Evaluation of response to vaccination with a bacterial-produced plasmid DNA, Zelnate, on feedlot performance of weaned calves

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Our objective was to evaluate the response of a vaccination protocol with Zelnate for bovine respiratory disease complex on growth performance and feeding behavior in recently weaned calves. The use of Zelnate by itself and in combination with a modified live vaccine did not negatively affect growth performance or feeding behavior.

Summary

Bovine respiratory disease complex (BRD) persists as the single most costly disease syndrome associated with commercial beef production in the U.S. To help combat this costly inefficiency, cattle producers have implemented vaccination protocols for their beef herds. Exposing an animal to an antigen can affect their performance in the feedlot negatively (Stokka et al., 1994). To investigate the effects of vaccination on feedlot performance, newly weaned calves (n = 65) were adapted to the Insentec roughage feeders at NDSU's Beef Cattle Research Center. Treatment one was a 2-milliliter (ml) sterile saline negative control subcutaneously injected in the neck. Treatment two was a 2-ml MLV (IBR, PI3, BRSV, BVDV type 1 and 2) vaccine in combination with a *Mannheimia haemolytica toxoid* injected subcutaneously in the neck. Treatment three was 2 ml of Zelnate injected intramuscularly into the neck, and treatment four was a 2-ml MLV (IBR, PI3, BRSV, BVDV type 1 and 2) vaccine in combination with *Mannheimia haemolytica toxoid* and 2 ml of Zelnate. Calves were vaccinated on day 0 of the trial, and weights and blood samples were collected on days 0, 1, 3, 6 and 28 of the trial. Feeding intake and behavior were unaffected by the use of vaccines. All feedlot performance variables were not different among treatment groups. The use of an immune stimulant, Zelnate, by itself or in combination with a modified live virus to newly weaned calves may bolster the calves' ability to fight off infectious agents without negatively affecting feeding behavior or feedlot performance.

Introduction

In livestock, the major causes of death preceding slaughter are due to infectious diseases (Babiuk, 2002). Bovine respiratory disease complex (BRD) persists as the single most costly disease syndrome associated with the commercial beef production in the U.S., accounting for losses in 2010 of 1,055,000 animals valued at $643 million (NASS, 2011). Increased morbidity and mortality, decreased weight gains, decreased feed utilization and decreased carcass quality account for the economic losses associated with BRD (Edwards, 2010).

BRD originally was termed "shipping fever" because signs often occur shortly after arrival at the feedlot (Urban-Chmiel and Grooms, 2012). The morbidity risk of BRD cases in feedlot cattle occurs in the first 45 days after arrival at the feedlot, and the highest risk occurs in weeks 1 to 3. After that, morbidity declines (Buhman et al., 2000; Edwards, 1996).

Vaccination for viruses and bacteria associated with BRD are widespread (Taylor et al., 2010). The viral component of BRD consists of bovine herpesvirus type 1, also known as infectious bovine rhinotracheitis (IBR); bovine viral diarrhea (BVD); parainfluenza virus type 3 (PI-3); and bovine respiratory syncytial virus (BRSV) (Urban-Chmiel and Grooms, 2012). The bacterial component of BRD consists of *Mannheimia haemolyticam, Pasteurella multocida* and *Histophilus somni* (Urban-Chmiel and Grooms, 2012).

Killed and modified live vaccines (MLV) are available in different combinations of viral pathogens (Urban-Chmiel and Grooms, 2012). The appropriate use of these vaccines can reduce the risk of BRD (Urban-Chmiel and Grooms, 2012). The immune responses, which include antigen-specific antibodies, have been shown to confirm vaccine-induced protection against numerous diseases (Casadevall, 2004).

To elicit a vaccine response, the vaccine must provide enough signals from the antigen, or with an adjuvant, to trigger the inflammatory

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reaction that is mediated by cells of the innate immune system (Hoebe et al., 2004). Injection of a vaccine antigen initiates an acute phase inflammatory response, which develops within minutes (Tizard, 2013). In addition, sentinel cells synthesize and secrete a mixture of molecules that trigger inflammation and initiates the first steps of the adaptive immune system (Tizard, 2013).

Immunity is achieved by the maintenance of antigen-specific immune effectors and/or by the induction of immune memory cells that can reactivate if re-exposed to the antigen. These antigen-specific antibodies have been shown to confirm vaccine-induced protection against numerous diseases.

The time required to induce antigen-specific antibodies is approximately 14 days. This delayed response may not confer immunity in time to protect high-risk cattle entering the feedlot. Classically, this delayed response has been covered by the use of prophylactic antibiotic regimes across the first 14 to 28 days to at-risk cattle in the feedlot.

Zelnate is a bacterial-produced DNA liposome that has been shown to increase innate immune cell activity and decrease morbidity and mortality risks in calves exposed to challenge models (Bayer Healthcare Animal Health). This ability to enhance the innate immune system and defend against *Mannheimia haemolytica* within 24 hours may improve feedlot calf health. In addition, enhancing preventive vaccine protocols can result in a more judicious use of antimicrobial treatment regimens.

The objective of this study is to evaluate the response of a vaccination protocol with Zelnate for bovine respiratory disease complex on feedlot performance in newly weaned backgrounding steers.

Experimental Procedures

Animal care and use was approved by the Institutional Animal Care and Use Committee at NDSU, Fargo. This study utilized 65 weaned commercial Angus and Simmental beef calves born Jan. 1, 2015, to March 31, 2015, at NDSU beef barns.

At birth, the calves were vaccinated with Inforce 3 (Zoetis; 100 Campus Drive, Florham Park, NJ 07932) administered via the intranasal route and Ultrabac C & D (Zoetis) administered via the subcutaneous route. On April 1, 2015, calves were vaccinated with Bovishield Gold 5 and Ultrabac 7 subcutaneously and received Dectomax administered via the subcutaneous route. On Sept. 1, 2015, calves received Bovishield Gold VL5 and One Shot Ultra 7 subcutaneously and Dectomax as a pour-on.

Calves were weaned 30 days before being transported to the NDSU Beef Cattle Research Complex. Upon arrival on Oct. 15, 2015, calves (n = 65, body weight [BW] = 797 ± 20.2) were trained for 21 days to the Insentec Roughage Feeders (Insentec; Insentec B. V. Repelweg 10, 8316 PV Marknesse, The Netherlands).

Insentec Roughage Feeders measure feed intake and time of each visit, dry-matter intake (DMI), time spent at the feeder measured in minutes and the number of visits, and the number of meals can be calculated. Body weight was determined on days minus 21, 0, 1, 3, 6, 28 and 29, and average daily gain (ADG), feed conversion ratio (FCR) and gain-to-feed ratio (G:F) were calculated.

Time spent at the feeder, the number of visits and meals were calculated on a 24-hour cycle. A meal is defined as a distinct, separate eating period and visit not separated by intervals longer than seven minutes.

On day 0, calves were blocked by weight, randomly assigned and administered one of four possible treatments. Treatment one was a 2-ml sterile saline negative control subcutaneously injected in the neck. Treatment two was a 2-ml MLV (IBR, PI3, BRSV, BVDV type 1 and 2) vaccine in combination with a *Mannheimia haemolytica toxoid* injected subcutaneously in the neck. Treatment three was 2 ml of Zelnate injected intramuscularly into the neck. Treatment four was a 2-ml MLV (IBR, PI3, BRSV, BVDV type 1 and 2) vaccine in combination with *Mannheimia haemolytica toxoid* and 2 ml of Zelnate.

All data were analyzed using the mixed procedure of SAS (SAS Ins. Inc., Cary, N.C.). Significance was determined with an alpha of $P \leq 0.05$.

Results and Discussion

During an immune response to a pathogen, upregulated signal molecules can have adverse effects on temperature regulation, appetite, energy metabolism and endocrine functions (Klasing, 1988). This could be induced by vaccines with enough antigenic load or adjuvant to elicit a significant immune response. However, in this study, feeding behavior and growth performance were not negatively affected by the injection of a modified live vaccine and adjuvant or a bacterial-produced DNA liposome (See tables 1 and 2).

Treatments one and three tended to have an increased DMI per minute vs. the other two treatments ($P = 0.06$). Treatment one was the negative sterile saline control and treatment three was the bacterial-produced DNA liposome. This tendency was only for an increase of a hundredth of a pound of feed (DM basis) per minute and was not associated with improved growth performance when compared across treatment groups.

The calves used in this study were exposed to vaccine antigens three times prior to the study, were from the same herd and were allowed to acclimate to their new environment for 21 days before the start of this study. Our results suggest that feeding behavior and growth performance were not negatively affected by the injection of a modified live vaccine and adjuvant or a bacterial-produced DNA liposome.

Results using high-stress animals that are weaned, vaccinated and comingled with calves from different herds may have much different results. Further research is needed to evaluate unvaccinated, immune-naïve calves that are weaned and brought together in a backgrounding feedlot environment.

Table 1. Influence of vaccination on feeding behavior in backgrounding steers.

	Treatment[a]					
Item	1	2	3	4	SEM[b]	*P* Value
DMI	18.1	18.3	19	18.7	0.59	0.67
Eating events, no./day						
Visits	23.9	28.9	29.7	26.1	2.5	0.35
Meals/d	10.1	10.5	10.9	9.9	0.83	0.54
Eating time, minutes						
Per visit	6.82	7.17	5.74	7.24	0.55	0.21
Per meal	16.3	17.5	15.2	18.2	1.2	0.25
Per day	157	171	161	173	5.8	0.15
Feed DMI, lbs.						
Per visit	0.79	0.76	0.68	0.8	0.06	0.47
Per meal	1.89	1.86	1.79	2	0.13	0.77
Per minute	0.12	0.11	0.12	0.11	0.003	0.06

[a]1: Sterile saline, 2: Bovishield Gold/Oneshot, 3: Zelnate, 4: Bovishelied Gold/Oneshot + Zelnate
[b]Standard error of the mean (n = 65).

Table 2. Influence of vaccination on growth performance in backgrounding steers.

	Treatment[a]					
Item	1	2	3	4	SEM[b]	*P* Value
Initial BW, lbs.	802	782	793	799	19.9	0.89
Final BW, lbs.	857	846	854	864	21.9	0.95
Gain, lbs.	54.5	64.1	60.3	64.8	6.22	0.62
Weight change						
3 day	1.24	12.09	5.00	5.11	4.43	0.38
6 day	3.61	13.03	4.06	5.71	3.86	0.29
ADG[c]	1.95	2.29	2.15	2.32	0.22	0.62
G:F	0.10	0.12	0.11	0.10	0.01	0.47

[a]1: Sterile saline, 2: Bovishield Gold/Oneshot, 3: Zelnate, 4: Bovishelied Gold/Oneshot + Zelnate
[b]Standard error of the mean (n = 65).
[c]Calculated by dividing the total gain calculated from the average initial and final weights by 28 days

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