3rd Annual TVMDL Amarillo
BOVINE RESPIRATORY DISEASE
Conference

July 7, 2018

Can we be good stewards of antimicrobials when battling bovine respiratory disease?

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INTRODUCTION

> *"Antimicrobial stewardship refers to the actions veterinarians take individually and as a profession to preserve the effectiveness and availability of antimicrobial drugs through conscientious oversight and responsible medical decision-making while safeguarding animal, public, and environmental health."*
> (AVMA, 2018)

Antimicrobial stewardship reflects the commitment of veterinarians and animal care-givers to take actions that preserve the effectiveness of antibiotic without sacrificing animal health and welfare; making evidence-based decisions about the use of antimicrobial drugs; and using antimicrobials judiciously, sparingly, and with ongoing evaluation of the outcomes of therapy. Antimicrobial stewardship must occur in reasonable context of the animal care-giver's available resources, which can present a challenge to veterinarians in practice. The American Veterinary Medical Association has defined five principles of antibiotic stewardship:

1. ***Commit to stewardship***
2. ***Advocate for a system of care to prevent common diseases***
3. ***Select and use antimicrobial drugs judiciously***
4. ***Evaluate antimicrobial drug use practices***
5. ***Educate and build expertise***

(https://www.avma.org/KB/Policies/Pages/Antimicrobial-Stewardship-Definition-and-Core-Principles.aspx. Accessed June 11, 2018)

Central to antibiotic stewardship is the veterinarian's role in helping the animal care-giver maintain a system of husbandry that avoids common bacterial illnesses, thereby reducing reliance on antibiotic therapy to maintain animal health.

Systems thinking about antibiotic stewardship

Livestock production systems are complex adaptive systems. Food production is a system (systems have numerous parts that affect each other); the system is a complex mix of physical, behavioral, biological and economic components with unpredictable outcomes (the parts interact with each other to produce variable outcomes); and the system is adaptive because it changes over time in response to those outcomes. Even within a given food animal commodity (e.g. beef cow-calf, dairy, broiler, catfish) the specific components and outcomes of a production system are variable. For example, a beef-cow calf farm in the southeast US may not look or behave like a ranch on the high plains. These differences in the way food animals are produced are due to differences in environmental resources, human resources, and capital –factors which themselves change over time. Within this complexity are biological systems of people, animals, pests, and pathogens –which are also interactive. In spite of the complexity, people make adaptive management decisions hoping to maximize utility (profit, pride, productivity) while minimizing losses due to disease. However, managing complex adaptive systems is not easy because outcomes are difficult to predict.

The need to treat bacterial infections today may be due to decisions made earlier. System dynamics can help cattle producers and veterinarians understand how actions and decisions far removed from the immediate problem could cause a problem [1]. For example, drought could cause cow-calf producers to wean calves early, house cows in feedlots, or to depopulate their herds –all of which may have effects on feedlot management and health. Small herd cow-calf producers may decide not to dehorn, castrate, vaccinate, or deworm calves on the farm because they lack facilities or fail to recognize an economic signal to do so. Decisions made months ago, possibly hundreds of miles away, can increase the risk for sickness or death in the feedlot [2]. Those decisions don't always reflect sub-par husbandry. Pneumonia (bovine respiratory disease or BRD) in calves prior to weaning is a systems problem paradoxically associated with highly managed herds [3,4].

PNEUMONIA IN CALVES PRIOR TO WEANING

Pneumonia is a leading cause of sickness and death of calves in some cow-calf herds –especially after the first few weeks of life [5]. This is perplexing because ranch calves typically live in conditions of little stress and relative isolation. Surveys of beef cattle producers [3] and veterinarians [4] from the northern plains region and southeastern US indicate that pre-weaning BRD is a problem for approximately one out of five cattle producers. Pre-weaning BRD may affect up to 10% of U.S. beef calves [6], resulting in death of 0.6% - 1.4% of all calves [7-9]. Calves affected with pre-weaning BRD may weigh 17 - 37 pounds less at weaning, compared to calves not affected [9,10].

The cost of pre-weaning BRD

A risk analysis of the cost of pre-weaning BRD is currently underway (Wang et al, unpublished), but "back of the envelope" calculations considering death loss, morbidity, and treatment costs indicate that BRD in pre-weaned calves might currently cost the US cattle industry $150-200 million annually (Smith et al, unpublished). If so, then that is approximately $5-7 for every beef cow in the country, or $25-35 per cow in affected herds.

Epidemiology of pre-weaning BRD

As with all infectious diseases, the occurrence of BRD is affected by factors of host immunity, presence of specific pathogens, and opportunity for transmission of pathogens between or within herds. It may be useful to think of the various factors that contribute to risk for respiratory disease as component causes. Each factor that contributes to the development of disease is a component cause. Disease is observed when component causes add up to complete a sufficient cause [11]. Without completing a sufficient cause there is no expression of disease. Component causes explain why we might recover *Mannheimia hemolytica* from a deep nasopharyngeal swab of a calf without respiratory disease (other component causes being absent), or why a rancher might observe greater rates of BRD with changes in the weather, whereas another rancher observes BRD following a pasture move (different component causes completing the sufficient cause). Each outbreak of respiratory disease is the result of the completion of a sufficient cause, which might have also included components of viral and bacterial pathogens, a certain state of immunity, or other component causes of respiratory disease in cattle that we fail to understand. Removing one or more component cause prevents the expression of disease. Manageable component causes are called key determinants.

Agents

Although the bacterial pathogens of pneumonia are commonly found in the upper respiratory tract of cattle, the inciting damage is often due to viral infections that may not be present in all cattle herds all of the time. Commonly recognized viral BRD pathogens are bovine herpes virus 1, bovine viral diarrhea virus, and bovine respiratory syncytial virus, but many others, including bovine coronavirus [12,13], are likely to be involved.

Pathogen transmission

In confinement systems the opportunity for pathogen transmission is high because of animal density. But, even in extensive pasture-based systems typical of cow-calf production, opportunities for pathogen transmission may be high because cattle congregate closely around water sources, feedbunks, in shade, and when bothered by flies. Some management practices such as pasture moves and gathering for sorting result in high animal density and greater opportunity for pathogen transmission.

Age associated immunity

Passively acquired maternal immunity is important for protecting calves against respiratory pathogens. However, maternal antibodies wane with time. Approximately every 16 to 20 days after ingestion, the amount of maternal antibodies left in the blood stream is halved, so that by 96 to 120 days of age, a calf retains less than 2 percent of the antibodies it absorbed from colostrum. The immune system is functional but unprimed at birth and prior to 5 to 8 months of age the immune response of calves is weak, slow, and easy to overcome [14]. Therefore, even in the absence of additional stressors, calves 3 to 5 months of age may be particularly susceptible to pneumonia.

Herd immunity
Herd immunity is the protection afforded to susceptible individuals because the majority of the individuals in the population are immune. In herds with a narrow calving window, calves are similar in age and herd immunity is lost in a short span of time as calves approach 90 to 120 days of age. Vaccines to improve immunity against respiratory pathogens have been important for reducing the incidence of BRD in feedlot calves. However, the optimum vaccination protocol to prevent BRD in calves less than 5 months of age remains an important subject of investigation. Weaning, commingling groups, and exposure to severe weather can be powerful stressors that further reduce a calf's ability to resist disease.

Other factors affecting risk for pre-weaning BRD
Health records representing over 9,900 calves from 28 cattle management groups within 7 beef cattle ranches were analyzed to test the effect of calf gender and age of the dam (Smith et al, unpublished). We concluded that the sex of calves affects their risk for BRD (males at greater risk than females). Also, of calves affected with BRD, those calves born to 2-year-old dams were more likely to become sick at an earlier age. This is consistent with the knowledge that the male sex of other species has been associated with greater risk for pneumonia [15,16]. The age of the dam may be a correlate of colostrum absorption. Colostrum ingestion may be delayed for calves born to a young dam because of dystocia or poor mothering skills. Also, the young dam's colostrum may not contain as many antibodies, in quantity and range of protection, as older dams [17-19].

Prevention of pre-weaning BRD
Management and environment-related risk factors for pre-weaning BRD have been the subject of research [3,4,6,8]. Management practices prior to weaning, such as gathering and sorting for artificial insemination, provide opportunity for pathogen introduction and transmission. Activities such as gathering, commingling, sorting, and weaning that increase stress and opportunities for pathogen transmission may have less impact on health if they are completed prior to or after calves are 3 to 5 months of age (Smith, unpublished) or if they were managed to reduce stress and commingling of different groups of calves. Anecdotal evidence indicates that vaccination programs intended to induce adequate acquired immunity in calves prior to 90 days of age have shown some efficacy, but require further study.

PNEUMONIA IN CALVES AFTER WEANING
It is not a secret that the first several days from farm of origin to the stocker operation or feedlot can result in the accumulation of stress events that are detrimental to calf health, especially pneumonia. Most morbidity occurs in the first 21 days after arrival in the stocker operation. By far, the most common illness in stocker calves is bovine respiratory disease. Other important receiving period diseases are lameness, musculoskeletal injury, diarrhea (e.g. rumen acidosis, Salmonellosis and coccidiosis), and bloat.

Systems perspective on post-weaning pneumonia
Many small farm operations lack sufficient natural, human, or capital resources to provide an optimum health program while the calf is on the home farm. For example, the farm may lack facilities, manpower, or sufficient knowledge to dehorn, castrate, or vaccinate calves prior to weaning. Weaning often occurs the same day the cattle are marketed from the home farm resulting in an important abrupt stress event. In addition, the common

systems of marketing calves contribute additional stressors to the auction market calf. Calves may not have access to adequate feed or water, or may not know how to drink from tanks or consume feed from bunks during transportation to and from the auction market. Calves are likely to be commingled with other calves, and after long distance transportation, may spend a number of days in an order-buyer facility as other calves are purchased to fill an order. During the phase of marketing, calves may lose rumen fill from not eating, may have shrink from dehydration, and be exposed to a variety of enteric and respiratory pathogens. By the time calves have moved through these marketing channels and arrive at the destination feedlot or stocker facility, they may be exhausted, dehydrated, challenged by a variety of social and physical stressors, and incubating a respiratory or enteric infection.

Unfortunately, the marketing system may not reward the small cow-calf farmer for adopting practices that improve immunity and decrease stress. In contrast, calves marketed directly from the (typically larger) cow-calf farm to the stocker or feedlot operation may experience some, but often not all of the stressors of auction market calves. Because direct marketing is often based on the farmer's reputation, these calves are more likely to have been preconditioned by receiving deworming treatment, vaccination at a prior to weaning, and castration and dehorning at a young age. Calves that are marketed directly, especially those undergoing a pre-conditioning program, may have less morbidity and mortality in the post-weaning phase and are, therefore, often considered calves at low risk for disease. Interestingly, commingled, low body condition, freshly weaned calves, transported long distances, and marketed through a sale barn are often considered high risk for disease. Paradoxically, some cattle feeders and stocker operators have a preference for light weight high risk calves because they can be purchased for less total dollars and, if they survive, often grow efficiently because of compensatory gains.

Prevention and control of pneumonia in the post-weaned calf

The goals of stocker and feedlot cattle receiving programs are to alleviate dehydration and hunger, resolve stress and exhaustion, remove endoparasites (and sometimes exoparasites), and improve immune function. For convenience, sometimes receiving programs at arrival include dehorning (or horn tipping) and castration although these procedures, at this time, are recognized as important stressors detrimental to calf health.

Typical stocker cattle receiving programs (e.g. vaccination against bovine viral respiratory pathogens, bacterins against common respiratory bacterial pathogens, and *Clostridium* spp. diseases may, in some situations, be detrimental to calf health. The problem is that vaccination immediately after arrival may be too late to change the course of a viral or bacterial respiratory infection that may already be incubating. Further, the metabolic cost of additional antigenic challenges may, at least sometimes, be detrimental to calf health (Griffin et al. 2018. unpublished). The parasite load of calves at arrival may increase the susceptibility of calves for other diseases. However, it is not clear if deworming calves at arrival has a short term (first 85 days) benefit to the health or performance of stocker calf health (Griffin et al. 2018. Unpublished). It may be that vaccination and deworming during the early stocker phase help set up the calf for success in the finishing feedlot.

When calves are likely to be incubating bovine respiratory diseases, the receiving program may include mass medication with an antibiotic delivered in the feed, water, or by injection. Mass medication on arrival for the purpose of treating incubating but unapparent infections is termed metaphylaxis. Metaphylactic use of antibiotics has been shown in many studies to reduce morbidity. In keeping with antibiotic stewardship principles, there are certainly times when mass medication strategies are cost effective and improve animal health and well-being; however, more work is needed to objectively determine those particular conditions, and to provide scientifically justifiable indications for prophylactic or metaphylactic use of antibiotics.

Conclusions

We can be good stewards of antimicrobials when battling bovine respiratory disease, but it is not always easy and may require a change in paradigm. The principles of antibiotic stewardship require that veterinarians commit to actions that preserve antibiotic effectiveness. As antibiotic stewards, veterinarians should help cattle producers in all stages of production implement systems of husbandry that reduce the risk for pneumonia. When pneumonia does occur, or is likely to occur, then antibiotics should be used judiciously and records should be used to evaluate therapeutic success. Antibiotic stewardship is an evolving concept requiring veterinarians to actively update their expertise on the subject and share that knowledge with others.

Acknowledgements
A contribution of the Beef Cattle Population Health and Reproduction Program at Mississippi State University. Funded by the Mikell and Mary Cheek Hall Davis Endowment for Beef Cattle Health and Pfizer Animal Health.

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