

Vaccinating high-risk calves against BRD

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Abstract

Prevention of infectious disease by vaccination is a cornerstone of animal health management. Almost all commercial feedlots in the US (>90%) vaccinate newly received beef calves against viral respiratory pathogens, whereas a few majority use bacterin and/or toxoid agents. Many of these calves arrive as high-risk for developing clinical signs of bovine respiratory disease (BRD) because predisposing factors can cause stress-induced immune dysfunction, and previous virus transmission is plausible during the marketing process. Published studies that utilize a non-vaccinated control treatment under commercial conditions are limited, thus it is difficult to elucidate the efficiency of respiratory vaccines used in high-risk calves. Health and performance outcomes of vaccinates in such studies range from beneficial to detrimental, yet the variable research results are confusing. Inconsistent research outcomes may be explained by: 1) different vaccine products or regimens used, 2) differences in stress, population dynamics, or natural virus challenge conditions between studies or treatment pens within a study, 3) poor sensitivity and specificity of current BRD diagnostic methods used to determine morbidity outcome, and 4) issues with sample size when comparing pen means of binary data (i.e., morbidity and mortality) and risk of type II statistical error. Similarly, controlled studies evaluating the efficacy of respiratory vaccines used in beef calves subjected to chronic physiological stress are rare. The humoral immune response to vaccine antigens administered in stressed cattle may depend on the duration and severity of stress imposed, and whether live-attenuated or non-replicating vaccine agents are administered. Current dogma indicates the immune response to a respiratory vaccine is diminished for stressed calves, but this philosophy will require refinement with further research and understanding.

Key words: bovine respiratory disease, BRD, stress, vaccine

Résumé

La prévention de maladies infectieuses par la vaccination est une pierre angulaire de la gestion de la santé animale. Presque tous des parcs d'engraissement commerciaux aux États-Unis (>90 %) vacciner les veaux récemment reçus contre des pathogènes respiratoires virales, tandis qu'un moins grand usage majoritaire bactériennes et/ou agents d'anatoxine. Beaucoup de ces veaux arrivent comme présentant un risque élevé de développer des signes cliniques d'une maladie respiratoire chez les bovins (BRD) parce que les facteurs prédis-

posants peut provoquer un dysfonctionnement immunitaire induite par le stress, et transmission de virus précédents est plausible pendant le processus de commercialisation. Les études publiées qui utilisent un traitement de contrôle non vaccinés sous des conditions commerciales sont limitées, il est donc difficile d'élucider l'efficacité de vaccins contre les maladies respiratoires utilisés dans les veaux à haut risque. La santé et les résultats de rendement de vaccine dans ces études vont de bénéfiques pour nuire, encore la variable des résultats de recherche sont déroutantes. Les résultats de la recherche incohérents peut s'expliquer par : 1) Des vaccins différents produits ou schémas posologiques utilisées, 2) des différences dans le stress, la dynamique de la population, défi virus naturel ou des conditions entre les études ou de traitement au sein d'une étude, des stylos 3) manque de sensibilité et de spécificité des méthodes de diagnostic BRD actuel utilisé pour déterminer la morbidité résultat, et 4) Problèmes avec la taille de l'échantillon lors de la comparaison de données binaires moyens de plume (c'est-à-dire, la morbidité et la mortalité) et risque de type II L'erreur statistique. De même, des études contrôlées évaluant l'efficacité des vaccins contre les maladies respiratoires utilisés en veaux de boucherie soumis à un stress physiologique chroniques sont rares. La réponse immune humorale en réponse aux antigènes du vaccin administré en a souligné le bétail peut dépendre de la durée et de la sévérité de la contrainte imposée, et si vivants et atténués ou vaccin sans répliation agents sont administrés. Dogme actuel indique la réponse immunitaire à un vaccin respiratoire est diminuée pour souligner les veaux, mais cette philosophie devra être affinée avec davantage de recherche et de compréhension.

Introduction

Bovine respiratory disease (BRD) is a complex illness that is often initiated via stress-induced immune dysfunction, advances with viral infection, and culminates with bronchopneumonia caused by bacterial species that are found in the nasopharynx of healthy cattle. Also, BRD is the most expensive disease associated with cattle production in the US, and the prevalence and impact of BRD are greatest in the stocker and feedlot sectors of the beef production system.⁹ In a recent survey,²⁰ consulting feedlot veterinarians unanimously recommended administration of a multivalent respiratory vaccine during initial processing of high-risk cattle. However, research-based evidence to support the validity of this practice in high-risk newly received beef calves is limited. A vaccine is considered efficacious provided it is shown to be biologically active and safely stimulates an active immune

response against the agents contained in the vaccine. For a vaccine to demonstrate efficiency, it should result in a significant reduction in clinical illness, improvement in weight gain, and a clear economic advantage (cost:benefit) in the commercial production setting. Previous literature reviews on respiratory vaccination outcomes in the production setting were published in 1983,¹² 1997,¹⁵ and 2013,²¹ and these illustrate a general lack of evidence for vaccine efficiency in high-risk, newly received beef cattle.

Physiological stress is inherent in the high-risk calf, resulting from multiple stressors that typically occur during relocation from the ranch origin to the feedlot. These stressors may include handling, weaning, transportation, dehydration, commingling, and environmental changes that may result in the increased synthesis and release of glucocorticoids (cortisol in cattle) upon activation of the hypothalamic-pituitary-adrenal axis. With regard to BRD, stress is likely to play a pivotal role in host susceptibility and pathogenesis of the disease because stress has been shown to cause immunosuppression and enhanced viral-bacterial synergy.¹⁰ Regarding respiratory vaccine response, the stress condition (i.e., acute or chronic) of an animal or group of animals may differentially impact the humoral immune response to vaccine agents essential for virus neutralization. Furthermore, the antibody titer response in high-risk, immunosuppressed cattle may also differ for modified-live virus (MLV) or killed virus agents. The aim of this review is to discuss vaccine efficiency in high-risk beef cattle and provide a brief framework for the bovine practitioner to better understand potential consequences of vaccination concurrent with chronic physiological stress.

Categorization of Physiological Stress

Stress hormones such as glucocorticoids and catecholamines are well known to interact with virtually every component of immunity. However, it is important to determine the differential impact that acute or chronic stress may have on vaccine response in order to determine the efficacy and efficiency of administration of respiratory vaccinations at specific times during the beef production cycle. Acute stress is short-term (<24 hours) and may actually prime the immune system resulting in enhanced vaccine response;¹¹ however, this is extremely difficult to control and evaluate in research studies. Chronic stress conditions exist when the duration of stressor(s) is extended for days to weeks and is known to interfere with the humoral response to vaccination in adults.⁵ Typically, acute stress conditions occur for well-handled cattle during routine vaccination procedures on the ranch origin; whereas, chronic stress is common in high-risk calves during initial processing at a stocker or feedlot facility. Although additional research is needed in the bovine model, it is plausible to suggest that vaccine response is enhanced for cattle undergoing acute stress due to the immunoprime effects of short-term stress, while chronically stressed cattle

will exhibit a blunted vaccine response due to the immunosuppressive effects of chronic stress.

Impact of Stress on Vaccine Efficacy

Because stress is generally known to inhibit inflammation, it has been widely accepted that stress reduces the immune response to vaccination in cattle. Yet, the literature clarifies distinct immunological consequences attributed to acute vs chronic stress. Briefly, chronic stress was shown to delay skin healing,⁶ reduce NK cell responsiveness to cytokines,⁸ and diminish secretory IgA concentrations.² Acute stress is often shown to have an opposing, enhanced effect on the immune system as illustrated by increases in the number of cytotoxic T- and NK cells,¹⁴ and enhanced secretory IgA production.²

Much of the research knowledge surrounding stress-induced immune alteration must be extrapolated from the human or murine model. However, an excellent review by J. A. Roth¹⁸ provides bovine-specific information on glucocorticoid-induced immunosuppression, and further suggests differences in the humoral immune response dependent upon the type of vaccine administered (i.e., live-attenuated vs killed). It was proposed that although glucocorticoids may cause decreased antibody titer concentration via suppressed antibody production or enhanced catabolism, the effect depends upon the timing and duration of elevated glucocorticoid concentration and the nature of the antigen in question. After exogenous cortisol administration and simultaneous vaccination with a non-replicating antigen (*Salmonella dublin*), the antibody response was inhibited. Conversely, when replicating MLV vaccine antigens (bovine herpesvirus-1 (BHV-1) and bovine viral diarrhea virus (BVDV)) were administered concurrent with increased glucocorticoid concentration, the antibody response to these viruses was enhanced. This is likely due to increased cortisol causing an immunosuppressive state, which allowed enhanced replication of MLV vaccine antigens, increased antigenic stimulus, and a subsequently enhanced antibody titer response. This occurrence was recently reproduced in our laboratory.¹³ Cattle treated with an acute, chronic or control stress model induced by dexamethasone injection and vaccinated with a multivalent, combination respiratory vaccine-bacterin^a had different antibody titer responses depending upon the antigen-specific antibody evaluated. The leukotoxin-specific antibody response from a non-replicating toxoid (e.g., Pre-ponse SQ; Boehringer Ingelheim Vetmedica, Inc.) was least in the chronically stressed steers, intermediate for acute stress, and greatest for control. Conversely, both the BHV-1- and BVDV-specific antibody response from the MLV component of the vaccine (e.g., Pyramid 5; Boehringer Ingelheim Vetmedica, Inc.) was greatest for chronically stressed steers, intermediate for acute, and least for control. Because antibody titer concentration is often used as a proxy for vaccine response and is a major component of vaccine efficacy, researchers

and practitioners should consider the apparent differential response to vaccine antigen type in stressed cattle. This also poses the question: is enhanced viral replication from an MLV vaccine administered to stressed calves consequential? Furthermore, because of the latent properties known to exist for BHV-1, whether transmitted naturally or via MLV vaccine, the potential exists for recrudescence during subsequent periods of increased stress. Further research is needed to determine the safety and efficacy of different vaccine antigens administered to high-risk (chronically stressed) cattle.

Respiratory Vaccine Efficiency in High-risk Calves

Previous field studies have evaluated the timing of vaccination,^{16,17} effects of revaccination^{19,22}, or compared different vaccine products;^{3,4} however, a negative control treatment is rarely used. A recent study¹⁷ was conducted in which high-risk calves were vaccinated with a MLV respiratory vaccine^b on either day 0, day 14 or assigned to a non-vaccinated control group during a 42-day receiving period. Although overall BRD morbidity was not different, the relapse rate was increased for the non-vaccinated cattle and suggests at least some degree of respiratory vaccine efficiency occurred in this trial. Average daily gain was reduced transiently for either vaccinated group, which may be explained by vaccine-induced stimulation of the acute phase response, which is both catabolic and metabolically demanding.¹ On the contrary, vaccine administration (intranasal vs intramuscular vs unvaccinated control) was evaluated in newly received beef calves and no differences in BRD health outcomes were observed.⁷ In another study¹⁶ evaluating the timing of MLV vaccine^c (day 0 or 14 from arrival) in high-risk calves, cattle administered the delayed procedure had slight improvement in performance, but a true negative control treatment was not evaluated.

It is important to note that most of these studies were conducted in a small-pen scenario, which can be problematic when binary variables such as morbidity and mortality are primary study outcomes. When pen is the experimental unit, and a small sample size (i.e., <20 animals/pen) is present, proportional data means are particularly challenging to analyze statistically and risk of type II statistical error is increased compared to the large-pen scenario with greater sample size (i.e., >50 animals/pen). When interpreting morbidity or mortality data from small pen studies, the practitioner should consider biological relevance that may exist in the absence of statistical significance.

Additional considerations regarding vaccine efficiency include differences in disease risk and epidemiologic factors that surely exist from one study population to another. It is likely that within a given population of high-risk cattle, some may clearly benefit from MLV respiratory vaccine upon arrival while others may not, yet treatment means are determined and reported on a treatment population basis. Further, the evaluation of BRD morbidity data from research trials con-

ducted under commercial conditions can be problematic because current BRD diagnostic methods in the field are poorly sensitive and specific, resulting in confounding from false-negative and false-positive diagnoses, respectively. Therefore, practitioners and researchers should also consider objective outcome variables such as gain performance when interpreting vaccine efficiency.

Conclusions

Respiratory vaccine efficiency in high-risk, newly received beef calves is difficult to determine, especially given the lack of research publications with a negative control treatment. Although the current literature does not clearly validate respiratory vaccination to effectively reduce clinical BRD morbidity and mortality in high-risk calves, almost all feedlot veterinary consultants recommend the practice because of the relatively inexpensive cost of vaccine and the unknown disease risk associated with exclusion. Equally challenging is the elucidation of stress-induced immune dysfunction and its impact on vaccine safety and efficacy. Interactions of stress, respiratory vaccination, and the nature of the vaccine antigen in question are important considerations that would benefit from further research.

Endnotes

^aPyramid[®] 5 + Presponse[®] SQ, Boehringer Ingelheim Vetmedica, Inc., St. Joseph, MO

^bBovi-Shield Gold[®] 5, Zoetis, Kalamazoo, MI

^cExpress[®] 5, Boehringer Ingelheim Vetmedica, Inc., St. Joseph, MO

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