Bovine respiratory disease complex (BRD) is the primary infectious disease affecting stocker and feedlot cattle. A number of factors combine to initiate most cases of BRD. These factors are stress (shipment, social interaction, and nutritional), viral infection, and bacterial infection. BRD is generally considered to be a disease of stocker and feedlot cattle that are trucked to a feeding facility, exposed to new animals, and new feed and water sources. Age is also a factor with recently weaned calves and light stocker calves having higher morbidity and mortality risk than yearling cattle. Despite the investment of substantial financial and intellectual resources, the risk of death and monetary loss due to BRD has not decreased significantly.\textsuperscript{1,2,3} I readily admit that I do not know why more effective control of BRD is elusive, but I investigated the question by first posing it to a number of experts from the fields of veterinary epidemiology, internal medicine, pharmacology, genetics, pathology, and private feedlot practice. Our collective perspectives reveal a number of potential obstacles to progress against BRD.

\textbf{Obstacles to decrease stocker feedlot morbidity due to BRD}

If we assume that overall morbidity due to BRD in U.S. feedlots is not decreasing despite efforts to produce more effective vaccines and immunization programs, then several possibilities should be considered. Either vaccination with available products does not produce immunity in feedlot cattle, the immunity produced is not protective, or while improving the animals' immune response to infectious pathogens, other factors that contribute to BRD are increased.

\textbf{Do BRD vaccines work?}

To begin the discussion of vaccines, I want to explain my understanding of the difference between the terms "vaccine efficacy" and "vaccine effectiveness". I use the term efficacy to mean that in a certain setting, vaccinated animals have measurable differences from non-vaccinated animals. These differences may be laboratory findings such as titer level, tests for cell mediated immunity, haptoglobin level, and so on. Challenge studies may demonstrate vaccine efficacy via clinical differences such as decreased percent lung damaged, decreased morbidity percent, or decreased mortality percent, but the setting and exposure are not natural – i.e. using a nebulizer to dose IBR into the nose of calves previously treated with dexamethasone to mimic stress and housed in 10-head pens. In contrast, I use the term vaccine effectiveness to mean that in common production settings, vaccinated animals have clinically and economically important differences from non-vaccinated animals (i.e. ADG, morbidity percentage, case-fatality risk, etc.). You may be surprised to learn that the USDA approval process for vaccine and bacterin labels requires proof of safety as well as efficacy in challenge studies but does not require evidence of field effectiveness.\textsuperscript{4}
In 1997, Drs. Perino and Hunsaker reviewed the literature for evidence of BRD vaccine clinical effectiveness in U.S. feedlots and reported that relatively few (22) field studies without major experimental design flaws were available.\textsuperscript{5} Recently, Dr. D.L. Step and I completed a review of available studies reporting the effects of vaccination against bacterial BRD pathogens.\textsuperscript{16} Data was extracted from twenty-two trials that tested the effectiveness of vaccination against one or more of the bacterial pathogens: \textit{Mannheimia haemolytica}, \textit{Pasteurella multocida} and \textit{Histophilus somni} in feedlot cattle for mitigating the number of cattle affected and/or reducing the negative effect of bovine respiratory disease using feedlot cattle with naturally occurring disease in order to calculate the risk ratio (RR) for each trial. The summary data indicated potential small to moderate benefit for vaccination of feedlot cattle against \textit{Mannheimia haemolytica} and \textit{Pasteurella multocida} with no evidence of benefit for vaccination against \textit{Histophilus somni} for mitigating the incidence and effect of bovine respiratory disease complex. Unfortunately, the published body of evidence does not provide a consistent estimate of the direction and magnitude of effectiveness in feedlot cattle vaccination against these bacterial BRD pathogens.

The assumed role of vaccines to decrease the biologic and economic cost of BRD is largely based on logical extrapolation from challenge studies, rather than controlled field trials.\textsuperscript{5} While important for providing supportive evidence for field efficacy, laboratory experiments do not provide as high a level of evidence as do field trials. I think the reason that efficacious BRD vaccines are less clearly clinically effective is that BRD is a multifactorial disease with important pathogen, environmental, and animal factors. In a disease complex with many interrelated contributing factors, changing one factor alone is not likely to have a substantial impact on outcome.

\textbf{Multifactorial nature of BRD}

Single infectious agents are seldom if ever able to cause BRD without contributing factors from other infectious agents and/or the cattle’s environment. Therefore, to develop control plans for BRD, veterinarians must consider pathogen, environment, and animal factors. The difficulty in implementing many of the components of a sound BRD control program is that these components commonly are at odds with well-established feedlot management practices.

\textbf{Pathogen Factors} - All of the bacterial pathogens considered important in BRD can be isolated from the upper respiratory tract of healthy cattle and are readily identified in the nasopharynx of some animals in most populations.\textsuperscript{6} Viral infection usually precedes bacterial pneumonia, though it is not required for BRD. Infectious bovine rhinotracheitis (IBR), bovine viral diarrhea (BVD), parainfluenza virus (PI3), and bovine respiratory syncytial virus (BRSV) are known to cause damage to the epithelial lining of the respiratory tract which causes inflammation, damage to the pulmonary clearance mechanism, and to allow suitable sites for bacterial replication. The damage is not confined to the upper respiratory tract, but extends to the lung bronchi and alveoli.
The viral pathogens associated with BRD are ubiquitous; however, commingling cattle from multiple sources may increase exposure to antigenically novel pathogens. Emerging or suddenly more virulent pathogens are extremely rare. Almost all disease is the result of a change in the pathogen-environment-animal interaction (higher pathogen dose, poorer immune response, greater stress, etc.) or the introduction of a stable, but novel (to that population) pathogen, rather than by the introduction or emergence of a more infectious or more virulent strain of virus or bacteria.

**Environmental Factors** - A cattle population’s environment includes housing type, animal density, air quality, weather effects, mud, dust, footing, and health antagonists such as parasite burden, and social stress. These environmental factors influence the innate immunity of a herd by their impact on immunosuppression. In addition, a herd’s environment also dictates the “animal flow” or contact and mixing patterns of potentially infectious and susceptible animals.

Transmission of respiratory pathogens occurs by close nose-to-nose contact, environmental exposure, and airborne exposure. Nose-to-nose contact increases when animal density increases and the number of unique contacts increases as group size increases. Environmental exposure to BRD pathogens occurs at areas of common oral or nasal contact such as feed bunks and water troughs. Environmental survival time for most viral respiratory pathogens is only a few minutes to several hours. Survival times for bacterial pathogens may be longer depending on the environmental conditions and the organism. Airborne transmission is dependent on numerous factors including ambient temperature, relative humidity, airborne particle (dust) density, ventilation, prevailing wind, and structural or geographic obstructions. Airborne transmission of typical viral respiratory pathogens can occur over distances as far as 4 meters and possibly further.

Assembling groups of feeder calves often involves mixing cattle from several different origins over several days and then shipping them in close contact. These management practices increase the risk of BRD because of increased exposure to BRD pathogens (including novel pathogens) and induced stress which reduces disease resistance.

Group size and animal contact pattern are important environmental factors because sub-clinically infected and clinically ill cattle support growing pathogen populations and tend to secrete far larger numbers of pathogens than to which they were exposed. Therefore, larger animal populations and populations with continuous flow contact patterns can allow greater amplification of pathogen numbers than smaller populations and populations with all-in/all-out contact patterns.

**Animal Factors** - When causative pathogens are endemic in a population (as is the case with BRD) and individual susceptibility is dependent on numerous interrelated factors, the management of animal risk factors may be more important for disease prevention than biosecurity practices such as limiting animal contact with the pathogen.
The two primary animal factors that affect protection of cattle herds from infectious disease are specific and innate immunity. Specific immunity relates to an immune response directed at a specific infectious agent that the animal has been exposed to in the past, either via natural infection or vaccination. Innate immunity is strongly influenced by the overall health of the animal. Nutritional status such as adequate energy, protein, vitamins, and minerals impacts an animal's overall health and immune status. Stress due to crowding, inclement weather, unsanitary housing, or concurrent disease can cause varying levels of immune suppression. Age affects the immune response, and it is possible that a shift to a younger average age at arrival may express itself as reduced innate and/or specific immunity for feedlot cattle.

Another animal factor that is beginning to be addressed is the possibility that genetic contributors to cattle health are being inadvertently selected against as we select for increased rate of weight gain. Cattle health is not measured under current progeny testing methods, and because heritability of most health traits is low (<10%), more progeny are needed for accurate evaluations of health traits than other production traits. So although genetic contributors to health may be changing, or could be manipulated for a health advantage, large databases with both parentage and health information or gene mapping technologies will have to be utilized to test these possibilities.

Metaphylaxis
Because accurate identification of individual cattle with BRD is difficult, some producers utilize mass-medication at arrival or a few days later with injectable, long-acting antibiotics or feed-grade antibiotics for high-risk cattle in an effort to reduce the number and severity of sick animals. The practice of providing prophylactic or metaphylactic antimicrobial therapy upon arrival to a stocker or feedlot facility has been intensely studied and repeatedly shown to be a cost-effective option in many production settings. To date, several drugs are approved for the treatment and control of calves exhibiting clinical signs of BRD or calves at high-risk of developing BRD.

One or more effects of metaphylaxis may be decreasing the risk of BRD in stocker cattle. Mannheimia haemolytica is commonly found in the nasopharyngeal area of healthy cattle, and in most situations is unable to move to the lower respiratory tract (lung) and cause pneumonia unless stress and/or viral infection compromise the innate immune system. Metaphylaxis may decrease the colonization of Mannheimia and other pathogens in the upper respiratory tract so that a smaller infectious population is available to follow a viral infection. Another potential method of disease avoidance due to metaphylaxis is that cattle may already be suffering from bacterial infection of the lung, but are able to hide clinical signs of disease – so that metaphylactic treatment may not be preceding bacterial disease, but actually following pre-clinical or sub-clinical bacterial infection of the lung.

A high percentage of the published trials investigating metaphylaxis in stocker and feedlot cattle report biologically and economically significant reductions in BRD with a 20-44% reduction in morbidity risk and 0-24% reduction in risk of dying. In addition, most
published trials report an improvement in growth performance due to reduced negative
effects of BRD.

**Obstacles to improvement of the effectiveness of BRD treatments**
I did not find any clinical trials that report the case fatality risk (CFR) of BRD treatment
regimens over time. I have received anecdotal opinions that CFR is not significantly
improved using modern antimicrobial regimens compared with regimens available more
than 20 years ago. If CFR has not significantly improved, then several possibilities
should be considered.

Specific and sensitive diagnostic aids for identifying BRD cattle are lacking
Diagnostic tools to correctly identify cattle that have bacterial pneumonia and that would
benefit from antimicrobial therapy are not available. Gardner et al. (1999) reported that
37% of cattle that had clinical signs consistent with BRD and that were treated with
appropriate antimicrobial therapy during the feedlot phase of production had lung
lesions at slaughter.\(^{11}\) In comparison, 29% of cattle not identified with clinical signs of
BRD had lung lesions.\(^{11}\) This apparent lack of strong association between clinical signs
of BRD and lung lesions has been reported by others.\(^{12,13}\) The lack of lung lesions in
cattle diagnosed by clinical signs and treated for BRD could be explained by several
scenarios: upper respiratory tract disease or transient lower respiratory tract disease
does not result in lung pathology, full recovery from lower respiratory tract disease
with complete resolution of lung lesions, or incorrect clinical assessment for the
presence of BRD. In contrast, the presence of lesions at slaughter in the lungs of cattle
not diagnosed with BRD could be due to respiratory tract disease that was not
accompanied by clinical signs of BRD, chronic lung damage that occurred due to a BRD
event prior to the time period of the investigation, or incorrect clinical assessment for the
absence of BRD. Not all feedlot calves infected with known respiratory tract pathogens,
as evidenced by seroconversion during finishing, are identified as having clinical signs
of BRD.\(^{14}\) It is not known if these subclinical infections could result in visible lung
damage at slaughter.

Because current diagnostic criteria (visual appraisal and presence of fever) are not
sensitive or specific for BRD, a fairly high percentage of animals treated do not appear
to be at risk of dying from BRD. This creates difficulty when using comparisons of CFR
(# BRD deaths ÷ # BRD treated) to detect differences in antimicrobial effectiveness
because the denominator is artificially inflated.

**Animal and environmental factors involved with response to therapy may have
regressed**
If genetic or environmental factors are associated with increased BRD morbidity, they
could also be associated with poor response to antimicrobial treatment. It is logical that
factors that increase the risk of BRD also decrease the ability of the immune system to
clear infectious pathogens even with the aid of efficacious antimicrobial treatments.
Modern antimicrobials’ greatest improvements may be in the areas of decreased meat quality concerns and labor requirements rather than improved bacterial killing. While efficacy, as measured by the ability to penetrate diseased tissue and kill BRD pathogens, has undoubtedly been a goal in the development of new antimicrobials, other goals have also been important. Modern antimicrobials have been developed to decrease negative effects on meat quality as well as for longer activity and shorter withdrawal times compared to previously available products. Treatment regimens using long-acting antimicrobials reduce the number of times an animal is treated, thereby reducing labor costs and cattle handling. This longer activity may have trade-offs in efficacy when compared to more frequent dosing or longer duration regimens.

Modern antimicrobials may be more efficacious, but lack an improved clinical response. It is possible that even though in vitro and experimental challenge models support more rapid killing or killing a larger percentage of BRD pathogens, lung damage or clinical outcome is not significantly affected.

Modern antimicrobials may be more efficacious, but higher cost clouds the cost:benefit. Antimicrobial regimen cost using modern products is much higher than when using products that have been available for many years. Product characteristics may account for some of the difference as does the fact than several commonly used antimicrobials are still under patent and generic competitors are not available. Determining the actual cost:benefit when comparing two BRD treatment regimens is strongly influenced by the differences in case fatality risk and re-treatment proportion. Other variables that do not relate to treatment efficacy but are important for selection of a BRD treatment regimen are sale price and cost-of-gain. If two BRD treatment regimens differ in case fatality risk and re-treatment proportion, the dollars available to move to the more effective treatment is greater when sale price is high or cost-of-gain is low.

Management changes that should be investigated for their cost-effectiveness. Modern feedlot management practices have evolved in response to economic and biologic pressures. As these pressures change, new management practices to decrease the effects of BRD may become advantageous. Field trials to test the cost effectiveness of new practices will be needed. Some potential management practices to be investigated include: utilizing smaller pen size (i.e. single truck load lots) during the arrival/acclimation phase and isolation off the premise or semi-isolation at the edge of the feedyard during the arrival/acclimation phase. Testing whether arrival pens should be located off the premise or on the edge of the feedlot (either up-wind or down-wind) to improve arrival and overall health would be an interesting study. Other management practices that would reduce the cost of BRD and that could be implemented under the right economic pressures include reduced commingling of animals, improved animal transportation and feedlot receiving practices, improved ventilation and reduced crowding in some situations, reduced animal stress, and improved nutrition.
Technology may provide genetic, vaccine, and diagnostic tools that reduce the risk of BRD. It may be advantageous in the future for gene or progeny testing to identify bulls whose progeny have either higher or lower than average health risk. Vaccines that prevent the establishment of latent IBR infections or prevent the recrudescence of latent IBR infections could reduce the negative effects of an important viral BRD pathogen. Diagnostic tests for persistently infected BVD cattle could become faster (chute-side) and less expensive, allowing the rapid adoption of this practice to remove a known BRD pathogen reservoir.

Summary

Bovine respiratory disease complex is likely to remain the primary infectious disease affecting feedlot cattle. New technologies may provide some decrease in the cost of BRD, but at this time, we are still investigating whether the biologic and economic losses due to BRD are sufficient to force management changes. If the current reality changes, it is likely that BRD control can be enhanced by the integration of several management changes that affect a combination of pathogen, environment, and animal factors.

References


