Evaluation of the serologic effect of concurrent IBR, BRSV, PI3 and Mannheimia vaccination and time interval between the first and second dose on the subsequent serological response to the Mannheimia toxoid and BRSV fractions on spring-born beef calves in North Dakota

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The objective of this study was to evaluate the response to vaccine doses given 153 days following the first dose in spring-born suckling beef calves. The results indicate that a second dose of BRSV and Mannheimia hemolytica vaccine given 153 days following the initial dose will result in a serological response that reflects a memory response to the second dose of vaccine.

Summary

A 174-day study was conducted at Central Grasslands Research Extension Center (CGREC), Streeter, N.D., to assess, under field conditions, the impact on immunological response of calves administered an intranasal three-way (IBRV, BRSV, PI3) MLV vaccine (Inforce 3, Zoetis, 100 Campus Drive, Florham Park, N.J.), an MLV BVDV (type 1 and 2) vaccine (Bovi-Shield Gold BVD, Zoetis, 100 Campus Drive, Florham Park, N.J.) and a *Mannheimia haemolytica* bacterial-extract toxoid (One Shot, Zoetis, 100 Campus Drive, Florham Park, N.J.) (T01), compared with a new five-way (IBRV, BVDV [type 1 and 2], BRSV, PI3) MLV vaccine in combination with a *Mannheimia haemolytica* bacterial-extract toxoid (Bovi-Shield Gold One Shot, Zoetis, 100 Campus Drive, Florham Park, N.J.) (T02), to low-infectious bovine rhinotracheitis virus serum neutralization titer (≤ 8) nursing range beef calves. One-hundred ninety spring-born calves native to the ranch were screened for existing IBRV, BRSV SN titers and *Mannheimia haemolytica* leukotoxoid antibody 30 days prior to the initiation of the study. One hundred fifty calves with day 0 IBRV titers of less than ≤ 8 were blocked based on the age of calf, sex of calf and existing IBRV titers, and randomly allocated to one of two treatment groups. The remaining calves were removed from the study. Seventy-five calves were assigned to each treatment group. On day 0, all calves allotted to the study were treated with their assigned treatment products (T01, T02) and blood samples were collected. On day 153, the calves in both treatment groups were administered a subcutaneous dose of the five-way MLV vaccine combined with a *Mannheimia haemolytica* bacterial-extract toxoid (T02) and a blood sample was collected. On day 174, the calves again were processed for blood sample collection. This study demonstrated the ability of spring-born beef calves approximately 8 to 13 weeks of age to respond to respiratory vaccines. In addition, calves given a second dose 153 days following the first dose developed an anamnestic, or booster, response to the initial dose. The intranasal administration of a three-way MLV vaccine resulted in the greatest BRSV serological response on days 14, 153 and 174 (T01), whereas the subcutaneous administration of the five-way MLV vaccine combined with a *Mannheimia haemolytica* bacterial-extract toxoid (T02) resulted in the greatest leukotoxoid serological response on days 14 and 174.

Introduction

Spring-born beef calves routinely receive vaccinations at a young age to aid in the prevention of specific infectious diseases. Commonly, the vaccine protocols will include a seven-way clostridial vaccine (blackleg, malignant edema, etc.) and other viral and bacterial antigens to reduce the risk of clostridial and respiratory disease.

While young beef calves have a functioning immune system, several potential inhibitors can prevent them from developing a strong immune response. Calves with high levels of passive immunity transferred via the colostrum from the dam can inhibit some of the humoral response to vaccination. While this inhibition impacts antibody production, what is clear is that memory immune cells instrumental

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in responding to secondary vaccination have been recruited and replicated. These cells are instrumental in the protection of the animal and their actual exposure to viral and bacterial pathogens.

Vaccine labels carry important information about the product. Indications on the label provide information about the pathogen and disease conditions for use. The directions give a description as to how to mix if necessary, the dose volume to be administered and the route of administration.

Vaccines are not evaluated as to ideal dose intervals, but instead receive a default label to administer a second dose in 21 to 28 days. Second, or booster, doses rarely are given according to label, and much discussion has focused on the time interval from first to the second dose. Unless compelling evidence exists for administering a second dose according to label, most booster doses will not be administered for at least 90 to 150 days following the first dose.

Experimental Procedures

This study utilized 150 calves born at the NDSU CGREC during the spring of 2013. They ranged from 55 to 99 days of age on day 0 of the study, with a mean of 74 days of age at that time. The calves were blocked by date of birth and sex and randomly assigned to one of two treatment groups. They were maintained as a single group with their dams on native pasture throughout the study. The treatments were assigned as described in Table 1.

All dams of calves included in the study were identified individually and received a pre-breeding dose of a MLV reproductive vaccine (Preg-Guard 10, Zoetis, 100 Campus Drive, Florham Park, N.J.) during the spring of 2013. All calves in the study were identified individually and received no additional vaccines, bacterins or toxoids prior to or during the study other than all calves received a subcutaneous dose of seven-way clostridial bacterin-toxoid (Ultrabac 7, Zoetis, 100 Campus Drive, Florham Park, N.J.) on day 0. On day 30, the calves meeting the age requirement for the study had blood drawn for serological examination for existing passive antibody titers for IBRV, BRSV and *Mannheimia haemolytica* leukotoxin. One hundred fifty calves sero-negative to IBRV(≤ 8) were blocked and randomly assigned to treatments groups 1 and 2.

Calves in treatment group 1 were identified, had blood drawn and received a subcutaneous dose of a *Mannheimia hemolytica* leukotoxoid, a MLV BVDV in the neck and a dose of a three-way MLV IBRV, BRSV, PI3 of 1 cubic centimeter per nostril on day 0 (T01). The calves again were processed on days 14 and 27, at which time they were identified and had blood drawn. Serum was prepared from the blood drawn on days 0 and 14 and held frozen until the completion of the 27-day portion of the study, at which time all serum was submitted to the Oklahoma State University Veterinary Diagnostic Laboratory for analysis. The calves were returned to their dams following each processing and returned to pasture.

On day 112, the calves were weaned, given a control dose of the broad spectrum antibiotic tulathromycin (Draxxin, Zoetis, 100 Campus Drive, Florham Park, N.J.) and placed in a drylot at the research facility. On day 153, the calves were identified, had blood drawn and received a subcutaneous dose of five-way MLV vaccine combined with a *Mannheimia haemolytica* bacterial extract toxoid (T02). The blood was prepared as previously described and held frozen until the completion of the 174-day portion of the study. On day 174, the calves again were identified, and had blood drawn and prepared as previously described and submitted for analysis along with the serum from the 153-day bleeding.

Calves in treatment group 2 were identified, had blood drawn and received a subcutaneous dose of five-way MLV vaccine combined with a *Mannheimia haemolytica* bacterial-extract toxoid (T02) in the neck on day 0. The calves again were processed on days 14 and 27, at which time they were identified and had blood drawn. Serum was prepared from the blood drawn on days 0 and 14 and held frozen until the completion of the 27-day portion of the study, at which time all serum was submitted to the Oklahoma State laboratory for analysis. The calves were returned to their dams following each processing and returned to pasture.

Table 1. Vaccine treatments (yes = vaccine administered).

No.	Vaccine Treatment Description	Day 0	Day 153
T01	MLV Intranasal 3-way	Yes	No
	plus		
	MLV BVDV + M. hemolytica leukotoxoid (separate injections)		
	MLV 5-way + M. hemolytica (combination)	No	Yes
T02	MLV 5-way + M. hemolytica (combination)	Yes	Yes

On day 112, the calves were weaned, given a dose of the broad spectrum antibiotic tulathromycin for control of bacterial respiratory pathogens and placed in a drylot at the research facility. On day 153, the calves were identified, had blood drawn and received a subcutaneous dose of five-way MLV vaccine combined with a *Mannheimia haemolytica* bacterial-extract toxoid (T02; Table 1). The blood was prepared as previously described and held frozen until the completion of the 174-day portion of the study. On day 174, the calves again were identified, and had blood drawn and prepared as previously described and submitted for analysis along with the serum from the 153-day bleeding.

Results and Discussion

These results suggest that either calf vaccination program at the time of turnout would be highly successful in stimulating a humoral immune response. However, vaccination of the calves with the intranasal component of T01 resulted in the most significant BRSV response initially, 153 days later and again following a revaccination with the five-way MLV combined with a *Mannheimia haemolytica,* bacterial-extract toxoid (see Table 2).

In contrast, the most significant leukotoxoid response occurred following initial vaccination and again following revaccination when T02 was used at both vaccination times (Table 3).

This study demonstrated that beef calves vaccinated at approximately 2 months of age with the intranasal three-way MLV vaccine (T01), followed with a second dose of the five-way MLV vaccine (T02), resulted in a significantly greater serological BRSV response than similar calves administered the T02 product at initial and second-dose events.

Beef calves vaccinated at approximately 2 months of age with the T02 combination product developed significantly greater serological *Mannheimia haemolytica* leukotoxoid response following vaccination than did similar calves vaccinated with the T01 protocol. In addition, a second dose given 153 days following the initial dose resulted in an anamnestic (booster) response in calves. This time interval matches management strategies regarding cattle handling and vaccination events.

For spring-born calves, the interval from grass turnout and initial vaccine administration to preweaning or weaning vaccinations may range from 120 to 180 days. The results provide veterinarians and beef producers with evidence that vaccination can elicit an immune memory response 153 days following the initial dose.

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Table 2. Serological LIvels for BRSV for various days of the study.

Treatment	Vaccine	Day 0	Day 14	Day 27	Day 153	Day 174
T01	Intranasal MLV 3-way + BVDV + M. hem.	13.1	7.7	23.1	1.8	14.3
T02	MLV 5-way + M. hem. (combination)	11.9	6.4	13.7	1.1	6.2
p value		ns p=0.63	ns p=0.33	*p=0.003	*p=0.001	*p=0.006

Table 3. Serologicall for *Mannheimia haemolytica* LKT for various days of the study.

Treatment	Vaccine	Day 0	Day 14	Day 27	Day 153	Day 174
T01	Intranasal MLV 3-way + BVDV + M. hem.	0.25	0.40	0.38	0.62	1.19
T02	MLV 5-way + M. hem. (combination)	0.26	0.47	0.43	0.69	1.43
p value		ns p=0.51	*p=0.10	ns p=0.15	ns p=0.24	*p=0.02