery collection, and consists of 163 epidemiologically-unlinked strains originating from 29 U.S. states, as well as the Canadian provinces of Alberta, Ontario, and Saskatchewan. Strains of the validation collection were isolated from beef or dairy cattle from 2002-2011, with a higher representation of dairy cattle germplasm than the discovery population. These two collections represent a deep sampling of North American M. haemolytica genetic subtypes that cause or associate with respiratory disease. Additionally, a third M. haemolytica collection has just recently been assembled that is comprised only of nasopharyngeal isolates of US cattle that were not afflicted with respiratory disease.

Whole genome sequencing of the M. haemolytica strains from the collections described above will reveal genetic diversity across the entire genome that will serve as a roadmap for defining M. haemolytica subtypes, and for testing them for an association with respiratory disease. Tests will be developed that will identify M. haemolytica subtypes. The results from this study will be published and placed into the public domain for use without restriction.

Acknowledgments

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References


The Effect of Stress on Microbial Growth
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Abstract
The neurophysiological response of an animal to stress involves the production of a number of stress-related neurochemicals including the catecholamines norepinephrine and epinephrine. It is generally believed that such neurochemicals belong exclusively to the animal kingdom and that any role such neurochemicals play in the infective process is largely confined to host physiology and immunology-related parameters. This, however, is wholly incorrect as many of the bacteria species that are known to cause infections possess the capacity to not only recognize neuroendocrine hormones produced by the host in response to stress, but also synthesize the very same neurochemicals as produced by the host. As such infectious microorganisms are capable of directly responding to the neurochemical outflow resulting from a stress event and initiate pathogenic processes. While the neuroendocrine environment of the lung following a stress event is not fully understood, it most likely possesses abundant levels of stress-related neurochemicals due to its rich blood supply and rich noradrenergic tissue innervation. The ability of the microorganisms to recognize and produce neurochemicals that can influence the host, known as microbial endocrinology, provides for a mechanistic basis with which to examine the ability of stress to influence the health and susceptibility to disease.

Microbial endocrinology – intersection of microbiology and neurophysiology
The environmental factors within the lung that may influence the ability of bacterial pathogens to initiate and maintain an infective process are still incompletely understood. The recognition that bacteria possess the ability to both produce and recognize the very same neurochemicals that are present within the mammalian neurophysiological system strongly indicates the commonly shared neurochemicals represents a mechanistic pathway by which these two kingdoms can interact. This intersection of mammalian neurophysiology and microbiology has been termed microbial endocrinology (Lyte, 2004, Lyte, 2010).

The range of both hormone-like materials and the variety of microorganisms in which they have been identified is very large. For example, the presence of gamma amino butyric acid (GABA), which is the primary inhibitory neurotransmitter found in the mammalian brain as well as possessing immunomodulatory properties (Bhat et al., 2010, Song et al., 1998, Bjurstom et al., 2008) is produced in large quantities by a number of commensal and pathogenic microorganisms (Di Cagno et al., 2010, Guthrie et al., 2000, Minuk, 1986). Numerous other neurochemicals that are usually associated only with mammalian nervous and endocrine systems, such as histamine and acetylcholine, as well as the presence of the corresponding putative receptor, have also been demonstrated in various microorganisms (Roshchina, 2010). Interestingly, the complete biosynthetic pathway for the catecholamines exists in bacteria that is precisely the same as exists in animals which has led to the theory that the acquisition of cell-
cell signaling pathways in animals is due to late horizontal gene transfer from bacteria (Iyer et al., 2004).

Investigators have debated the significance of such hormones in microorganisms for decades. The most widely accepted theory concerns the use of such hormones as a form of intercellular communication (Leroith et al., 1986). Indeed, studies have shown that the growth of colonies of *Escherichia coli* involves a high degree of specialization of function by individual bacteria (Budrene and Berg, 1991) and presumably the need for some form of intercellular communication to accomplish this goal. This concept of microorganisms both producing and responding to endocrine hormones has been expanded to the realm of infectious disease and been termed microbial endocrinology (Lyte, 1993). According to a microbial endocrinology-based approach microorganisms entering into a host, whether through an intravenous catheter, wound, lung or any other entry point, could utilize the endocrine hormones present within the host to serve as environmental cues by which they would sense their surroundings. The development of pathogenicity would then, in part, depend on the ability of the particular microorganism to respond to the type of endocrine hormonal environment that it encounters upon entrance into the host.

**Stress and infection - the response of bacteria to stress-related neurochemicals**

At its beginnings the demonstration that the neurochemical outflow resulting from a stress event, namely the elaboration of the catecholamines norepinephrine and epinephrine, could *directly* affect the growth and expression of virulence-related factors in pathogenic bacteria was investigated in gut-related pathogens such as *Yersinia enterocolitica*, *Escherichia coli* and various *Salmonella* and *Shigella* species (Lyte and Ernst, 1992, Lyte et al., 1996, Lyte et al., 1997, Nguyen and Lyte, 1997). Other laboratories have not only noted similar ability of stress-related neurochemicals to not only increase bacterial growth and virulence factor production (Belay and Sonnenfeld, 2002, Rahman et al., 2000, Bearson et al., 2008, Nakano et al., 2007), but also increase the rate of conjugative gene transfer between enteric bacteria thereby increasing the evolution and adaptation of pathogens to new environments through, for example, transfer of drug resistance genes (Peterson et al., 2011). From a historical viewpoint, it must be noted that the description of the ability of catecholamines to affect bacterial growth and virulence was noted as early as 1930 (Renaud and Miget, 1930) although the prevailing thought was that such ability must be due to inhibitory effects on immune cells (Miles et al., 1957). The possibility that the bacteria were directly interacting with the catecholamine was not envisioned until many years later (Lyte, 2004).

**Stress and the bovine lung**

The lungs are extensively innervated by nerves belonging to the autonomic nervous system (ANS). For example, adrenergic and cholinergic components of the (ANS) have been demonstrated to extensively innervate pulmonary tissue in the pig (Wojtarowicz et al., 2003). ANS innervation serves a number of functions in the regulation of normal pulmonary homeostasis such as control of smooth muscle tone, secretion of mucus from submucosal glands and blood flow within the lungs themselves (Belvisi, 2002). While there is understandably a large body of literature on ANS-related receptors in the human regarding
treatment option for a number of pulmonary-related disease states, there is little knowledge of the neural innervation of the bovine lung and correspondingly, little, if in fact any, reports of the neuroendocrine environment within the bovine lung following a stress-related event. It can reasonably be assumed that given the extensive blood flow in the lung as well as the abundant noradrenergic nerve innervation that a stress-related event would result in substantial amounts of catecholamines being present within the lung space that would be available to interact with any bacterial pathogens that might also be present. One study which indicated that this would indeed be the case was performed in sheep where endotoxin-mediated injury to the lung resulted in elevated plasma levels of both norepinephrine and epinephrine presumably originating from the lung space (Hofford et al., 1996).

If concentrations of catecholamines, such as norepinephrine, are indeed elevated within the stressed lung it is likely that it would contribute to the infective process by directly interacting with bacterial pathogens. Anderson and Armstrong (Anderson and Armstrong, 2008) have shown that the in vitro growth of the respiratory pathogen Bordetella bronchiseptica is greatly increased in the presence of norepinephrine and that this ability is, in part, mediated by the ability of norepinephrine to increase acquisition of transferrin-bound iron by B. bronchiseptica. That the interaction of stress-related neurochemicals with the bovine lung may be an area worth investigating can best be seen in a study which examined the interaction of the Mycoplasma hyopneumoniae with norepinephrine. Global transcriptional analysis of M. hyopneumoniae following exposure to norepinephrine revealed numerous changes with the overall pattern of up regulation of protein expression and down regulation of general metabolism (Oneal et al., 2008).

In conclusion, considering that microbial endocrinology-based interactions between host and pathogen are well-recognized across a wide spectrum of clinical-related infections including that involved in the development of catheter-related infections (Lyte et al., 2003), it may be of scientific merit to investigate its role in the development of bovine lung infections.

References


Strengths and Weaknesses of the Current Diagnostic Testing
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Histopathology

Routine

- **Requirements**
  - Timely collection – fresh tissues
  - Suitable handling/fixation
  - Appropriate tissues selection

- **Weaknesses/Undesirable outcomes**
  - Target tissues not collected/submitted
  - Microscopic lesions not found
  - Advanced autolytic state

- **Strengths/Advantages**
  - Make/confirm a diagnosis - pathognomonic lesions
  - Non-pathognomonic lesions – limit some possibilities
  - Insidious lesions – many possibilities
  - Results possibly at 2-3 days
  - Lesions used to categorize type of disease
    - Infectious or Non-infectious
    - Toxic or nutritional

Immunohistochemistry (IHC)

- **New histopathology technology**
  - Relatively new tool - Last 10 to 15 years
  - Prepare antibody against infectious agent(s) to be detected

- **Unlimited possibilities**

- **Can confirm the presence of infectious agent at the lesion site**

- **Utilizes fixed tissues**

- **Does not require a live organism**

Interpreting results

**Bacterial detection**

Routine Bacterial culture

- **Requirements**
  - Requires live organism in submitted samples

- **Weaknesses/Undesirable outcome**
  - Negative culture

- **Strengths/Advantages**
  - Definitively identify pathogens
- Sensitivity testing
- Further typing/characterization
- Vaccine production
  - **Malditoff Mass spectrophotometry**
    - Allows rapid and accurate bacterial identification
    - Primary culture still required

**Interpreting results**

**Virus Detection**

**Routine Virus isolation**
- **Requirements**
  - Live virus in specimens submitted
- **Weaknesses/Disadvantages**
  - 5 - 7 days minimum turnaround time
  - Will isolate ML vaccine viruses
- **Strengths/Advantages**
  - Can provide definitive answers
  - Gold Standard (?)
  - Isolation allows further characterization

**Antigen Capture ELISA**
- **Requirements**
  - Relatively fresh specimens with virus present
- **Weaknesses/Undesirable Outcome**
  - Detection of vaccine virus
  - Testing not available for all bovine viruses
  - Less sensitive than PCR
- **Strengths/Advantages**
  - Rapid Test – minimal turnaround time
  - Relatively inexpensive
  - Diverse-use (detection of difficult-to-isolate viruses such as BRSV)
  - More sensitive than EM
  - Can detect viable an non-viable viruses

**Electron Microscope**
- **Requirements**
  - Specimen with a relatively large number of viral particles
- **Weaknesses/Disadvantages**
  - Less sensitive than antigen capture ELISA
  - Identify to family only
- **Strengths/Advantages**
  - Rapid turnaround time (3-5 hours)
  - Positive results suggest relatively large number of viral particles
  - Identify to family only
  - Viable viruses not required
Interpreting results
Serology/Antibody detection

Serum neutralization/virus neutralization (SN/VN)
- Titration of known amount of viral particles with serial dilution of serum being tested
- Requirements
  - Relatively clean serum
- Weaknesses/Limitations
  - Detects IgG antibody only
  - Requires multiple animal testing. Single animal serology is very difficult to interpret except to confirm an animal serologically negative
  - Cannot confirm active/ongoing infection in one sample
  - Lack of uniform animal response
  - Vaccinations will interfere
- Strengths/Advantages
  - Detects neutralizing antibody
  - Determine vaccinial response/protection/exposure
  - Results highly reproducible (within a lab)

Molecular Diagnostics

Realtime PCR (RT PRC)
- Requirements
  - Appropriately collected specimens- no transport gel
- Weaknesses/Disadvantages
  - Can be expensive
  - Detection of vaccine viruses
- Strengths/Advantages
  - Very sensitive & specific
  - Live pathogens are not required for detection
  - Relatively rapid turnaround time
  - Multiplexing is possible
  - Semi-quantitative results

Gel PCR
- Less sensitive than RealTime PCR
- Longer turnaround time
- Otherwise similar to RealTime PCR

Interpreting results
Will antimicrobial resistance of BRD pathogens impact BRD management in the future?
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Abstract
Resistance is a qualitative interpretation of antimicrobial activity in vitro. Critical to management of BRD is the clinical response in vivo. Attempts to connect activity in vitro to response in vivo have been complicated by the complexity of BRD, interpretation of antimicrobial activity in vitro, and inconsistent measures of clinical success or failure. During recent history, the discovery, development, and commercialization of antimicrobials have decreased. In response to resistance, voluntary and imposed restrictions on use of antimicrobials have been implemented. Resistance can be reversed using technology and knowledge of mechanisms of resistance. Perhaps approaches that reverse resistance will be used in clinical management of BRD in the future.

The short answer to the question posed in the title is, “yes.” Since antimicrobial drugs were discovered, resistance has been a consideration for selection of treatment of any infectious disease; and, Bovine Respiratory Disease (BRD) is not unique. In the opinion of the author, the more important question is, “How antimicrobial resistance of BRD pathogens will impact BRD management in the future?”

Resistance is one of 3 qualitative interpretative categories (“susceptible”, “intermediate”, or “resistant”) based on measures of antimicrobial activity in vitro, and is defined in the USA by the Clinical and Laboratory Standard Institute™ (CLSI) as follows: “This category implies that there will not be a favorable clinical outcome, because the achievable systemic concentrations of the agent will be lower than the MIC of the causative organism with normal dosage schedules and/or fall in the range where specific microbial resistance mechanisms are likely (e.g., beta-lactamase), and clinical efficacy has not been reliable in treatment studies” (CLSI 2002a, CLSI 2002b, Silley, 2012). Break-points are semi-quantitative (arguably) measures (usually minimum inhibitory concentration [MIC], or diameter of the zone of inhibition) that distinguish among the 3 qualitative categories. There are no details about how data from “treatment studies” are considered during the establishment of breakpoints (CLSI 2002a, 2002b).

Standard procedures described by the CLSI are designed to be optimal for the pathogen; and, are used for identification of the pathogen as well as for assessment of antimicrobial activity in vitro.

Confusion about how to interpret results in vitro is multi-factorial as is the nature of BRD (Taylor et al. 2010a; Taylor et al. 2010b). Many of the simple questions have not been
answered. If more than one pathogen is isolated, what is the fractional contribution of each? What is the influence of resistance with one pathogen but not the other(s)? Are resistant organisms found in animals that do not have clinical signs? Do they remain in treated and recovered animals?

“Concerns” about antimicrobial resistance are not new. Before penicillin was commercially available, Dr. Fleming raised awareness that bacteria could change after exposure to penicillin (Rosenblatt-Farrell, 2009). Surveillance/monitoring of in vitro activity of antimicrobials began in 1951 (Giles, 1958). Focus on antimicrobial activity in vitro has been intense, perhaps because it is the easiest to identify of the factors that contribute to clinical failure. However, clinical correlation of those data has not been evaluated effectively. Using non-standardized procedures for studies in vivo further confuses attempts to correlate in vitro activity and response in vivo (O’Connor 2010).

Resistance is not to blame for all clinical failures. Clinical response is the net effect of all factors that contribute to BRD – including antimicrobial resistance. Factors other than antimicrobial resistance play a role in the death of feedlot cattle with BRD (Lamm, et al. 2012). Is there a point ( % resistance) at which medications should not be selected from clinical use? Should selection only include compounds for which susceptibility (what %?) is identified? Patterns of practice for human patients with community acquired pneumonia (CAP) were “shifting in response to the perception that current levels of drug resistance necessitate changes in treatment patterns (Metlay, 2004). This is unfortunate because it severely limits one’s ability to continue to monitor the effectiveness of available therapies in light of changing patterns of antibacterial drug resistance.” Dr. Metlay summarized, “..., antibacterial drug resistance has not reduced substantially the effectiveness of first-line treatments for CAP. Whether levels of drug resistance will continue to increase or decline is unknown. Therefore, carefully designed outcomes studies likely will continue to be essential to help define optimal therapy for patients who have CAP.” Could those statements apply to BRD?

Antimicrobial resistance and clinical failure are not directly, quantitatively correlated (Lamm et al., 2012; McPherson, 2012). Likewise, clinical success is not inseparable from antimicrobial susceptibility. Basic definitions distinguish them; and, the labeling of antimicrobial products contains statements similar to the following: “The correlation between in vitro susceptibility data and clinical effectiveness is unknown.” Treatment failures occurred when susceptible organisms were isolated; and, treatment successes occurred when resistant organisms were isolated (Apley, 2003; McClary et al., 2011). Clinical failure, when BRD is associated with susceptible organisms, cannot be due to antimicrobial failure! The association of clinical response with antimicrobial activity in vitro is not the same for all BRD pathogens (McClary et al., 2011). Virulence of the organism, the host’s resistance to infection, and the host’s tolerance to presence of pathogens are also distinct considerations deserving of greater attention (Jamieson et al., 2013; Beceiro et al., 2013). Antimicrobial medications are important; but, the entirety of clinical response is not the responsibility of the medication.
The strongest evidence for clinical decisions is derived from head-to-head, randomized, controlled clinical studies (Karriker, 2007). Techniques such as risk assessment and survival analysis could contribute greatly to evaluating clinical response and the relationship of antimicrobial activity in vitro with clinical response. Appropriate economic evaluation of treatments is also warranted (Simoens, 2010).

Driven by fear of resistance, pharmaceutical companies in the USA have re-labeled products to clarify indicated therapeutic uses; and, decreased research of new antimicrobial agents (FDA GFI#213, 2013; Silley, 2012; Wright, 2013; Spellberg, 2004). Regulatory activities are directed toward reclassifying products so that they will be available only with “veterinary oversight;” and, have the stated purpose of reducing resistance (FDA GFI #213, 2013).

Realistic considerations for the future should include management of fears of resistance, to utilize understanding of mechanisms of virulence and mechanisms of antimicrobial resistance, to improve designs of clinical studies, and to develop technologies or products that could reverse resistance (Wright, 2013; Spellberg, 2004; Tillotson & Echols, 2008). Clinical studies with appropriate designs will require many animals and considerable financial investment.

Non-traditional methods of treating infectious diseases have included technologies that reverse resistance. The dogma that mutations only progress toward resistance is wrong. Genetic mutations can be induced to reverse resistance (Cirz & Romesberg, 2006; Katsuda et al. 2009; Ricci et al. 2006). Bacteriophages have been used to reduce bacterial contamination of food; change virulence of bacterial pathogens, alter damage created by bacterial pathogens or enhance the host’s tolerance of the pathogen; or, reverse antimicrobial resistance (Abedon, 2011; Abuladze et al. 2008; Beceiro, 2013; Hong et al. 2014;Rasko & Sperandio, 2010; Vale et al., 2014; Wright, 2013;). Might it be possible to administer a vaccine that targets BRD pathogens in the upper respiratory tract of cattle and cause those bacteria to become susceptible to treatment; or, concurrently administer medications that reverse/prevent resistance while others inhibit or kill the pathogen? “Concerns” and “perceptions” are driving regulations, corporate decisions, public response, and therapeutic decisions. Are results of a scientifically-based future of treatment of BRD worth the risks of taking that “bull by the horns”?

References


FDA 2013. Guidance for Industry #213: New animal drugs and new animal drub combination products administered in or on medicated feed or drinking water of food-producing animal: Recommendations for drug sponsors for voluntarily aligning product use conditions with GFI#209.


Evidence-based Approach to Improving Immunity to Manage Cattle Health

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One challenge the beef industry faces today is the supply of cattle. The feeder calf supply available in the southeast US generally originate from small herds. Groups of feeder cattle are acquired through various auction markets or buying stations and are commingled with cattle of like frame size, weight, type, and gender. After an order is grouped, the cattle may be transported over many miles which take several hours to reach a preconditioning/backgrounding or finishing facility in the Plains. These cattle typically arrive at their new destination with unknown health histories and would be considered at high-risk of developing bovine respiratory disease (BRD). The development of BRD involves complex interactions between respiratory pathogens and stressors.

Approaches to managing this disease generally involves preventing or minimizing exposure of the animals to the various potential pathogens, decreasing the challenge load of the potential pathogens, and increasing the level of immunity to the respiratory pathogens. Good management practices that minimize stress on cattle should also be recommended. In general, if the level of immunity in a group of cattle can be increased, especially prior to anticipated exposure, the severity and number of clinically affected animals are decreased. Hence, veterinarians focus on developing preventive health protocols to increase resistance to the common respiratory pathogens through administration of respiratory vaccines. Several of these preventive health protocols utilize modified-live viral (MLV) vaccines. One of the concerns expressed by veterinarians and producers is that stressed cattle may not respond to vaccination with optimal immunity. Thus a common practical approach is the recommendation to administer a second dose of MLV vaccine commonly referred to as “REVAC” to the group of feeder calves to allow more animals to develop immunity and thus protection when exposed to respiratory pathogens under normal field challenge situations.

The objective of a research study was to compare the administration of a MLV BHV1-PI3V-BVDV1a-BVDV2a-BRSV once or twice on the health and performance in high-risk cattle. Six-hundred twelve (612) crossbred beef cattle (body weight average = 483 lbs.) originating from auction markets in Arkansas and Oklahoma were assembled and shipped to Oklahoma State University (OSU) Willard Sparks Beef Research Center (WSBRC). The cattle were randomly assigned to either SVAC (vaccinated once) or REVAC (vaccinated twice, 11 days apart). The cattle were observed daily by trained clinical evaluators. The preconditioning–backgrounding period was for 60 days, at which time the steers were shipped to a research feedlot for finishing. The primary arrival health care protocol at the feedlot involved vaccination with the same 5-way MLV vaccine or no vaccination (½ SVAC and ½ REVAC vaccinated; ½ SVAC and ½ REVAC received no vaccine on arrival).
There were no significant differences in performance parameters measured in the SVAC and REVAC steers during the preconditioning–backgrounding period. BRD-related morbidity (SVAC 36.3% REVAC 44.5%) and total morbidity (SVAC 37%, REVAC 44.7%) were different. The days to first treatment (SVAC = 7.62d, REVAC = 7.21d) were not different. No cattle exhibited any clinical signs consistent with BRD during the finishing phase of production. Additionally, there were no significant differences for performance parameters measured (preconditioning–finishing phase vaccination treatment interaction). Interesting, the REVAC steers had a lower feed:gain (F:G) than the SVAC steers during the finishing phase. The REVAC–finishing vaccination and SVAC–no finishing vaccination had higher marbling scores than the other two treatments.

In conclusion, the preventive health protocol administered in the preconditioning–backgrounding phase of production provided health benefits for the cattle during the finishing phase of production. The REVAC cattle experienced higher morbidity than the SVAC cattle; however, the days to first treatment were the same for both treatments and occurred prior to the second vaccination for the REVAC group. The differences were most likely an artifact of the randomization process.

Observations of commingling cattle from multiple sources with unknown health histories contribute to the BRD complex. The objectives of another research project were to determine the health and performance of ranch-origin calves administered various preventive health protocols and to evaluate commingling ranch-origin calves with calves of unknown health histories. Five-hundred nine (509) crossbred beef steers were enrolled in the study. Two-hundred sixty (260) steers (MARKET) originated from multiple auction markets located in the southeast and assembled in Mississippi prior to shipment to OSU WSBRC. Two-hundred forty-nine (249) steers were from one ranch (RANCH). At weaning, the RANCH steers were randomly assigned to WEAN (shipped directly to OSU WSBRC), WEANVAC45 (administered preventive health protocol and weaned at the ranch of origin for 45d) or WEAN45 (weaned at the ranch of origin for 45d) with no administration of a preventive health protocol (vaccinations). The preventive health protocols included administration of 5-way MLV vaccine plus 7-way clostridial bacterin/toxoid plus Mannheimia haemolytica toxoid. Steers received a 5-way MLV + 5-way lepto vaccine at 14 days after initial processing. MARKET steers served as the controls. Half (½) of each of the ranch-origin treatment group were commingled with MARKET steers (COMM). The WEANVAC45 steers did not receive any vaccinations upon arrival or at 14 days at the OSU WSBRC; however, an endectocide was administered at arrival processing and these steers were processed through the processing facility (pens, alleys, chutes) as the other treatment groups.

Fourteen steers were removed during the study due to severe respiratory distress. Regarding calf origin and commingling; RANCH steers experienced less morbidity (11.1%) than MARKET (41.9%); COMM steers were intermediate (22.6%). Mortality rate was significantly less in RANCH origin steers. WEANVAC45 and WEAN45 steers experienced significantly less morbidity than WEAN steers. Hot carcass weights and USDA Quality grades were not affected by calf origin and commingling, but USDA Yield grades were affected (RANCH=2.61, MARKET=1.97, COMM=2.28). Even though factors that may have affected the outcomes were attempted to be
eliminated, the WEANVAC45 steers had significantly heavier arrival body weights than the other steers. No factor was identified that would have contributed to the difference. The average health care costs were different (MARKET & WEAN $13.39 vs WEANVAC45 and WEAN45 $8.62). In conclusion, WEANVAC45 and WEAN45 had similar benefits and had an economic benefit with lower average health care costs. Commingling of steers had less potentially negative effects with preconditioned steers than if weaned and immediately shipped from the ranch of origin.

References
Field epidemiology to manage BRD risk in beef cattle production systems
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Abstract
Field disease investigations can help to identify patterns of disease that lead to causal hypotheses and, hopefully, effective disease risk management strategies. The most common way of doing this would be to characterize the outbreak by subject, time, and space. One of the perplexing animal health problems on some beef cattle ranches is the occurrence of pneumonia in calves prior to weaning in conditions of little stress and relative isolation. Field investigation of outbreaks of pneumonia in ranch calves prior to weaning has revealed patterns of sporadic illness in calves less than 30 days of age, and rapidly occurring outbreaks in calves 90 to 150 days of age. We speculate that the causes of these two patterns may be failure of passive transfer resulting in more sporadic cases in very young calves, or a large proportion of the population losing maternal antibody protection (i.e. losing herd immunity) resulting in rapid and widespread onset of pneumonia in older calves.

Principles of field investigation
Field investigations are studies of causation. We conduct field investigations for the purposes of 1) reducing the losses associated with existing cases; and 2) preventing new cases from occurring. The challenge is to conduct an investigation that leads to a solution to the problem. Unfortunately, in veterinary medicine, we often spend considerable time and money to name the pathogen without solving any problems. To be fair, knowing the pathogens involved in a disease outbreak can sometimes be useful; however, outbreak investigations can become sidetracked in the sole pursuit of an etiologic agent rather than identifying more useful explanations for the outbreak. Knowing the etiologic agent may provide an explanation for the proximal cause of disease and might provide therapeutic insight, but that knowledge only rarely explains the course of events that led to the outbreak, or provides a solution for preventing future problems. Often, we are more successful at meeting the objectives of a field investigation if we can identify the actions or behaviors associated with the production system that led up to (caused) the problem. For example, recognizing that the incidence of mastitis on a dairy is highest on Mondays might give an investigator reason to investigate the weekend milking process; recovering coliform bacteria from mastitic milk would not be as informative.

Systematic approach to field investigation
It can be difficult to provide solutions to disease outbreaks, but success is more likely if an organized, epidemiologic approach to outbreak investigation is followed (Waldner and Campbell, 2006, Hancock and Wikse, 1988). Field investigations involve an orderly process to characterize the outbreak (Smith, 2012):
1) Interview key individuals (e.g. owners, caretakers, veterinarians, and other stakeholders)
2) Verify the clinical diagnosis and assure that treatments are appropriate
3) Identify the factors responsible for the outbreak
4) Develop strategies to prevent new cases and future outbreaks
5) Communicate your observations and recommendations with the key individuals

Detailed discussion on these steps of the field investigation have been published elsewhere (Smith, 2012).

**Risk assessment**
Risk assessment is a process of: 1) Evaluating the likelihood and costs (or benefits) of potential hazards (or opportunities) –termed risk analysis; 2) Determining what actions, at what relative cost, can be taken to mitigate those hazards –termed risk management; and 3) Sharing the action plan with all members of the team, as well as keeping records to show what was done and whether the actions were successful –termed risk communication.

From a risk assessment standpoint, field investigation steps 1-3 above are risk analysis, step 4 is risk management, and step 5 is part of the documentation and risk communication phase. During the risk analysis phase, it may be useful to supplement published data with herd-specific data from health records (Rae, 2006), outbreak investigation (Smith, 2012), or clinical trials (Sanderson, 2006). It may be possible to recognize important hazards and estimate their costs without ranch data, but it is more difficult to evaluate progress or compliance in the risk management stage without using records. Unfortunately, few cow-calf operations collect animal health data in an easily analyzable format (National Animal Health Monitoring System (U.S.), 2008). The lack of a simple record keeping system on many farms hinders the process of recognizing important hazards and their costs and makes it difficult to document that risk management actions were implemented and to evaluate if those actions were effective.

**Causal inference**
On-farm investigations of cattle diseases are more often qualitative than quantitative because useful quantitative data (e.g. from health records) are often not available for analysis. A qualitative investigation relies on more subjective observations including partial records, memory, and perceptions of relationships. Causal inferences in qualitative investigations are largely based on the logic of: 1) method of agreement; 2) method of difference; or 3) concomitant variations (Gay, 2006). A causal factor might be identified by the method of agreement if the factor is common to multiple instances of the outcome when other factors are dissimilar (e.g. finding that BRD outbreaks are common to herds using a particular receiving ration, even though other management practices differ). A causal factor might also be identified by the method of difference if a particular factor differs while others remain the same (e.g. if incidence of BRD is greater among calves receiving one particular vaccine than calves on the same farm receiving a different vaccine). Finally, causal relationships may be revealed by the method of concomitant variations if the risk for the outcome changes with the level of the risk factor, all other factors being the same (e.g. the longer calves are in transit to the feedyard, the greater the incidence of BRD).
Outbreak characterization
Field investigation relies heavily on pattern recognition to generate causal hypotheses. The most common way of doing this would be to characterize the outbreak by subject, time, and space. The “subject” may be specifically identified individuals, or it may be group-level information (e.g. herds or pens). Time may be by the calendar or it may be relative to a relevant point in time (e.g. age, or time since feedlot entry). It may be useful to graphically portray the data; for example, in the form of maps or frequency histograms (Fig. 1). A frequency histogram of particular interest is the count of cases plotted by calendar time, also known as an epidemic curve (Fig. 2). Disease outbreaks may occur because of a common point-source epidemic exposure (e.g. the bacteria contaminated potato salad at the community picnic). These types of outbreaks are typically rapid in development and resolution, or they may become propagated epidemics (e.g. you got sick from the community picnic, and then you infected your family and they passed the infection on to friends at school). Propagated epidemics are typically characterized by less rapid, but ongoing, transmission from animal to animal. Observing the shape of the epidemic curve may reveal the nature of the disease process, identify potential risk factors preceding the onset of clinical signs, or suggest methods to prevent new cases (e.g. by removing the potato salad, or isolating sick individuals)(Lessard, 1988). For example, outbreaks that occur as a point-source epidemic (e.g. because of a sudden exposure to a pathogen, the sudden loss of immunity, or something that suddenly facilitates pathogen transmission) may be evidenced as an epidemic curve with a high peak in a relatively short period of time. When the outbreak is propagated (e.g. when the disease process is one of ongoing transmission, or there is a continuous presence of risk factors) the epidemic curve may appear flatter over a longer period of time.

Figure 1. Age distribution of 87 pneumonia cases from among 296 pre-weaned calves in a Nebraska ranch.
Figure 2. Epidemic curve of 87 pneumonia cases from among 296 calves in a Nebraska ranch. Lines represent the proportion of calves at least 100 (solid) or 120 (dashed) days of age each week.

**Quantitative study designs**

When data are available, a quantitative approach is often more useful for discovering causal relationships and evaluating the effectiveness of interventions. The best study design for evaluating causal relationships depends on the circumstances. There are three basic observational study designs: 1) **case-control**; 2) **cohort or longitudinal**; and 3) **cross-sectional**. Case-control studies compare odds of exposure among cases to the odds of exposure among non-cases. Case-control studies excel when the disease is rare and when there are many potential exposures to test. Cohort and longitudinal studies compare incidence of disease among subjects with an exposure to the incidence of those without the exposure. Cohort and longitudinal studies are best when it is possible to follow subjects over time, either prospectively or retrospectively. Cross-sectional studies look at the relationship between disease and exposure prevalence at a point in time (Shott, 2011).

**Measures of association**

The measure of association is an important statistic because it helps quantify the strength of the relationship between the risk factor and the occurrence of disease. When the outcome is dichotomous (e.g. diseased or not diseased) the measure of association is the odds ratio (or, in
some situations, relative risk). These are comparisons of the odds, probability, or incidence of observing disease with one exposure level compared to another. If the odds ratio (or relative risk) has a value of one, then the exposure is not associated with the disease. If the odds ratio is greater than one, then that exposure is associated with the disease. If the odds ratio is less than one then the exposure is associated with the absence of disease (e.g. it is protective from disease). The further the odds ratio is from one the stronger the association.

**Epidemiologic principles relevant to BRD**

**Component causes**

In disease causal theory, each factor that contributes to the development of disease is a *component cause* (Rothman, 1976). Clinical signs of disease are expressed when various component causes add up to complete a *sufficient cause*. This explains why some component causes are observed in the absence of disease (e.g. we might recover *Mannheimia haemolytica* from nasal secretions of calves without signs of BRD). This concept also explains why the manager of a herd that reliably vaccinates against respiratory pathogens might blame BRD on bad weather, while the manager of a herd in a moderate climate might observe BRD when they’ve been lax on timely vaccinations. Removing one component cause means that the sufficient cause is not completed and thus disease is not observed, so in a field investigation we hope to determine which possible component causes are completing a sufficient cause, and determine which of those component causes (also known as *causal factors* or *risk factors*) are *key determinants*. Key determinants are those causal factors which are under management control.

**Herd immunity**

Herd immunity is when the proportion of immune individuals in a population is large enough to inhibit ongoing transmission of the pathogen; therefore individuals in the population who are not immune may be protected against disease because they do not experience an effective contact with the pathogen. So, in populations where herd immunity may be playing a protective role, it may not be sufficient to know an individual’s immune status – it may be necessary to interpret individual immunity in the context of the immune status of others in the immediate population. An *effective contact* is an exposure to sufficient pathogen dose-load for an adequate duration of time to transmit the infection. To the author’s knowledge, the proportion of a herd that must have protective immunity to prevent transmission of the common BRD pathogens in a herd of cattle has not been defined.

**Using the results of field investigation to manage BRD in beef cattle systems**

One of the perplexing animal health problems on some beef cattle ranches is the occurrence of pneumonia in calves prior to weaning. Studying patterns of disease occurrence may provide clues to disease causation and this knowledge can be used to develop methods to prevent or control important livestock diseases. Since 2008 we have conducted field investigations in ranch herds experiencing summer pneumonia. The results of this work may be relevant to cattle producers, veterinarians, and others interested in the health and well-being of cattle elsewhere.
In the course of our investigations we recognized two patterns of occurrence of summer pneumonia – either sporadically in young calves or as sudden outbreaks in older calves. We have observed that calves 90 to 150 days of age are at greatest risk for BRD in the absence of other management stressors, such as weaning (Fig. 1). We note that the sudden outbreaks of BRD in older calves usually occurs when a large proportion of the calves in the herd exceed 100 – 120 days of age (Fig. 2). We speculate that the causes of these two patterns may be failure of passive transfer resulting in more sporadic cases in very young calves, or a large proportion of the population losing maternal antibody protection (i.e. losing herd immunity) resulting in rapid and widespread onset of pneumonia in older calves. An additional factor was the influence of the age of the dam.

Each of these factors suggests that maternal immunity (or lack of it) may play an important role in the occurrence of pneumonia in ranch calves. We also recognized the need for better methods to record health data to investigate these types of health events.

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References
Control of BRD in large dairy calf populations

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As dairy cattle herd sizes have increased, there has been a concomitant increase in the number of dairy calves being raised as replacement heifers on those dairy farms. A dairy farm that milks a few thousand cows and raises its heifer calves will typically have a few hundred or more pre-weaned calves at any point in time. Additionally, in regions of the country, such as western U.S., where large concentrations of dairy cattle exist, specialized operations have developed that are dedicated to raising dairy calves including both bull calves for beef production and sometimes heifer calves being raised mostly under contract as dairy replacement heifers. These calf ranches may have as many as 40,000 pre-weaned calves and a similar number of weaned calves in group pens. With increasing specialization that is occurring in the dairy industry, dairy families that have several milking herds among family members in a local area may choose to combine calf raising operations at a centralized location for all calves from those dairies. This situation can result in a several thousand calves being raised for those dairies at that calf ranch location.

As calf raising operations have become larger, both opportunity and risk have increased. One of the goals of herd health programs is to meet the needs of the individual animal in a manner that is appropriately specific and yet efficient from a resource and labor perspective. Larger calf operations provide the opportunity to apply economies of size and scale to the raising of dairy calves and at the same time create the possibility for adverse outcomes due to the multiplication effect when health or other risk factors become uncontrolled. Although many of today’s calf raising operations strive for optimal health and growth and achieve satisfactory or better results, calf welfare and performance can quickly become unacceptable if health and management conditions result in increased levels of dairy calf morbidity and mortality.

Respiratory disease or BRD is the leading cause of death in weaned dairy heifers and the second most common cause of mortality in pre-weaned calves in dairy cattle herds in the United States (USDA, 2010). The susceptibility of newborn or young calves to a variety of pathogens, including those attributed to BRD, makes biosecurity and biocontainment efforts a top priority for preventing disease. Research continues to confirm the importance of colostral immunoglobulin concentration for health and growth in dairy calves (Furman-Fratczak et al., 2011; Priestley et al., 2013). Failure of passive transfer, especially in dairy bull calves, continues to be an ongoing concern for dairy calf health and welfare. Clinical experience has shown, however, that otherwise normal, healthy calves with adequate passive transfer of immunoglobulins can be overwhelmed and become morbidly ill if exposed to large numbers of even mildly virulent pathogens. Efforts to achieve suitable sanitation and hygiene become paramount in large populations of dairy calves if disease and death loss are to be avoided.
Strategic immunization programs including antigens associated with BRD play an important role for promoting health and reducing disease morbidity and severity. Antigen characteristics (such as killed or modified-live), potential for interference with maternal antibodies, route of administration (such as intranasal or subcutaneous), timing of administration to avoid concurrence with stressors and timing so that immune response can occur prior to anticipated challenges or exposures are just some of the factors that need to be considered in designing an effective vaccination program. Appropriate diagnostic strategies involving both clinically ill and dead calves in the context of an ongoing surveillance program are important for achieving an evidence-based approach for preventing and reducing BRD incidence.

Although primary prevention of BRD is the preferred goal, secondary prevention by accurately and quickly identifying calves that need treatment for BRD is important for promoting dairy calf health, performance, and welfare. Implementing a scoring system for consistent, early detection of BRD will provide the opportunity for better response to BRD treatment and reduce the risk of more severe, chronic cases of disease (Love et al., 2014; McGuirk, 2008).

Optimal dairy calf health and performance requires proper nutrition. Current research is providing insight into the benefit of increased levels of nutrition for achieving healthier calves that may have a resulting positive impact on future lactational performance (Le Cozler et al., 2008; Lohakare et al., 2012; Moallem et al., 2010). Interactions between nutrition and immunological function are critical for preventing BRD and other common calfhood diseases. Regrettably, it seemed to take much too long during past decades for veterinarians and producers to understand the most basic impacts of environmental (cold) stress on nutritional requirements for supporting health and growth of calves, even in southwestern regions of the U.S. where winter conditions are considered to be mild. Prevalent dogma during that time promoted reduced nutritional intake as a misplaced effort for reducing diarrhea and other disease conditions. More research is needed for developing improved housing and environmental management systems that will not only improve dairy calf health but will also consider normal behavioral activities within the context of controlling exposure to pathogens. Existing facilities may be an important limiting factor for preventing BRD and achieving calf health, such as management protocols and inadequate facilities that lead to mixing of too many calves of different ages during stressful periods such as weaning.

Proper management of these critical aspects of calf raising to achieve prevention of BRD in large calf populations requires a systems approach. Essentially, a system of good record keeping combined with analysis of outcomes is needed to document acceptable performance and to identify new problems that require attention. In practical terms, managers and veterinarians need to be involved with caregivers responsible for calves so that adherence to protocols can be assured and that any procedural drift or inadequate protocols can be quickly identified and corrected.
Proper management of calves to prevent and control BRD requires careful planning and follow through to achieve those results but will likely pay big dividends in improved calf health and future productivity.

References


BRD Control: tying it all together to deliver value to the industry  
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Abstract
Pasteur described an organism causing fowl cholera in 1880. In 134 years we have progressed from crude vaccines for Pasteurella, to some refined vaccines, to a name change (Mannheimia), to autogenous vaccines (back to crude). In the last 25-30 years we have attempted to mitigate the problem with antimicrobials and subsequently have a high incidence of multi-drug resistance. All of these attempts have resulted in little if any improvement in morbidity/mortality. Is it time to focus on the animal’s response or lack of response to infectious pressure? Instead of focusing on the 10-50% morbid cattle should we focus on the 50-90% that are not compromised and determine why they stay healthy under the same environmental conditions?

In 1880, Pasteur described an organism causing fowl cholera. In 1921 Jones studied an outbreak of hemorrhagic septicemia in a large herd of cattle and found one that hemolyzed horse and cow blood cells. The organism was named Pasteurella hemolytica. From these findings, crude vaccines were developed followed by more refined vaccines. The name was changed from Pasteurella haemolytica to Mannheimia haemolytica. During the last several decades numerous antibiotics have been used in an effort to mitigate the effect of this organism. Ironically, the use of so called autogenous vaccines is becoming vogue, which essentially, is a return to the crude vaccines of several decades ago.

Our practice group has monitored mortality from bovine respiratory disease since approximately 1990. Cattle recorded as dying from BRD are plotted by year in Table 1. There was a significant reduction in BRD mortality between 1991-1997 and since that time it has escalated above the 1991 level with some intermittent decreases.

Mortality from BRD varies with the time of year. Table 2 depicts the percent of the population dying from BRD by month. Lowest mortality occurs during the months of April/May at 0.08% followed by a steady increase to a high in December of 0.18%. The average percent of the population dying from BRD was presented at the BRD Symposium 2008. Table 3 illustrates an increase in BRD death loss by month for the period June-December when we combine the information for the last five years (1990-2008 versus 1990-2013). As the numbers indicate, our practice group has not improved the numbers for our clients in the last five years.
Table 1. Percent of Cattle Placed by VRCS, LLC Clients Dying from Bovine Respiratory Disease 1991-2013

Table 2. Average Percent of Population of VRCS, LLC Clients Dying from Bovine Respiratory Disease by Month 1990-2013
Table 3. Average Percent of Population of VRCS, LLC Clients Dying from Bovine Respiratory Disease by Month 1990-2013 vs 1990-2008

It is not uncommon to operate under the mindset of “vaccine can do no harm”. Table 4 refutes this paradigm. In a study that was replicated three times, we demonstrated two different brands of commercially available vaccines containing the antigens of *Mannheimia haemolytica* and *Pasteurella multocida*. *Pasteurella multocida* increased the mortality by 2-3X when compared to negative controls. This study supports the fact vaccines are not innocuous.

Table 4. Comparison of Negative Control vs. *M. haemolytica/P. multocida* Commercial Brands

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For various reasons so-called “autogenous vaccines” have become vogue. One dictionary’s definition of an autogenous vaccine is “a vaccine prepared from cultures obtained from a specific lesion of the patient and used to immunize him against further spread and progress of the same organism”. I seriously question how our profession can justify using so-called autogenous bacterial vaccines in a feedlot setting. It seems illogical to culture one lung isolate from a calf for example from Alabama, prepare a vaccine, and inject it into a group of calves that arrive several weeks later from Texas or some other state. Our group has not seen any results of controlled studies with autogenous vaccine in a feedlot setting.

There are two types of EBM. One is evidenced-based medicine, which we as a profession espouses we practice. The second EBM is economic-based medicine, which is probably the one that fits the use of autogenous vaccines in a feedlot setting.

One reason provided by vaccine manufacturers for the negative effects observed in the trial in Table 4 was endotoxin levels. The endotoxin levels detected in two different commercially available *Mannheimia haemolytica* vaccines were 40,000 and 20,000 EU per ml. One could logically conclude these levels would be much higher if the vaccine contained the *P. multocida* antigen such as used in the study conducted summarized in Table 4, but the levels were not determined. One could probably conclude endotoxin levels in autogenous vaccines would be highly variable and much higher, but to my knowledge none have been tested.

For the last approximately three decades our profession has attempted to reduce morbidity/mortality by metaphylactically treating incoming cattle. There is copious data available indicating approximately 50% reduction in morbidity and 30-50% reduction in mortality using this practice. A recent publication by Brian V. Lubbers, et al (Lubbers and Hanzlicek, 2013) would indicate our success rate with this practice is declining. Table 5 demonstrates a decline in susceptibility and an increase in the resistance for the years 2009-2011.

In order to determine if the population with which we as a practice were involved was seeing a similar pattern we worked with Brian Lubbers on a culture and sensitivity study. We cultured lung from cattle with no known previous antimicrobial treatment, those that received a metaphylactic treatment on arrival, as well as those receiving a metaphylactic treatment followed by one hospital therapy. The results are in Table 6. Pan-resistance was reported in 24 of the 46 isolates. No organisms were reported resistant to ceftiofur. Unfortunately, we can find very little correlation between in *vitro* and in *vivo* with this compound.
Table 5. **Antibiotic resistance.** The percentage of *Mannheimia haemolytica* isolates, by year that were resistant to 0, 1, 2, 3, 4, and 5 antimicrobials, respectively. Isolates in the 0 column would be considered pan-susceptible isolates. There were no isolates resistant to all 6 antimicrobials over the course of the survey. (Lubbers and Hanzlicek, 2013)

![Graph showing antibiotic resistance](image)

Table 6. **Mannheimia haemolytica** antimicrobial susceptibility by treatment classification

![Graph showing antimicrobial susceptibility](image)

(Lubbers, 2014)
Considering all of the above, one could surmise it is time to try something different. Questions are:
1. Is it time to look for ways to improve death loss other than continuing to focus on the pathogen?
2. Is it time to focus on the animal’s response to the pathogens instead of the pathogens? Work by Aich, Potter, and Griebel (Aich, Potter, Griebel, 2009) demonstrated stress doubled the mortality even though the pathogen load remained constant.
3. Instead of focusing on the 10-50% morbid cattle should we focus on the 50-90% that are not morbid and determine why they stay healthy in the same environmental conditions?

As a group, we have been searching for management interventions on high-risk cattle that lower stress. We have no controlled studies at this time but some of these practices appear to decrease morbidity/mortality as effectively as metaphylactic treatment. Obviously, no commercial company is willing to fund management studies since they are unable to market them. It is my hope by the time of the 2019 BRD Symposium we and others will present results of just such studies.

References
Factors That Influence Producer Decisions to Implement Management Strategies
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Abstract
Cow-calf enterprises in the United States are widely divergent in size, locale, resource availability, management skill and market focus. Furthermore, variation in dependence on the cow-calf enterprise as a primary source of income, perception about the utility of a particular management practice or technology, and assessment of cost: benefit resulting from implementation impact decisions. Enterprises with larger cow inventories, greater dependence on income from the cattle enterprise, and that retain ownership further into the supply chain beyond the cow-calf operation are more likely to institute management protocols such as vaccination programs, defined calving seasons, and reproductive technologies.

Successful cow-calf managers place highest priority on herd nutrition, pasture and range management, herd health, financial management marketing, production management, and genetics. Management practices are more likely to be adopted when they align with a manager’s perception of the utility, labor availability, favorable cost: benefit outcomes, and profit motivation.

Introduction
The beef production model in North America is complex involving large numbers of independent producers operating in widely dispersed geographical locations with a variety of management practices suited to regional, size of enterprise, business goals, resource constraints, and market opportunities. This paper will focus on those U.S. producers who own cows and may retain ownership of some or all of their calves into the stocker and/or feedyard phase of beef production.

Producer Demographics
Ownership of the U.S. beef cow herd is nearly evenly split between herds with fewer than 100 head of breeding age females and those with inventories greater than 100 (Fig. 1). However, there is significant divergence in enterprise numbers within these categories with 90% of cow-calf enterprises having less than 100 cows (45% of the national inventory) while 10% of the herds have greater than 100 head (55% of the national inventory). Herds with greater than 500 head comprise less than 1% of the enterprises but hold nearly 17% of the inventory (NASS, USDA, 2013). As herd size increases, producer commitment of time to the enterprise increases as does reliance on the cow-calf enterprise as a primary income source (Table 1).
Figure 1. Percent of enterprises and cow inventory accounted for by various sized cow-calf herds.

Table 1. Key Demographic Factors Related to Size of Cow-calf Enterprise (Adapted from NAHMS Cow-calf Studies)

<table>
<thead>
<tr>
<th></th>
<th>1-49 hd</th>
<th>50-99 hd</th>
<th>100-199 hd</th>
<th>200+ hd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Owner work time devoted to cow-calf enterprise (%)</td>
<td>29</td>
<td>47</td>
<td>55</td>
<td>68</td>
</tr>
<tr>
<td>Cow-calf enterprise is primary income source (%)</td>
<td>5</td>
<td>24</td>
<td>43</td>
<td>65</td>
</tr>
<tr>
<td>Communicate health program information to buyers (%)</td>
<td>28</td>
<td>43</td>
<td>57</td>
<td>74</td>
</tr>
<tr>
<td>Vaccinated any beef animal (%)</td>
<td>59</td>
<td>87</td>
<td>96</td>
<td>92</td>
</tr>
<tr>
<td>Vaccinated calves against respiratory disease (birth to sale) – 1 time (%)</td>
<td>14</td>
<td>22</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>Vaccinated calves against respiratory disease (birth to sale) – 2 or more (%)</td>
<td>13</td>
<td>41</td>
<td>46</td>
<td>58</td>
</tr>
<tr>
<td>No respiratory disease vaccination (birth to sale)</td>
<td>73</td>
<td>36</td>
<td>28</td>
<td>18</td>
</tr>
</tbody>
</table>

Cow-calf enterprises are widely distributed across all fifty states with the greatest concentration of production in the northern and southern Great Plains. The average herd size for the western region of the U.S. is 155 head, for the Northern and Southern Plains 105 and 75 head respectively, while the North Central region has average herd sizes of 56 head and the Southeast at 59 head (NASS, USDA, 2013).
The age of agricultural producers is not normally distributed given that 18% are younger than 45, 40% are between the ages of 45 and 59, and 42% are 60 years of age or older (19% are older than 70) (NASS, USDA, 2013).

**Enterprise Categories**

Cow-calf enterprises are highly heterogeneous with differences arising from factors such as percent of income derived from cow-calf production, level of profit motivation, lifestyle factors, and resource limitations (time, labor, capital, expertise). One approach to categorize cow-calf producers is as follows:

- Professional cattlemen – information driven, value creation and capture focus, innovation friendly
- Professional cattlemen – tradition driven, commodity focus, change resistant
- Professional farmer – cattle as a by-product of land ownership or as alternative marketing option for grain production (significant variation in level of passion for the cattle enterprise)
- Professional in other industry – cattle as a secondary source of income
- Recreational cattle producer – lifestyle is primary focus – income from cattle not the critical factor due to other income streams
- ‘Cattle as cash’ producer – margin operators, cattle marketing to meet specific needs of the family (Field, et al, 2007)

These categories were formed from a qualitative approach and have not been quantified. However, they have been presented to numerous audiences and almost without exception have been received as an appropriate approach to defining the various categories of beef cow owners.

**Externalities**

Cattle producers across segments and categories face an increasingly chaotic business environment where volatility has become the norm due to economic, social movement, regulatory, consumer preference and market forces. Lawrence and Minert (2010) examined the Porter Competitive Forces model applied to the beef industry and determined that barriers to entry, substitute product availability and technology were the most likely factors to impact beef producers in the short run. These three forces coupled with regulatory actions focused on markets (COOL, trade agreements), environment (water and air quality, T&E species), energy policy (ethanol, wind energy), and labor (immigration, wages) will exert substantial pressure on producers (Lawrence and Minert, 2010; Field, 2000, Field, et al, 2007; Field 2010).

The influence of any one of these forces has the potential to affect the decision of an individual enterprise manager but taken in total, the combined impact of these forces creates a burden of accumulated aggravation that contributes to the search for low risk strategies, rising frustration levels that may lead to producers exiting the industry as well as decisions by the next generation not to enter the beef business.
Producer Priorities and Behaviors
In a study conducted in 2006, leading cow-calf producers (n=130) and industry specialists/advisors (n=87) quantified their management priorities. The pooled results ranked herd nutrition, pasture and range management, herd health, financial management marketing, production management, and genetics as the top 7 categories in order of priority from a listing of 15 (Field, 2006). Clearly successful producers viewed herd health as a critical step in assuring the sustainability of their enterprises. Furthermore, results from the study showed that maintaining herd health costs at below industry average levels was not a priority.

The NAHMS Beef survey conducted by USDA Veterinary Service in 2007-08 showed that herd size has a dramatic impact on whether or not veterinary consultation was utilized. Forty-three percent, 63%, 76%, and 82% of herds less than 50 head, 50 to 99 head, 100 to 199 head, and greater than 200 head respectively utilized veterinary service in the year previous to the study. The primary use of veterinary consultation was to prevent or treat disease. However as herd size increased, veterinary consultation broadened to incorporate nutritional management and production practices not related to disease. Furthermore, as herd size increased, the likelihood that any vaccinations were administered increased (Table 1). Regional variation in vaccination protocols were also demonstrated in the NAHMS study with 91, 76, and 60% of central, western, and southeastern herds vaccinating at least one animal respectively.

Specific to respiratory disease, larger herds were significantly more likely to administer vaccines against respiratory disease to calves either once or on multiple occasions (Table 1). Enterprises in the southeastern U.S. were least likely to vaccinate against respiratory disease (73% - no vaccination) while enterprises centrally were most likely to utilize preventative protocols (67% - 1or more vaccinations). In total, 69% of U.S. calves are sold by cow-calf producers having received at least one vaccination against respiratory disease (NAHMS, 2010).

Technology
Technology adoption varies widely across beef cattle enterprises. Factors such as size of enterprise, marketing strategy, and regional location help to describe differences (Table 2 and 3); however, variation in technology and best practice protocol adaptation varies considerably within these categories. Clearly, not all producers pursue the same goals or are motivated by the same influences. Furthermore, individual enterprises within and across geographic regions do not share the same resource constraints.

Ward, et al (2008) evaluated factors affecting production practice adoption rates by Oklahoma cow-calf producers and determined that labor reduction, dependence on the cow-calf enterprise for family income, age and educational level of producers, and herd size were the significant influencers. For example, as age of producer increased resistance to labor intensive protocols rises. Conversely, new practices and technologies (even if they require more time and labor) are typically more appealing to younger, better educated producers who depend on the cow-calf enterprise as a primary income source.
In practice, cow-calf producers evaluate new protocols or technologies from a partial budgeting perspective where either directly or intuitively the expected benefit is weighed against the cost of implementation. Furthermore, producers compare novel, innovative practices as to their anticipated utility. Thus both cost: benefit analysis as well as assessment of functionality and convenience of the proposed technology are brought to bear on the decision making process. In light of this model, beneficial innovations may be rejected if they are viewed as too labor and time intensive or if they excessively disrupt established routines and logistics of the enterprise.

Cow-calf enterprise managers are diverse and make decisions upon a variety of motivating factors. One size fits all strategies are unlikely to be effective. However, management protocols designed with sufficient flexibility to allow alignment with the goals, resources, human capacity, and labor availability of a particular enterprise are more likely to find acceptance.

Table 2. Demographic and Production Practice Implementation Differences by Cow-Calf Enterprises Marketing Calves Following Weaning, Stocker Backgrounding, or Finishing. (Source: McBride and Mathews, USDA: ERS, 2011)

<table>
<thead>
<tr>
<th></th>
<th>Cow-Calf – Sell at weaning</th>
<th>Cow-Calf – sell following stocker phase</th>
<th>Cow-Calf – sell following finishing</th>
<th>Cow-Calf - all</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cows (N)</td>
<td>64</td>
<td>93</td>
<td>86</td>
<td>79</td>
</tr>
<tr>
<td>Weaning Wt. (lb)</td>
<td>502</td>
<td>499</td>
<td>523</td>
<td>502</td>
</tr>
<tr>
<td>Weaning %</td>
<td>82.6</td>
<td>83.0</td>
<td>84.5</td>
<td>82.9</td>
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<tr>
<td>Calves sold at weaning (%)</td>
<td>100</td>
<td>21</td>
<td>28</td>
<td>59</td>
</tr>
<tr>
<td>Calves sold following Backgrounding Stocker (%)</td>
<td>0</td>
<td>79</td>
<td>15</td>
<td>36</td>
</tr>
<tr>
<td>Calves sold following finishing (%)</td>
<td>0</td>
<td>0</td>
<td>57</td>
<td>5</td>
</tr>
<tr>
<td>Farm income from cattle (%)</td>
<td>36</td>
<td>43</td>
<td>34</td>
<td>39</td>
</tr>
<tr>
<td>Production Practices</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defined calving season</td>
<td>54</td>
<td>66</td>
<td>79</td>
<td>61</td>
</tr>
<tr>
<td>Use A.I.</td>
<td>4</td>
<td>11</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>Calfhood growth implant</td>
<td>9</td>
<td>17</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td>Rotational grazing</td>
<td>59</td>
<td>62</td>
<td>56</td>
<td>60</td>
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<tr>
<td>Individual cow records</td>
<td>40</td>
<td>50</td>
<td>56</td>
<td>46</td>
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</table>
Table 3. Demographic and Production Practice Implementation Differences in Cow-Calf Enterprises Across Geographical Regions of the U.S.

<table>
<thead>
<tr>
<th></th>
<th>North Central&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Southeast&lt;sup&gt;b&lt;/sup&gt;</th>
<th>N. Plains&lt;sup&gt;c&lt;/sup&gt;</th>
<th>S. Plains&lt;sup&gt;d&lt;/sup&gt;</th>
<th>West&lt;sup&gt;e&lt;/sup&gt;</th>
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<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cows (N)</td>
<td>56</td>
<td>59</td>
<td>105</td>
<td>75</td>
<td>155</td>
</tr>
<tr>
<td>Weaning Wt. (lb)</td>
<td>501</td>
<td>480</td>
<td>543</td>
<td>493</td>
<td>538</td>
</tr>
<tr>
<td>Weaning %</td>
<td>83.6</td>
<td>80.9</td>
<td>87.3</td>
<td>82.9</td>
<td>82.8</td>
</tr>
<tr>
<td>Calves sold at</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>weaning (%)</td>
<td>44</td>
<td>70</td>
<td>41</td>
<td>69</td>
<td>53</td>
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<tr>
<td>Calves sold following</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Backgrounding Stocker</td>
<td>45</td>
<td>28</td>
<td>49</td>
<td>29</td>
<td>39</td>
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<tr>
<td>Calves sold following</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>finishing (%)</td>
<td>11</td>
<td>2</td>
<td>10</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Farm income from cattle (%)</td>
<td></td>
<td>23</td>
<td>25</td>
<td>38</td>
<td>67</td>
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<tr>
<td><strong>Production Practices</strong></td>
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<td>Defined calving season</td>
<td>82</td>
<td>45</td>
<td>92</td>
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<td>85</td>
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<tr>
<td>Use A.I.</td>
<td>11</td>
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</tr>
<tr>
<td>Calfothhood growth implants</td>
<td>28</td>
<td>7</td>
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<tr>
<td>Rotational grazing</td>
<td>54</td>
<td>60</td>
<td>58</td>
<td>62</td>
<td>71</td>
</tr>
<tr>
<td>Individual cow records</td>
<td>52</td>
<td>35</td>
<td>59</td>
<td>45</td>
<td>52</td>
</tr>
</tbody>
</table>

<sup>a</sup> IA and MO  
<sup>b</sup> VA, TN, KY, AR, MS, GA, AL, FL  
<sup>c</sup> KS, NE, SD, ND  
<sup>d</sup> OK, TX  
<sup>e</sup> MT, WY, CO, NM, CA, OR  


References
Poster 1
Integrated program for reducing bovine respiratory disease complex in beef and dairy cattle coordinated agricultural project (BRD CAP).
The Bovine Respiratory Disease Consortium Coordinated Agricultural Project Team\textsuperscript{1}, A. L. Van Eenennaam\textsuperscript{2}, J. E. Womack\textsuperscript{3}.
\textsuperscript{1}http://www.brdcomplex.org; \textsuperscript{2} Dept. of Animal Science, University of California, Davis, CA; \textsuperscript{3} Dept. of Veterinary Pathobiology, Texas A&M University, College Station, TX.

The BRD CAP is a 5-year USDA-funded Coordinated Agricultural Project to address the problem of BRD in dairy and beef cattle. This multi-institutional team, led by Dr. James Womack at Texas A&M University, collaborates to conduct a combination of BRD-related research, education, and extension activities. One of the primary research aims of the BRD CAP is to reduce the prevalence of BRD in beef and dairy cattle through the identification of genetic loci associated with host susceptibility to BRD, and to use this information to develop DNA-based selection tools. Numerous approaches are being employed to achieve this goal including two large genome wide association studies (GWAS) on beef and dairy cattle, the identification of DNA structural variants that have major effects on BRD susceptibility; gene expression studies from challenged animals to identify genes differentially expressed in cattle in response to BRD pathogens; analysis to identify important biological pathways in BRD susceptibility; and animal behavioral studies have been conducted to determine how BRD impacts animal welfare. 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 causal single nucleotide polymorphisms (SNPs), and integration of predictive markers for BRD susceptibility into genetic tests and national cattle genetic evaluations. The educational team is focused on developing online graduate level courses on the integration of animal health management with genomic and animal breeding approaches to reduce livestock disease, sponsoring undergraduate students to attend the Southern Great Plains Dairy Consortium (sgpdct.tamu.edu), and the development of graduate and undergraduate internships to expose students to multidisciplinary integrated research to reduce BRD prevalence. The extension team is developing outreach materials on best-management practices to reduce BRD incidence in both the dairy and beef industry, providing content on BRD to eXtension, working with dairy and beef cooperators interested in improving their BRD management, and evaluating the economic impact of BRD on dairy and beef operations. For more information see the website http://www.brdcomplex.org.

Poster 2
Delivery and evaluation of the BRD Curriculum and On-Farm Assessment of BRD Risk from the Washington State University Extension BEEF team
Washington State University Veterinary Medical Extension Pullman, WA
The 2007-2008 USDA National Animal Health Monitoring System Beef Study documented that Bovine Respiratory Disease (BRD) is a serious health challenge for U.S. beef cow-calf producers: respiratory disease is the most common cause of death in calves over three weeks old. The WSU Beef Team, already engaged in a five-year USDA-funded project called “An Integrated Approach to Control of Bovine Respiratory Diseases”, obtained additional funding from the Western Center for Risk Management Education to fund an outreach series to present newly-developed, evidence-based educational materials to cow-calf producers throughout the state. Team members conducted workshops in five locations, directly reaching 104 producers. At each workshop, producers were asked to complete a self-assessment of their ranch’s BRD risk, received notebooks with 11 educational modules, interacted with Extension professionals delivering educational content and were encouraged to request an on-farm BRD risk assessment conducted by team members. Educational module topics focusing on reducing BRD risk included managing pregnant cows; calving management; optimizing calf care; weaning procedures; cattle handling; vaccinations; preconditioning; transportation; biosecurity; and documenting BRD incidence and health costs. An audience response system was used to measure knowledge gains immediately after each workshop. Results indicate substantial increases in all evaluated areas. The fact sheets generated through this program will enter the WSU Fast Track system to increase their access and impact. BRD team members have visited and will continue to visit cow-calf ranches to conduct requested BRD risk assessments and help producers develop management plans to lower the BRD risk of their herds.

**Poster 3**

Investigation Into an Outbreak of Respiratory Disease in Nursing Calves in a South Georgia Beef Herd

J. Brown¹, A. Woolums¹, L. Jones², G. McKinnon³, R.W. Fulton⁴ and J. Ridpath⁵

¹Dept. of Large Animal Medicine and ²Dept. of Population Health, University of Georgia, Athens GA; ³Mac Farms, Ambrose GA; ⁴Dept. of Veterinary Pathobiology, Oklahoma State University, Stillwater OK; ⁵NADC ARS USDA, Ames IA.

An outbreak of nursing calf bovine respiratory disease (BRD) in a South Georgia commercial beef cow herd was investigated in July 2013. The owner reported a group of nursing beef calves had signs of respiratory disease and treated the calves via mass antimicrobial treatment. Within a week, another group of calves were showing respiratory signs at a separate location. One calf had died but no postmortem samples were obtained. Two other groups of cow-calf pairs were not showing signs of BRD. All calves in the second herd were administered mass medication, and rectal temperatures were obtained and recorded. At that time nasal swabs for virus identification and ear notches (pooled 5 per test) for BVD virus antigen capture ELISA were obtained from all 180 calves. Paired serum samples were collected from a convenience sample of 7 calves. All ear notches were subsequently found to be negative for BVDV. Nasal swabs from 60 calves were selected for multiplex real time polymerase chain reaction (RT-PCR) testing for bovine herpesvirus-1 (BHV-1), bovine viral diarrhea virus (BVDV), bovine respiratory syncytial virus (BRSV), and bovine coronavirus (BoCV). Fifty-six of the sixty swabs (93% of swabs tested) were positive for BoCV by RT-PCR; no swabs were positive for BHV-1, BRSV, or
BVDV. Thirty swabs were also tested for BoCV by virus isolation, and five tested positive. Paired serum samples were tested for serum neutralizing antibodies to BoCV, BVDV1, and parainfluenza type 3 virus (PI3V). Two calves seroconverted (4-fold rise in titer) to BoCV; no calves seroconverted to BVDV or PI3V. Following treatment all calves were reported to be doing well, and no additional calves in any group on the operation required additional treatment. No additional calves died. Bovine coronavirus was associated with this outbreak of respiratory disease in nursing beef calves.

**Poster 4**

**Trace Mineral deficiency at arrival and its association with clinical Feedlot Respiratory Disease**


Department of Veterinary Clinical Sciences, Washington State University, Pullman, WA

This pilot study evaluated the effect of blood trace mineral status in comingled sale barn and ranch calves entering a Washington feedlot on their clinical bovine respiratory disease (BRD) risk. Pacific Northwest feeds commonly have trace mineral levels below National Research Council recommended levels. Trace mineral deficiencies of selenium (Se), copper (Cu), and zinc (Zn) are known to be detrimental to immune function.

Four hundred and twelve calves (189 heifers and 223 steers) were obtained from three sale barns and one ranch in California and Washington. The majority of cattle were black hided *Bos taurus* weighing between 560 and 640 lbs. Cattle were processed the day after arrival and received individually numbered ear tags to track them through the feeding period.

At least 5 ml of blood was drawn into a 10 ml heparin Vacutainer tube (BD Diagnostics, Franklin Lake, NJ) and into a 10 ml red topped Vacutainer tube (no additive) from each calf. Serum was separated from the red topped tubes and frozen while the whole blood samples were refrigerated for future analysis.

The cattle were housed in two open lot pens sorted by gender. Any sick or injured animals were removed from the pen daily, moved to hospital pens, and treated according to the veterinarian’s recommendations. Physical examination findings and treatments were recorded in a computerized health record system. Blood and serum samples from animals that were pulled and treated for respiratory disease were sent to the state diagnostic lab to be analyzed for trace mineral content. Samples from the controls were randomly matched to the cases in a one to one ratio on the basis of origin and gender and were then analyzed.

The data was analyzed to determine the proportion of cattle deficient in Cu, Se, and Zn upon arrival at the feedlot. The likelihood of contracting clinical BRD was compared with Cu status, Se status, and Zn status as a whole and within each origin.
The incidence of Se deficiency (<0.12 µg/g) at arrival was 65%, of Cu deficiency (<0.7 µg/g) was 52%, and of Zn deficiency (<0.8 µg/g) was 10%. Deficient selenium status was associated with increased incidence of clinical BRD (p=0.04).

We conclude that a significant number of animals were deficient in Cu and Se upon entry into the feedlot and those arriving with a selenium deficiency are at higher risk for acquiring BRD.

**Poster 5**

**Cobalt supplementation in pre-weaned beef calves affects humoral immune response, feedlot health and final carcass characteristics**

R. B. Sager, 1,2* C. J. Yeoman1, and G. C. Duff 1

1. Department of Animal and Range Sciences, Montana State University, Bozeman, 59717
2. Medicine Creek Bovine Health Services, Wilsall, Montana 59086

Economic losses from morbidity and mortality associated with bovine respiratory disease (BRD) in beef cattle are approaching $2 billion annually. Mineral supplementation during pre-weaning has potential to reduce sickness and improve health. The mineral cobalt (Co) is used by rumen-inhabiting microbes for the production of vitamin B₁₂. Vitamin B₁₂ is a cofactor for vital metabolic pathways in tissue carbohydrate and lipid metabolisms required for maintenance and growth. Vitamin B₁₂ is also vital for B cell proliferation to form plasma cells that secrete antibodies. Recent studies have shown increases to NRC-recommended Co supplementation levels enhanced antibody response in weaned beef calves. The objective of this study was to evaluate if an orally-supplied Co (30 g) bolus dosed pre-weaning affects the humoral immune system during the post-weaning feeding period, reduces the incidence of BRD, and improves final carcass characteristics. Five different ranches with similar genetics, forage, mineral, water aquifer bases, and the same preconditioning health program were utilized. Calves were weaned and transported the same day to the same feedlot. Two hundred, six to eight month old beef calves were randomly selected from 2,000 head (BW 220 ± 24 kg). All calves were vaccinated for *Mannheimia haemolytica* three weeks before weaning. At vaccination one hundred calves were randomly selected to receive an oral Co (30 g) sustained release bolus and one hundred calves randomly selected as controls. Both treatment and control calves were bled at vaccination to analyze initial *M. haemolytica* leukotoxin antibody titers and again at d 70 in the feedlot. Calves were fed the same rations during the feeding period until harvest. There was a 42% increase (P = 0.06) in *M. haemolytica* leukotoxin antibody titer in calves treated with Co. Feedlot health (morbidity and mortality) was evaluated pre-weaning and daily during the feeding period. Co treatment decreased (P = 0.02) the incidence of BRD. Final carcass characteristics showed no statistical differences in Yield or Grade but HCW increased 17.81 kg for an increased economical return of $90.31 per carcass.
Poster 6
Induction of tracheal antimicrobial peptide expression for prevention of bacterial pneumonia in cattle.
Department of Pathobiology, University of Guelph, Guelph, ON, Canada.

Bacterial pneumonia results from complex interactions among host, pathogens, and the environment, and can be considered to result from failure of the respiratory defenses against these pathogens. This presentation summarizes findings on the role of tracheal antimicrobial peptide (TAP) in pathogenesis and prevention of pneumonia in cattle. TAP gene expression was measured by quantitative RT-PCR in cultured bovine tracheal epithelial cells following exposure to various agonists, corticosteroids, and signaling pathway inhibitors. Antimicrobial effects of synthetic TAP were studied in vitro against isolates of Mannheimia and other pathogens. We show that bovine tracheal antimicrobial peptide—a beta-defensin important in innate immunity—has bactericidal activity against the pathogens that cause this disease in cattle, with no evidence that these host-adapted pathogens have evolved resistance to these peptides. However, genetic polymorphisms affect function and expression of this peptide. Further, we show that well-recognized risk factors for development of bacterial pneumonia in cattle, including corticosteroids (as a model of stress) and BVD viral infection, act to reduce the inducible expression of tracheal antimicrobial peptide, and thus impair innate immunity and contribute to development of bacterial pneumonia in stressed or virus-infected cattle. We are interested in developing methods to stimulate expression of this protein, as a strategy to prevent the disease. We characterized the effect of various agonists of cell surface receptors on induction of tracheal antimicrobial gene expression, and found that in addition to LPS, agonists of TLR 1/2 and interleukin-17AR induce gene expression via an NF-kB-dependent mechanism. Thus, these signaling pathways are targets for development of methods to stimulate innate immune responses in the lung of cattle, at risk of developing this important disease.

Poster 7
Substance P Plasma Concentrations of Bovine Calves in a Bacterial Respiratory Challenge Model
R. Dewell*1,2, C. Hanthorn1, V. Cooper1, M. Stock3, H. Coetzee1, G. Dewell1
1 Veterinary and Diagnostic Production Animal Medicine, College of Veterinary Medicine, Iowa State University, Ames, IA
2 Department of Veterinary Microbiology and Preventive Medicine, College of Veterinary Medicine, Iowa State University, Ames, IA
3 Department of Biomedical Sciences, College of Veterinary Medicine, Iowa State University, Ames, IA

Introduction: Substance P (SP) is a proinflammatory neuropeptide that is a neurotransmitter of pain and is reported to serve as a modulator of stress as well as other physiologic functions. The
in vivo role of SP in bovine pneumonia, particularly as its association with clinical scores or perceived stress or pain, has not been elucidated.

**Objective:** Assess the correlation of SP plasma concentrations in pneumonic calves with measured clinical and necropsy parameters.

**Materials and Methods:** Thirty five cross bred 2-3 month old dairy calves were enrolled and randomly assigned to one of 5 treatment groups for intra-tracheal inoculation: 1) leukotoxin negative *B. trehalosi* 2) leukotoxin positive *B. trehalosi*, 3) *Mannheimia haemolytica*, 4) combination of leukotoxin negative *B. trehalosi* and *M. haemolytica* or 5) negative control. Calves were monitored twice daily by researchers masked to treatment on Days 1–10. Calves were clinically assessed and assigned a respiratory (RS) and depression score (DS) ranging from 0-3. Blood samples were collected on Days 1, 3, 5, 7, 9, and 10. Substance P assay was performed using non-extracted plasma and analyzed in duplicate. Following euthanasia, calves were necropsied and estimated total lung involvement was calculated.

**Results:** There was no difference in Plasma Substance P concentrations between treatment groups (P=0.56) and values did not differ between sampling periods (P=0.4055). Substance P Plasma concentrations was not correlated with temperature (P=0.056), DS (P=0.81), RS (0.80), lung involvement (P=0.056).

**Conclusions:** Substance P plasma concentration is not a reliable indicator of bovine bacterial respiratory disease status. Plasma concentrations of Substance P were not correlated with clinical signs of disease.

**Poster 8**

**Serum concentrations of haptoglobin and haptoglobin-matrix metalloproteinase 9 (Hp-MMP 9) complexes of bovine calves in a bacterial respiratory challenge model.**

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**Objective**— Evaluate potential diagnostic applications of serum Hp and Hp-MMP 9 concentrations in calves with BRD and establish a timeline for their detection in calves experimentally challenged with *Bibersteinia trehalosi* and *Mannheimia haemolytica*.

**Animals**— 35 cross bred dairy calves

**Procedures**— Calves were inoculated via tracheal catheterization with either a PCR confirmed leukotoxin negative *B. trehalosi* isolate, a PCR confirmed leukotoxin positive *B. trehalosi* isolate, a *Mannheimia haemolytica* isolate, a combination of leukotoxin negative *B. trehalosi* and *M.
haemolytica, or a negative control. Serum samples were collected throughout the study. Calves were euthanized and necropsy performed on day 10 post inoculation.

Results—M. haemolytica inoculated calves had increased lung involvement. Serum Hp and Hp-MMP 9 concentrations were elevated compared to the other treatment groups. Increases in serum Hp and Hp-MMP 9 concentrations for the M. haemolytica group were significantly different from other study groups on day 7 of the study. B. trehalosi inoculated calves did not have increased lung involvement compared to control calves, but the leukotoxin positive B. trehalosi group demonstrated increased serum Hp-MMP 9 concentrations from day 3 to the end of the study compared to the pre-inoculation concentrations.

Conclusions and Clinical Relevance—Serum Hp-MMP 9 concentration is a useful diagnostic tool for detecting early pulmonary inflammation in calves challenged with B. trehalosi and M. haemolytica. Serum Hp-MMP 9 may also be a useful tool in detecting subclinical pulmonary inflammation in challenged calves.

Poster 9
Pathogenicity of Bibersteinia trehalosi in calves.
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Introduction - Bibersteinia trehalosi causes respiratory disease in ruminants particularly in wild and domestic sheep. Recently, there has been an increased number of B. trehalosi isolates obtained from diagnostic samples from bovine respiratory disease cases. This study evaluated the role of B. trehalosi in bovine respiratory disease using an intra-tracheal inoculation model in calves.

Objective — Determine if Bibersteinia trehalosi causes respiratory disease in cattle alone or in combination with Mannheimia hemolytica and if it can be recovered and cultured from lung tissue or lung wash.

Animals – 35 cross bred dairy steers

Procedures - Calves were inoculated intra-tracheally with either leukotoxin negative B. trehalosi, leukotoxin positive B. trehalosi, Mannheimia haemolytica, a combination of leukotoxin negative B. trehalosi and M. haemolytica, or negative control. Calves were euthanized and necropsy performed on day 10 of study.
Results - *B. trehalosi* inoculated calves did not have increased lung involvement compared to control calves. Additionally, *B. trehalosi* was only cultured once from the lungs of inoculated calves at necropsy.

Conclusions - Based on these findings *B. trehalosi* may not be a primary pathogen of respiratory disease in cattle. Culture of *B. trehalosi* from diagnostic submissions should not be immediately identified as a primary cause of respiratory disease.

Poster 10

A proof-of-concept study to explore safety and efficacy of oral modified-live virus respiratory vaccine administration in beef calves.

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Most viral and bacterial pathogens enter a host through mucosal surfaces, and mucosa-associated lymphoid tissue (MALT) of the respiratory tract is a critical mechanism for respiratory pathogen entry and immune defense when exposure via the nose and/or mouth occurs. Oral administration of a modified-live virus (MLV) vaccine may be less likely to induce clinical or subclinical effects from MLV antigens contained in the vaccine, lending potential to a mucosal vaccine product containing BVDV antigens, which currently does not exist on the market. Therefore, the objective of this study was to determine if oral administration of a MLV vaccine would safely and effectively stimulate local immunity and improve prevention of bovine respiratory disease. A total of 42 (n = 10 or 6/treatment) clinically healthy, previously unvaccinated crossbred beef steer calves were stratified by pre-trial serum BVDV type 1a antibody titer concentration, then assigned randomly to 1 of 5 vaccination treatment regimens applied on day 0: 1) 1 × dose oral – pentavalent MLV respiratory vaccine (OV1; 2 mL Pyramid® 5 without adjuvant administered in the buccal cavity), 2) 5 × dose oral – pentavalent MLV respiratory vaccine (OV5; 10 mL Pyramid® 5 without adjuvant administered in the buccal cavity), 3) 10 × dose oral – pentavalent MLV respiratory vaccine (OV10; 20 mL Pyramid® 5 without adjuvant administered in the buccal cavity), 4) positive control (PCON; 2 mL Pyramid® 5 with adjuvant administered subcutaneously in the neck), 5) negative control (NCON; 2 mL sterile saline administered in the buccal cavity). The positive control group had a greater BRSV antibody concentration when compared to negative control on day 28 (P = 0.04). No differences in the percent positivity of BRSV-specific secretory IgA from oral (P = 0.68) or nasal (P ≥ 0.07) swab samples were observed among treatments. An increase in basophils was observed for OV10 on day 2 (P < 0.001). Under conditions of this proof-of-concept study, oral vaccination did not clearly stimulate immunity in early-weaned beef calves; however, no clinical signs were observed during the study, and blood parameters were within normal reference range which suggests safety of the oral vaccination procedure.
Poster 11
Demonstration of Efficacy of Bovi-Shield Gold One Shot™ Vaccination Against Challenge with Virulent Bibersteinia trehalosi in Calves
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BRDC is a leading cause of morbidity and mortality of cattle in North America. The primary bacterial pathogens include P. multocida, M. haemolytica, H. somni, and M. bovis. B. trehalosi has been long recognized as a pathogen of sheep and wild ruminants. However, there are a growing number of cases of cattle respiratory disease associated with this organism. One of the key virulence factors of B. trehalosi is a leukotoxin similar to that found in M. haemolytica. It was hypothesized that One Shot (M. haemolytica toxoid) could provide cross protection to B. trehalosi. Therefore, a study was performed to evaluate efficacy of Bovi-Shield GOLD One Shot™ to reduce disease caused by B. trehalosi challenge in calves. In this study calves were vaccinated with 1) a negative control vaccine (Bovi-Shield GOLD 5°, or 2) Bovi-Shield GOLD One Shot. Calves were challenged 21 days later with a virulent strain of B. trehalosi. Clinical signs and body temperatures of calves were monitored over 6 days post-challenge. Mortality and lung lesion scores were determined for all calves. Results for BS Gold OneShot vaccinated vs BS vaccinated calves indicated reduced lung lesion scores (30 vs 43%), reduced mortality (13.2 vs 33.3%), reduced clinical scores (34.2 vs 72.2%) and increased serological titers (5254 vs 248). The results support that OneShot vaccinates had 1) reduced mortality 2) reduced lung lesion scores 3) reduced clinical scores compared to Bovi-Shield GOLD 5 vaccinated controls when challenged transtracheally with B. trehalosi.

Poster 12
Characterization of Mannheimia haemolytica in beef calves via nasopharyngeal culture and pulse field gel electrophoresis
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Mannheimia haemolytica (MH) is a major bacterial component of Bovine Respiratory Disease (BRD), yet relatively little is known about MH transmission dynamics. The objectives of this pilot study were to describe the arrival MH status of a group of calves, attempt to induce colonization and shedding of an artificially inoculated MH in negative calves, and describe the shedding pattern of healthy, naturally MH positive calves. In this study, two separate loads of 20 male calves (average weight 167.3 kg) were procured from an auction market. Deep nasopharyngeal cultures (NPC) were obtained from all calves upon arrival and if negative for MH, a second screening NPC was performed. Calves that were negative on both screening NPCs (NEG; n=4) were subsequently challenged both endoscopically and intranasally with a MH that
was previously isolated from a natural case of BRD. Following challenge, the NEG calves were individually housed, monitored for MH shedding via NPC at 0.5, 1, 3, 5, 7, and 9 days post-challenge, and necropsied on day 10. Four calves that were naturally positive on their initial screening culture were confirmed positive on a second screening culture (POS) and then cultured daily for 3 days. Individual animal MH status between study days for both the POS and NEG groups was inconsistent with some POS calves culturing negative and some of the challenged NEG calves remaining negative at some time points. Pulse field gel electrophoresis (PFGE) showed that the NEG calves did not shed the MH challenge strain, but rather two distinct clusters of MH that were similar among all calves in the study. Although sample sizes were small, these findings raise concerns about the use of a single NPC to establish the prevalence of MH within a pen or to guide treatment and management decisions.

**Poster 13**

**Use of Pulsed-Field Gel Electrophoresis for Characterization of *Mannheimia haemolytica* isolates from the Upper and Lower Respiratory Tracts of Cattle**

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The primary objective was to use PFGE to assess diversity in isolates from the upper (URT) and lower (LRT) respiratory tract of cattle. A second objective was to assess diversity within the URT or LRT, and whether a single colony is adequate for assessing the microbial population in the URT or LRT.

*M. haemolytica* isolates (137) were collected from 43 head of cattle. Samples were collected from: cattle undergoing processing at a sale barn (30 samples from URT of 10 head); processing at a backgrounding facility (16 isolates from URT of 7 calves); calves submitted for necropsy (73 isolates from 8 calves dying from BRD); and 18 isolates examined because of multi-drug resistance (MDR) (independent submissions, limited information on source).

Of 20 animals with more than one isolate, only 7 showed a single pulse-type. In many cases, a dominant strain could be identified (strain constituting ≥50% of all isolates). All isolates from clinically affected cattle fell into one of 10 groups, and all from non-affected fell into one of 15 groups. There was little overlap in these groups (p<0.005), with crossover in only one cluster, containing one isolate from an affected calf and one isolate from a healthy calf.

Isolates from the URT of calves that died from BRD produced a Simpson’s index of diversity (SID) of 70.1 (95% CI 62.3-77.8), while samples from the LRT of dead calves produced an SID of 73.6 (66.1 – 81.0). The MDR isolates had the highest SID value of any sub-population (SID of 90.2, 80.9-99.5). When MDR isolates were removed and isolates obtained from the LRT of calves from a known source were evaluated, SID dropped to 62.4 (54.1-70.6). This suggests modestly lower diversity in calves suffering from BRD than in samples from the URT of healthy calves (SID 76.7, 65.4-88.0).

Collection of multiple isolates from a given anatomic location may assist in better understanding the microbial population in cattle. Identification of a dominant strain may be
useful in determining if particular strains are more pathogenic. Clustering according to status of calf, as well as modestly lower diversity in isolates from clinically affected cattle, are consistent with the hypothesis that some strains are more virulent. Prospective studies are needed to determine when strain dominance emerges and whether disease can be predicted based upon presence of certain strains.

Poster 14

Associations between isolation of *Mannheimia haemolytica*, antimicrobial resistance and use, and morbidity and mortality in feedlot cattle

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*Mannheimia haemolytica* is a significant etiological agent implicated in bovine respiratory disease (BRD), and antimicrobial resistance (AMR) in this organism is thought to be a major factor in BRD treatment failures. However, few large-scale, field-based studies have investigated links between *M. haemolytica*, treatment with antimicrobials, AMR and health outcomes. Objectives of this study were to explore risk factors for isolation of susceptible and resistant *M. haemolytica* in a commercial feedlot setting, and to examine associations between isolation and health outcomes. Cattle (n=5,498) from 4 feedlots in Alberta, Canada were randomly enrolled and sampled via deep nasopharyngeal swab at arrival in the feedlot and later in the feeding period. Samples (n=10,477) were cultured for *M. haemolytica* and tested for resistance to 21 antimicrobials. Records of individual and pen antimicrobial use (AMU) and health events were collected. Associative analysis was conducted using multivariable GEE logistic regression to control for non-independent outcomes. Parenteral AMU rates were low, and resistance prevalence in *M. haemolytica* isolates was <5% for all 21 antimicrobials tested. Parenteral AMU in enrolled cattle decreased the likelihood of *M. haemolytica* isolation (OR 0.2, 95%CI 0.02 – 1.2, *P*=0.006), while parenteral AMU in penmates of enrolled cattle increased this likelihood (OR 1.5, 95%CI 1.05 – 2.2, *P*=0.02). Parenteral AMU was not associated with isolation of single-drug resistant *M. haemolytica*, but greatly increased the odds of recovering multi-drug resistant (MDR) *M. haemolytica* (OR 23.9, 95%CI 8.4 – 68.3, *P*<0.0001). Cattle from which *M. haemolytica* was cultured on arrival were more likely to be diagnosed with fever within 10 days of arrival compared to culture-negative cattle (OR 1.7, 95%CI 1.1 – 2.4, *P*=0.07). AMU is not likely the primary driver of antimicrobial resistant *M. haemolytica*, and AMU protocols that target high-risk and clinically ill cattle are likely efficacious and prudent. Contagious spread may underlie colonization and transmission dynamics, as AMU in penmates of enrolled cattle increased the risk of isolating both susceptible and MDR *M. haemolytica*. The link between...
AMU and MDR *M. haemolytica* warrants further investigation to determine the effects of such MDR on treatment efficacy.

**Poster 15**

**Effects of two dosages of tilmicosin on pathogen load reduction and clinical outcome in feedlot cattle with naturally occurring bovine respiratory disease**

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**Introduction**

Tilmicosin is a macrolide antimicrobial labeled for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* in beef and non-lactating dairy cattle and the control of BRD associated with *M. haemolytica*. BRD negatively impacts the health and well-being of beef cattle and the economic prospects of cattle owners. The objective of this study was to determine the effects of two dosages of tilmicosin (10 mg/kg and 20 mg/kg) on pathogen load reduction and clinical outcome of BRD in newly received feedlot cattle.

**Materials and Methods**

Five shipments of beef calves and yearlings were purchased at auction markets in California and transported to the study site in Parma, Idaho. Following processing, cattle were monitored once daily for clinical signs of BRD.

A clinical impression score (CIS) was assigned for respiration and signs of depression. For any animal receiving a score of 1 in both categories or ≥ 2 in either category, a rectal temperature was obtained. The case definition was met with a CIS of ≥ 2 and rectal temperature of ≥ 40.0°C.

Cases were enrolled on the study and randomly assigned to one of three treatments within a cohort. Treatments were: tilmicosin at 10 mg/kg BW (TIL10); tilmicosin at 20 mg/kg BW (TIL20); or untreated positive controls (POSCON). Four-animal cohorts were completed with the enrollment of a clinically normal (CIS = 0, rectal temperature < 39.5°C) asymptomatic negative control (ASYMP). Pathogen load was determined semiquantitatively by serial bronchial lavage (BL) procedures performed on days 0, 3, 6, and 9. In an on-site microbiology laboratory, serially diluted BL samples were plated on selective growth medium for isolation of Pasteurellaceae. One to three colonies with gross morphology consistent with *M. haemolytica* or *P. multocida* were subjected to biochemical tests (oxidase, catalase, indole spot). Isolates were subcultured onto Columbia blood agar, and identical biochemical tests were repeated 24 hours later for confirmation.

Pathogen load data were analyzed using RMANOVA in SAS (SAS 9.2, Cary, NC). Body temperature, CIS scores, and survival status were dichotomized and analyzed using Fisher’s exact test. Results were considered significant at \( P < 0.05 \).
**Results**

Thirty-six cohorts (28 full, 8 partial) representing 143 animals were enrolled on the study. At the time of enrollment, *M. haemolytica* levels (CFU/ml) were significantly greater \((P < 0.05)\) in cases (TIL10, TIL20, and POSCON) compared to AYSMP animals. On day 3, *M. haemolytica* levels in TIL10 and TIL20 treatments were significantly reduced \((P < 0.05)\) compared to POSCON. By day 9, there was no difference \((P > 0.05)\) in *M. haemolytica* levels between ASYMP, POSCON, and TIL10 treatments. Day 9 *M. haemolytica* levels of the TIL20 treatment group were equivalent \((P > 0.05)\) to the ASYMP treatment and significantly reduced \((P < 0.05)\) compared to the TIL10 and POSCON treatments.

Rectal temperature was reduced \((P < 0.05)\) on days 3 and 6 in TIL10 and TIL20 compared to POSCON. Rectal temperature and depression scores were similar \((P > 0.05)\) between TIL20 and ASYMP at post-treatment observations on days 3, 6, and 9.

Survival of TIL10 (93.75%) and TIL20 (93.33%) treatments did not significantly differ \((P > 0.05)\) from ASYMP (100.0%). Survival was significantly decreased (66.67%) \((P < 0.05)\) for POSCON compared to all other treatment groups. Across all treatments, for every 1-log increase in *M. haemolytica* levels, likelihood of death increased by a factor of 1.293 \((P = 1.293, 95\% CI: 1.159 \text{ to } 1.444)\). There was no discernable relationship between *P. multocida* levels and likelihood of death \((P = 1.011, 95\% CI: 0.913 \text{ to } 1.119)\).

**Significance**

Dosages of 10 mg/kg and 20mg/kg tilmicosin significantly \((P < 0.05)\) reduced pulmonary pathogen load and resulted in significantly \((P < 0.05)\) greater survival of newly arrived feedlot cattle compared to untreated positive controls. *M. haemolytica* levels were reduced by a greater amount in cattle treated with 20 mg/kg compared to those receiving 10 mg/kg at all post-treatment observations, although the difference was only significant \((P < 0.05)\) on day 9. Depression scores on day 9 were also significantly \((P < 0.05)\) improved in cattle receiving the higher dose. These results indicate tilmicosin administered at 20 mg/kg provides superior results in terms of pathogen load reduction and equivalent or superior results in terms of clinical response as compared to a dosage of 10 mg/kg.

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**Poster 16**

**Systematic thoracic ultrasonography in acute bovine respiratory disease of feedlot steers: impact of lung consolidation on diagnosis and prognosis in a case-control study**

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A study was conducted to evaluate the diagnostic and prognostic value of thoracic ultrasonography (TUS) in feedlot calves with clinical signs attributable to bovine respiratory disease (BRD). Twenty nine BRD cases and 15 asymptomatic controls were evaluated using
systematic TUS on the day of initial pull (day 0), 3, 6, 9 and 15. Four-second ultrasound loops were saved at 46 locations per animal and later evaluated offline for evidence of lung pathology. Five TUS indicators of lung lesions and 4 indices of consolidation were evaluated for ability to differentiate between healthy controls and BRD cases as well as predict death (negative outcome) among non-treated BRD cases.

The number of sites with consolidation (SITES), number of sites with pleural irregularities (PIRR), maximal depth of consolidation (DEPTH), maximal area of consolidation (AREA), and total consolidated area (TCA) were found to be significantly higher in BRD cases than controls at enrollment ($P<0.05$). These same parameters (SITES, PIRR, DEPTH, AREA, TCA) were found to be significantly higher at enrollment for BRD cases that died before the end of the 15-day observation period ($P<0.05$). Among BRD cases, 9/46 sites examined had an odds ratio of negative outcome significantly greater than 1 when consolidation was present at enrollment ($P<0.05$). This study demonstrates that TUS may prove useful in feedlot cattle for determining the extent of lung lesions and predict outcome in BRD cases.

**Poster 17**

**Evaluation of a computer-assisted electronic stethoscope (Whisper®) for diagnosis of bovine respiratory disease in feedlot cattle.**

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A computer-assisted electronic stethoscope (Whisper, Geissler Corporation, MN) that classifies acoustic patterns in lung scores was recently developed to diagnose bovine respiratory disease (BRD) in feedlot cattle. The objectives were to evaluate, in a case-control study, sensitivity [Se], specificity [Sp], positive [LR+] and negative [LR-] likelihood ratios of this chute-side test and determine how its use could influence accuracy of BRD diagnosis in feedlots. 561 Angus-cross steers (initial BW = 246 ± 45 kg) were observed during the first 50 DOF at a commercial feedlot. Steers with visual BRD signs were clinically examined by a veterinarian, including lung auscultation using a conventional stethoscope and lung auscultation using Whisper (the latter produced a lung score from 1 [normal] to 5 [chronic]). For each steer examined for BRD, 1 or 2 apparently healthy steers were concurrently selected as controls and similarly examined. Steers with visual BRD signs, a rectal temperature ≥40°C and abnormal lung sounds at veterinary auscultation were defined as true positive (TP) BRD cases. True negatives (TN) were defined as steers with no BRD signs, a rectal temperature <40°C and no abnormal lung sounds. Whisper’s performance was determined using TP and TN as gold standards. Influence of Whisper on accuracy of BRD diagnosis was determined in 2 scenarios (low = 40% and high = 80% pre-test BRD probabilities) using Bayes’ theorem and LRs from this study. Of the 561 steers, 33 and 37 were designated TP and TN. Of the 33 TP, 6, 15, 10, 1 and 1 steers had Whisper scores of 1, 2, 3, 4 and 5, respectively. Of the 37 TN, 35 had a score of 1 and 2 had a score of 2. Using a score ≥2 as a cut-off, Se, Sp, LR+ and LR- of Whisper to diagnose BRD were 81.8% (95% CI = 65.5-93.0%),
94.6% (81.8-99.3%), 15.1 (3.9-58.8) and 0.2 (0.1-0.4), respectively. A positive Whisper auscultation (score ≥2) substantially increased the post-test probability of BRD (>90%) even if pre-test BRD probability was low. However, due to the relatively high LR-, a negative Whisper auscultation only moderately reduced the post-test probability of BRD. In conclusion, Whisper was moderately sensitive and highly specific to diagnose BRD when compared to veterinary clinical examination. Its use in feedlots should significantly increase the proportion of cattle accurately diagnosed with BRD.

**Poster 18**

**Using an activity monitoring system for detecting early behavioral markers of respiratory disease development in young dairy calves.**

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Dairy calf pneumonia (DCP) is a prevalent, economically important condition affecting calves during the pre-weaning and/or post-weaning periods. The impact of DCP extends beyond the actual disease episode, having a negative effect on subsequent productivity and survivability of replacement stock. The ability to identify calves during the initial stages of respiratory disease development is difficult but objective monitoring of activity and feeding behavior may allow for earlier disease detection and intervention, potentially decreasing the consequences of DCP later on in the calf’s life. The objective of this study was to identify early behavioral changes during respiratory disease development in young dairy calves subjected to different milk feeding levels (standard or high) and housing (individual or group).

Forty Holstein calves from 9 different commercial dairy farms (3 for each of the treatments: standard milk/individual housing, high milk/individual housing, and standard milk/group housing) will be used in this study. Overall respiratory disease incidence was approximately 20%. Social interaction/activity levels as well as feeding behavior were measured by fitting calves with collars containing sensors during the pre-weaning period. Calves were screened daily for clinical signs of disease. Deep pharyngeal swabs were obtained from sick calves for detecting pathogens associated with respiratory disease by PCR and serum samples were collected for serology.

The automated sensor system successfully recorded activity levels of calves on the different farms. Total activity levels were correlated with milk consumption showing significant increases during the time preceding the feedings. In addition, a unique time series signature that corresponds with normal specific behaviors such as sleeping, standing, walking and/or bottle feeding was established from the acceleration data (activity levels). We used these data to identify any deviations from the norm. Behavioral data recorded for calves with respiratory disease showed maintained activity levels without the short bursts of activity that occurred in the healthy cohorts, particularly prior to feeding. Furthermore, no prolonged periods of rest
were observed in the sick calves when compared to the healthy ones. In conclusion, these results suggest that calf behavior may be a useful means of disease detection.

**Poster 19**

**Accuracy of remote early disease identification (REDI) system for detection of bovine respiratory disease in calves**

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Bovine respiratory disease (BRD) causes a large detrimental impact and current diagnostic methods rely almost exclusively on human observation which has limited accuracy. Correctly identifying the true BRD status is critical to prevent unnecessary antimicrobial use and optimize therapeutic response by treating the correct animals at appropriate times. A remote, early disease identification (REDI) system was developed using real time cattle locational and behavioral data to diagnose BRD. The objectives of this research were evaluation of REDI accuracy and agreement with a trained observer. Preliminary BRD status was determined on cattle in two trials based on clinical signs and rectal temperature (< 103.5°F), and cattle meeting initial enrollment criteria were then immediately euthanized and necropsied to determine true BRD status based on the level of pulmonary lesions (< 5%). The REDI algorithms were applied to data collected 96 hours prior to diagnosis/necropsy from BRD positive (n=8) and negative (n=7) calves, and REDI identified almost 40% of BRD cases more than 48 hours prior to the observer and all cases by the time of necropsy. REDI identified no false positives during the study period. In a subsequent blinded, randomized controlled clinical trial, calves within a single pen were treated based on BRD status as determined by an observer or REDI. The number of BRD calves identified were nearly identical (REDI n=17/40, observer n=16/40), and the systems agreed on 83% of all daily calf observations. One source of disagreement was REDI identifying BRD calves an average of 0.75 days before visual observation of clinical signs. The REDI system appears to offer an accurate method for early, remote BRD diagnosis.

**Poster 20**

**A meta-analysis of vaccine effectiveness against bovine herpes virus, bovine viral diarrhea virus, bovine respiratory syncytial virus, and parainfluenza-type 3 virus in cattle for bovine respiratory disease complex**

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Multiple vaccines against viral antigens with the goal to decrease the risk and severity of bovine respiratory disease complex (BRDC) are commercially available. Our objective was to perform a systematic review of published literature and a meta-analysis to evaluate the efficacy of vaccinating cattle with commercially available viral vaccine antigens to mitigate the effects of BRDC compared to unvaccinated controls. A literature search was performed to identify studies testing the effectiveness of bovine herpes virus-1 (BHV-1), bovine respiratory syncytial virus (BRSV), bovine viral diarrhea virus (BVDV), and parainfluenza-type 3 (PI3) vaccination in cattle. Inclusion criteria were appropriate allocation of experimental units to treatment groups and blinding of evaluators. Studies were categorized as natural exposure or induced-challenge, and the challenge studies were further divided by the viral antigen evaluated, and also whether the product was a modified-live (MLV) or inactivated vaccine. Thirty-one studies with 88 trials were included; however, few of the studies were natural-exposure. The natural challenge trials showed reduced risk of BRDC in vaccinated calves. Evaluation of commercially available BHV-1 and MLV BVDV vaccines using induced-disease challenge models demonstrated reduced morbidity risk; however, trials evaluating MLV BRSV and PI3 vaccines in challenge settings failed to demonstrate evidence of reduced morbidity and mortality risk in vaccinated calves. The published literature provides some assistance for veterinary practitioners, but does not provide sufficiently strong evidence to guide definitive recommendations for determining which viral components are necessary to include in a vaccination program to reduce BRDC risk in feedlot cattle.

Poster 21
A simulation model to determine the economic value of changing diagnostic test characteristics for identification of cattle for treatment of bovine respiratory disease
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Bovine respiratory disease (BRD) is an economically important syndrome for the beef industry, and diagnostic accuracy is important for optimal disease management. The objective of this study was to determine whether improving diagnostic sensitivity or specificity was of greater economic value at varied levels of BRD prevalence using Monte Carlo simulation. Existing published literature was used to populate stochastic model distributions of expected diagnostic sensitivity and specificity, and performance (average daily gain, carcass weight, yield grade, quality grade, and mortality rate) differences among calves based on clinical BRD status. Multiple cattle feeding operations were used to generate ranges of BRD prevalence and associated mortality. A single model was created that combined the input variables to calculate the estimated net returns for animals deemed as true positive, false positive, false negative,
and true negative for BRD based on the prevalence, sensitivity, and specificity for each iteration. Net returns for each category were multiplied by the proportion of animals in each category to determine group profitability. Apparent prevalence was categorized into low (<15%) and high (≥15%) categories. Increasing specificity created more rapid, positive change in net returns than improving sensitivity for both prevalence categories. Improvement of diagnostic specificity, possibly through use of a confirmatory test interpreted in series, can increase diagnostic value. Mortality risk was the primary driver for net returns. These results are important to analyze future research projects evaluating diagnostic techniques for BRD, and provide a novel way for modeling diagnostic tests.

**Poster 22**

**A stochastic model designed to estimate discrepancies in the relative economic value between cattle with and without lung lesions in U.S. feedlot production systems.**

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Despite a wide array of preventive and therapeutic modalities, bovine respiratory disease (BRD) continues to be the most prevalent infectious disease syndrome among feedlot cattle. Prior data have observed that feedlot cattle with lung lesions at slaughter (due to prior bouts of BRD) display average daily gain (ADG) estimates inferior to cattle without lung lesions. However, the true economic impact of lung lesions in feedlot cattle populations is unknown. The objective of this study was to compare the relative economic value between cattle with and without lung lesions by utilizing a stochastic modeling approach.

The model commenced at animal purchase and identified the prevalence of cattle with lung lesions within a pen. Cattle with and without lung lesions were modeled in parallel throughout the feeding phase incorporating all production expenses and revenue. The final outcome was the difference in economic value between both cohorts when marketed on a live-weight basis.

Within this model, cattle with lung lesions lost $77.07/head, on average, (90% probability interval [PI]: $35.35 – $165.17) compared to pen-mates without lung lesions. The sensitivity analysis suggested that the loss of ADG among cattle with lung lesions was the primary driver of the divergence in economic value between the two cohorts.

Based upon the static and probabilistic assumptions built into this model, these findings suggest that cattle with lung lesions at slaughter (due to BRD) are a significant economic drain. Continued efforts are necessary to reduce the prevalence of cattle with lung lesions by optimizing pre and post-weaning management, improvement of BRD diagnostic regimens, and improving the efficacy of BRD treatment modalities.
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