BRD Prevention Therapeutics-What's up with the Immune System? Vaccines and Handling the Thermostat of Inflammation

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Abstract

Bovine respiratory disease (BRD) remains a major problem in the cattle industry. This control of this disease involves immune system management and inflammation control. The critical role of the innate immune system in disease management underscores that vaccines, while helpful, are not the only solution for controlling BRD. Vaccines target the adaptive immune system and are effective against specific viral pathogens like bovine herpesvirus-1 (BHV-1), bovine respiratory syncytial virus (BRSV), and bovine viral diarrhea virus (BVDV). However, BRD is a multifactorial disease that involves multiple infectious agents and is influenced by environmental and management factors. This complexity makes complete disease control with vaccines challenging. Timing is vital in vaccination, as vaccination before stress or exposure to infection is most effective. Stress, such as

transportation and environmental changes, can compromise immune function and exacerbate disease. In the face of challenge, parenteral vaccination can sometimes provide partial protection within days, as seen with foot-and-mouth disease, BHV-1, and BVDV. Immune overreactions, such as systemic cytokine storms, can occur under stress and certain conditions, worsening outcomes. Therefore, balancing immune response and inflammation control is crucial in preventing BRD morbidity and mortality. Systemic inflammatory responses affect multiple systems, including bovine respiratory disease (BRD) and gastrointestinal tract (GIT) symptoms. Non-steroidal anti-inflammatory drugs (NSAIDs) are used in cattle to reduce fever and inflammation and have been used as metaphylaxis. Approaches to managing GIT health and, therefore, systemic inflammation and BRD have evolved, using traditional methods like probiotics and innovative techniques such as prebiotics, fecal transplants, and bacteriophage therapy. A multipronged approach is increasingly used in human and veterinary medicine to reduce reliance on antibiotics and steroids. Strategies also include region-specific microbial mixtures and IgY antibodies to enhance animal health against BRD. The future control of BRD must involve adaptive and innate immune strategies.

Introduction

The recent COVID-19 pandemic has impressed the world with the importance of immune dysfunction as the major cause of morbidity and mortality in respiratory disease. Traditionally, managing bovine respiratory disease immunity has been aimed at the use of vaccines. Although vaccines remain an important adjunct for BRD prevention, management of inflammation has become an important target for minimizing morbidity and mortality. This brief proceedings paper reviews the applications and important factors in vaccine usage and the opportunities to control the inflammatory "thermostat."

Vaccines and Unrealistic Expectations- Human and Animal Successes and BRD

The success of human vaccines generated the impression that vaccines are the only tool needed. Vaccines target the adaptive immune system with high specificity and duration of immunity, and the outcome is to lessen clinical disease. Their only "protective immune effect" on the innate system is the induction of the various classes of interferon, the potent antiviral cytokine. The successful eradication of smallpox, followed by the elimination of polio in most industrialized countries (although certainly not the eradication of polio), gave the impression that vaccines were the ultimate weapon (Shattock et al. 2024). This was then followed by the success of the rapid reduction in childhood diseases such as mumps, measles, rubella, pertussis, and diphtheria (Shattock et al. 2024). There have been similar successes in veterinary medicine with parvovirus and distemper in dogs, pseudorabies, and porcine circovirus 2 in swine, and rinderpest in cattle, to name a few (Aida et al., 2021). These diseases have a single causative agent, and all fulfill Koch's postulate. However, even the best vaccines will not result in 100% control as individual animal responses along with vaccine compliance frequently result in

response rates of 70 to 80%, which are adequate to provide herd immunity for many bovine viral pathogens (Woolums and Chase, 2024)

These “vaccine-controlled diseases” are in sharp contrast to bovine respiratory disease (BRD). BRD is a multifactorial disease frequently involving multiple infectious agents confounded by management and environmental factors that induce stress. Control of BRD involves a three-pronged approach involving biosecurity, management, and the use of vaccines (Woolums and Chase, 2024).

BRD Vaccines and Their Application

In the U.S., USDA-licensed vaccines are available for many agents contributing to endemic BRD (USDA 2024). Fully licensed vaccines decrease disease in experimental challenge studies. However, systematic reviews and meta-analyses indicate that, in the field, the benefit of vaccination to control all BRD is inconsistent (Theurer 2015; O’Connor 2019). Nevertheless, specific agents are impacted by widespread vaccination. For example, following decades of vaccination against bovine herpesvirus-1 (BHV-1) and bovine parainfluenza type 3 virus (BPI3V), these viruses are rarely identified in BRD cases, compared to historical trends (South Dakota State University Animal Disease Research and Diagnostic Laboratory, data on file).

Numerous variables related to animals and their management and the availability of multiple vaccine formulations no doubt complicate the assessment of respiratory vaccine efficacy. A complete evaluation of the evidence for the use of vaccines to prevent respiratory disease is beyond the scope of this review. The American Association of Bovine Practitioners guidelines recommend vaccinating all cattle against BHV-1, BVDV, BRSV, and PI3V(AABP 2021).

Vaccination is most effective when administered well before infection. Vaccination during physiological stress and immune dysfunction periods can reduce efficacy and may worsen outcomes. Many cattle are vaccinated late in the production chain, which may be less effective. Vaccination of co-mingled and transported cattle at or near arrival has little effect on BRD morbidity, resulting in recommendations to delay vaccination for 1-2 weeks (Richeson 2020). While vaccinations aren't typically expected to confer immunity immediately, the studies outlined below suggest that early benefits might be observed a few days post-vaccination, likely due to the activation of innate immunity. Although not well tested by field trials, in some cases, vaccines might be helpful as a biosecurity tool to "boost" previously vaccinated "protected" animals before the addition of "high-risk " animals. Clinical trials testing on-arrival vaccination of high-risk cattle, compared to unvaccinated control groups, have not demonstrated significant benefits.[57] As for low-risk cattle that haven't been recently co-mingled, transported, or stressed, early vaccination before exposure to "high-risk" newly introduced animals might reduce their disease incidence if quarantine is impossible. Yet, the absence of rigorously controlled research studies leaves us without high-quality evidence to confirm this hypothesis. Thus, while vaccines remain a crucial biosafety tool to mitigate risk, their effectiveness can vary significantly based on specific conditions and timing of administration.

Parenteral vaccines and early onset of protection

While vaccine efficacy is typically tested in animals 21-42 days post-vaccination, a few studies have demonstrated the benefits of vaccinating cattle a few days before exposure. This "early vaccination" was beneficial in cattle fully protected from foot-and-mouth disease virus (FMDV)

challenge seven days after vaccination (Duffy 2020) Similarly, well-acclimated 6- to 9-month-old steers and bulls were completely protected from disease following highly virulent BVDV challenge five days following vaccination;(Brock 2007) and cattle were completely protected from disease due to BHV-1 challenge three days post-vaccination(Fairbanks 2003). In these studies, partial protection occurred three days post-BVDV vaccination (Brock 2007) and two days post-BHV-1 vaccination (Fairbanks 2003).

Stress, Immunity, and Too Much of a Good Thing

There is ample evidence that both physical and psychological distress (stress) can cause immune dysfunction in animals, leading to an increased incidence of infectious disease (Salak-Johnson & McGlone, 2007). In cattle, several factors will compromise immune function. There is the stress of transportation, dehydration, feed change (with the resulting negative energy balance), excess heat or cold, crowding, mixing, weaning, limit-feeding, parturition noise, and restraint are stressors that are often associated with intensive animal production and have been shown to influence immune function. Also, social status, genetics, age, and the duration of stress (chronic vs. acute) are essential in the animal's response to stress (Hulburt et al., 2016; Salak-Johnson & McGlone, 2007). The immune system and the central nervous system (CNS) are a bi-directionally linked "two-way street," each influencing the other (Borghetti et al. 2009). In particular, there is a critical balance that exists between hormones [growth hormone (GH), GCs, prolactin (PRL), catecholamines, and insulin] and the proinflammatory mediators (IL-1, IL-6, and TNF-α) of the immune system.

Immunity, Negative Energy Balance, Microflora, and Cytokine Storm.

The immune system is a major energy consumer, and in times of negative energy, like seen in the newly weaned calf and the fresh dairy cow, it can be difficult for the immune system to respond (Sordillo 2016). In addition, the mobilization of energy from adipose tissue (fat) results in the infiltration of macrophages, as the activity of adipocytes (fat cells) results in inflammation. These macrophages are sensitive to gut bacteria signals, including gram-negative bacteria endotoxin (Winer & Winer, 2012). With changes in diet that occur at weaning or parturition for the dairy cow the microflora changes are considerable changing populations. This combination of adipose remodeling, macrophage activation, and microflora can result in a cytokine storm (Cluny et al., 2012; Tisoncik et al., 2012). A cytokine storm (hypercytokinemia) is the systemic expression of a healthy and vigorous immune system, resulting in the release of more than 150 known inflammatory mediators (cytokines, oxygen free radicals, and coagulation factors) (Tisoncik et al. 2012). It is an overreaction of the immune system. Both pro-inflammatory cytokines [such as tumor necrosis factor-alpha (TNF-alpha), interleukin-1, and Interleukin-6] and anti-inflammatory cytokines (such as interleukin 10 and interleukin 1 receptor antagonist) are elevated in the serum of people or animals experiencing a cytokine storm. This results in systemic spillover affecting other systems. An animal with a systemic inflammatory response (cytokine storm) will not only have gastrointestinal tract (GIT) symptoms but will have increased bovine respiratory disease. Cytokine storms were responsible for many of the human deaths from COVID-19 and also during the 1918 influenza pandemic, which killed a disproportionate number of young adults (Fajgenbaum DC & June CH, 2020). In the case of influenza, a healthy immune system may have been a liability rather than an asset. Preliminary research results also indicated this as the probable reason for many deaths during the SARS

epidemic in 2003 (Tisoncik et al. 2012). Human deaths from the bird flu H5N1 usually involve cytokine storms as well.

Turning Down the Thermostat- Nonsteroidial Drugs

The use of non-steroidal anti-inflammatory drugs (NSAIDs) (Edwards 2021) in the treatment of BRD is a common practice (APHIS 2001). NSAIDs include aspirin, flunixin, meglumine, and meloxicam, along with new-generation NSAIDs (Edwards 2021). One of the benefits of using NSAIDs is their ability to help reduce fever due to BRD, which is critical for the recovery of the affected cattle (APHIS 2001). Meloxicam has also been used as metaphylaxis to reduce shipping stress and neutrophil activation, major factors leading to cytokine storms (Van Engen 2014). The reduction in fever can improve the clinical picture and appetite of the animals, which is essential for their health and productivity. One of the key issues with NSAIDs is that their administration needs to occur prior to major inflammatory events to maximize their effectiveness.

Turning Down the Thermostat- Gut-Lung Axis

Although we have been using prebiotics, probiotics, essential oils, and/or organic acids in animal production for years, the approaches have often been empirical and based on one or two components with little understanding of the mechanism of action. In looking at human medicine and the prevention and treatment of inflammatory bowel disease, a more holistic multipronged approach has been developed (Santor 2017). Like veterinary medicine, the initial approaches for prevention and/or treatment of GIT disease were pharmaceutical-based, with antibiotics being a major tool. A multi-pronged approach has been used in humans to reduce the use of exogenous corticosteroids and/or antibiotics. There are several GIT health goals from

these multipronged approaches. These approaches may be accomplished using traditional approaches (probiotics, organic oils, high fiber diets, or combinations) and cutting-edge methods (fecal microbial transplants, synthetic mixtures of defined microbes, personalized for an individual's specific microbiota profile, and personalized diets). Then, there are novel experimental approaches (bacteriophages targeting key aggressive bacteria, using synthetic microbial metabolites or recombinant bacterial species) that also have promise.

In livestock, we have several other unique approaches to improving GIT health besides the traditional approaches (probiotics, organic oils, high-fiber diets, or combinations). These approaches include prebiotics {refined functional carbohydrates (RFC); inhibiting bacterial attachment, promoting a more anaerobic environment; blocking bacterial receptors; stimulating protective mammalian pathways}; mixtures of defined microbes based on culture and sensitivity testing that are herd and/or region specific and hen egg IgY antibodies against specific organisms. With ruminant housing and pasture management exposure to feces (and rumen content transplants), there is an on-farm "microbial transplant" opportunity.

Summary

BRD prevention and control methods continue to be an elusive target. The implications of COVID-19 on comorbidity factors and new investigations into the immune status of at-risk animals will allow us to develop better strategies to target both the adaptive and the innate immune response to prevent and treat BRD.

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