Clinical Response of Feeder Calves Under Direct IBR and BVD Virus Challenge: A Comparison of Two Vaccines and Negative Control

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Introduction

The objective of this study was to determine the effect of direct aerosol challenge with virulent IBR and BVD virus on vaccinated and non-vaccinated fall weaned beef calves. Morbidity and mortality data were collected and used to evaluate the response of each treatment group to virus challenge. These data provided the basis of comparison between treatment groups.

Materials and Methods

Sixty-four mixed breed beef calves were used in this study. The calves originated from one ranch in east Texas, and were determined to be sero-negative to IBR, BVD and BRSV. Sero-activity was determined by serum neutralization from a survey serum sample collected 2 weeks prior to study initiation (Table I). At the time of survey sampling, cattle were identified with sequentially numbered ear tags as they came through the chute. Allotment to treatment was both random and blind, and based solely on tag number.

Treatment I calves received a multivalent vaccine with chemically altered IBR-PI_3 viruses, inactivated BVD virus, modified live BRSV virus and 5 serovars of Leptospira.[a] Treatment II received an all killed virus IBR-BVD-PI_3-BRSV plus 5 serovars of Leptospira vaccine.[b] Treatment III calves were not vaccinated, and served as a negative control for the study (Table II). Vaccine products were administered per manufacturer's label specifications.

The calves received the appropriate initial treatment 18 days prior to weaning and were returned to the herd (11/23/90) (Table III). The calves were weaned and transported to Agri Research Center located three miles northwest of Canyon, Texas, on December 11, 1990. The calves were given booster vaccinations based on treatment group and placed in separate pens on December 12, 1990. Handling and observation of the cattle was in accordance with standard feed yard procedures from processing to virus challenge on January 12, 1991. Two animals were removed from Treatment II prior to challenge; one for CNS disease and one for non-responsive respiratory disease, and were, therefore, excluded from this study.

On January 12, 1991, the cattle were exposed to 2 x 10^8 TCID New York-1 strain BVD and 2 x $10^{9.4}$ TCID Cooper strain IBR. A total of 4 milliliters of the virus mixture was administered in multiple small doses via aerosol with one-half the dose being given in each nostril.

TABLE I Geometric Mean Titers

	IBR	BVD	BRSV	PI_3
11-23-90				
Treatment I	1.1[a]	3.0	1.0	1.8
Treatment II	1.0	3.0	1.0	2.1
Treatment III	1.0[b]	3.0[c]	1.0[b]	2.0
12-12-90				
Treatment I	4.1	3.2	4.0	5.7
Treatment II	1.5	3.0	1.1	5.1
Treatment III	1.0	3.0	1.0	1.9
1-12-91				
Treatment I	19.8	26.4	22.6	17.3
Treatment II	17.4	32.9	12.7	39.2
Treatment III	1.0	3.0	8.5	16.0
2-2-91				
Treatment I	668.4	1051.7	16.9	109.1
Treatment II	958.6	990.8	7.7	80.6
Treatment III	27.9	32.0	4.0	27.9

[a] Animal #12 was reported as sero-negative at survey sampling (11-4-90) and at 1:2 on 11-23-90.

[b] A geometric mean titer of 1.0 represents a serum neutralization titer of <1:2.

[c] A geometric mean titer of 3.0 represents a serum neutralization titer of <1:6.

TABLE II Treatment Groups

	Head Count	Product Type
Treatment I	26	Chemically altered IBR-PI_3 viruses, MLV BRSV, killed BVD, plus 5 Leptospira serovars[a]
Treatment II	24	All killed virus IBR-BVD-PI_3-BRSV, plus 5 Leptospira serovars[b]
Treatment III	12	Negative control

[a]*CattleMaster 4+L5™ – SmithKline Beecham Animal Health, 812 Springdale Drive, Exton, PA 19341*

[b]*Triangle 9™ – Fort Dodge Laboratories Inc., 800 Fifth Street N.W., Fort Dodge, IA 50501*

TABLE III Schedule of Events

Date	Event
11-04-90	Survey blood sample collected
11-23-90	Allot to treatment, collect blood sample, vaccinate
12-11-90	Animals shipped to Agri Research Center (ARC)
12-12-90	Revaccinate, weigh, collect blood sample
1-12-91	Observe, weigh, bleed, IRB & BVD virus challenge
1-13 to 18-91	Observe, daily temperatures taken
1-19-91	Observe, weigh, take temperature
1-20 to 24-91	Observe
2-02-91	Collect final blood sample, weigh, take temperature

Individual animal temperatures were taken for 7 consecutive days post challenge. Following day 7 post challenge, cattle that required treatment were handled as routine respiratory disease cases. Treatment was administered based on standard operating procedures for the feed yard. All animals were observed and handled as normal feed yard cattle from 7 days post challenge to study end. The study was concluded 21 days post challenge on February 2, 1991.

Morbidity and mortality data were collected and tabulated. Chi Square analysis was performed on appropriate data. Necropsy results were collected and evaluated.

Results

Mortality data by treatment is presented in Table IV and Graph I. It can be seen that 0 of 26 (0%) Treatment I calves died, while 3 of 24 (13%) Treatment II calves, and 7 of 12 (58%) Treatment III calves died. The cause of death as well as date of death for individual animals, is found in Table V. The time for virus exposure until the first and last animal died were 10 to 18 days, respectively. The median time from virus challenge to death was 13 days. There was consistent involvement of the respiratory tract (consolidation and hemorrhage) and the digestive track (ulceration and edema of abomasal folds) in all necropsied animals (Table V). Gross necropsy lesions were consistent with published reports for bovine respiratory disease having IBR and BVD involvement.[1,2]

Tissues from animals #51 and #8 were submitted to the Texas Veterinary Medical Diagnostic Laboratory for virus isolation. Animal #8 yielded IBR virus from lung, trachea, mediastinal lymph node, abomasum, and small intestine. Animal #51 yielded BVD virus from lymph nodes and small intestine.

Chi Square analysis was performed on the mortality data (Table IV). A statistically significant difference was shown for the reduced mortality in Treatment I as compared to Treatment II and III ($p < 0.0001$). The reduction of mortality in Treatment II versus Treatment III was also statistically significant ($p < 0.0001$) . Morbidity was determined by febrile reponse (Tables VI and VII) and the need for individual treatment for respiratory disease (Table IV and Graph I). By day two post challenge, all groups were showing an increase in the average rectal temperature (Table VII). The average temperature for Treatment I cattle continued to increase and peaked at 104.3°F on day 4 post challenge, and had returned to base line by day 7 post challenge. The temperatures for cattle in Treatment II and III reached a higher level and persisted longer than the temperature response recorded for Treatment I.

Table VI represents 3 day average temperatures from day 3 to day 5 post challenge. There was a significant reduction in the number of Treatment I animals showing sustained temperatures of 104.5°F as compared to Treatments II and III ($p < 0.0001$). The difference between Treatment II and Treatment III relative to the number of animals with sustained temperatures of 104.5°F during the 3 to 5 day post challenge period was not statistically significant ($p > 0.1$). On day 7 post challenge, animals requiring individual treatment for respiratory disease were identified and treated (Table IV). Two of the 26 (8%) Treatment I cattle were individually treated. Eight of 24 (33%) and 12 of 12 (100%) Treatments II and III calves, respectively, required individual treatment for respiratory disease.

Statistically significant differences were demonstrated with respect to the reduction of animals requiring antibiot-

ic therapy in Treatment I versus II ($p < 0.025$) and III ($p < 0.0001$) and for Treatment II versus III ($p < 0.0001$) (Table IV). There was also a statistically significant difference noted for the reduction in number of animals in Treatment I as compared to Treatments II and III showing a sustained body temperature from 3 to 5 days post challenge ($p < 0.0001$) (Table VI).

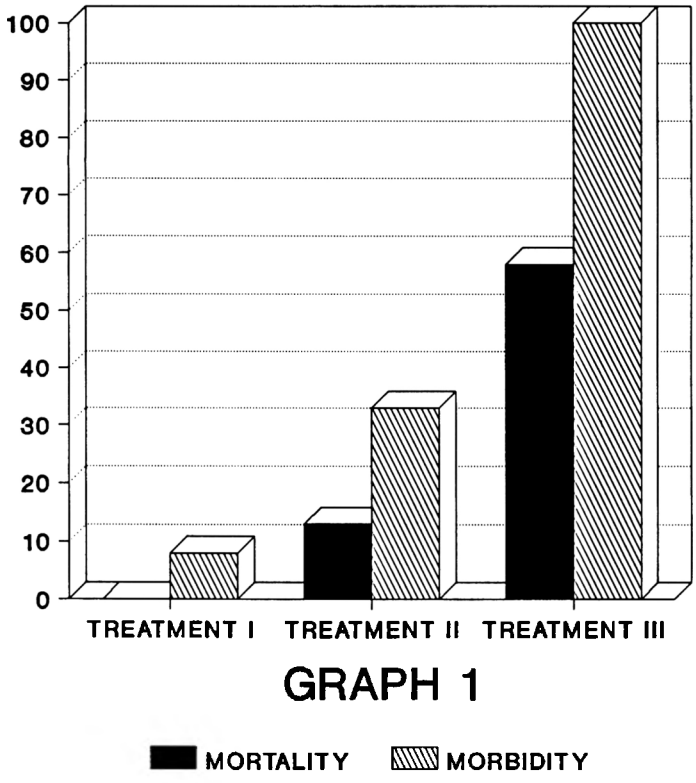
TABLE IV Morbidity and Mortality

	Head Count	Dead %	Sick %
Treatment I	26	0 (0)	2 (8)
Treatment II	24	3 (13)	8 (33)
Treatment III	12	7 (58)	12 (100)

p values for Chi Sq

Treatment	Dead	Sick (individually treated)
I vs II	< 0.0001	< 0.025
I vs III	< 0.0001	< 0.0001
II vs III	< 0.0001	< 0.0001

PERCENT MORTALITY AND MORBIDITY BY TREATMENT GROUP



GRAPH 1

TABLE V Death Loss by Date and Cause

	Animal Number	Date of Death	Necropsy Diagnosis
Treatment I	N/A	N/A	No death loss
Treatment II	51	1-22-91	Pneumonia (BVD isolated)
	12	1-25-91	IBR / BVD *
	46	1-30-91	IBR / BVD / Pasteurella **
Treatment III	8	1-22-91	IBR isolated
	1	1-25-91	IBR / BVD*
	5	1-25-91	IBR/ BVD*
	6	1-25-91	IBR/ BVD*
	9	1-25-91	IBR/ BVD*
	14	1-25-91	IBR/ BVD/ Pasteurella **
	3	1-27-91	IBR / BVD / Pasteurella **

* These animals were posted at Agri Research Center By Dr. David Bechtol.
Trachea - mild to extreme petechial and echymotic hemorrhages; mild to extreme fibrin
Lungs - dark red, hemorrhagic with edema and consolidation, greater than 20% involvement
Oral Cavity - normal to petechial hemorrhages to small ulcerations
Esophagus - generally normal
Abomasum - consistently inflamed and edematous, generally - elongated ulcers on folds
Intestine - generally inflamed

** In addition to IBR / BVD lesions, there was evidence of Pasteurella spp. involvement.

TABLE VI Individual Body Temperatures From Day 3 to Day 5 Post Challenge

	Number of Animals*	3 Day* Avg. Temp.	Group Avg. Temp.
Treatment I	6/26 (23%)[a]	105.2	103.8
Treatment II	21/24 (88%)[b]	105.5	105.2
Treatment III	12/12 (100%)	106.0	106.0

* 3 Day Average Temperatures of Animals Having a Sustained Temperature of 104.5°F or Greater

Statistical Difference on Chi Sq Testing
a - $p < 0.0001$ vs Treatment II & III
b - $p > 0.10$ vs Treatment III

TABLE VII Average Daily Body Temperatures* by Treatment Group

Date	Treatment I	Treatment II	TreatmentIII
1-12-91**	103.6	103.6	103.6
1-13-91	102.7	102.8	103.0
1-14-91	103.3	102.9	104.6
1-15-91	103.6	105.6	105.7
1-16-91	104.3	105.4	106.1
1-17-91	104.1	105.4	106.2
1-18-91	103.8	105.4	106.4
1-19-91	103.6	104.9	105.6

* The animals were restrained in a squeeze chute and rectal temperatures were taken.

** All cattle were exposed to virulent IBR and BVD viruses on 1-12-91.

Treatment I - a chemically altered virus, MLV, & killed virus combination vaccine plus Lepto 5.

Treatment II - an all killed virus vaccine plus Lepto 5.

Treatment III - no vaccine used (**Negative Control**)

Discussion

Involvement of more than one virus during bovine respiratory disease outreaks is generally felt to result in an increased severity of clinical disease.[3,4,5] In an attempt to simulate the clinical experience of new arrival fall weaned calves entering commercial feedlots and to increase the likelihood of generating sufficient clinical disease such that differentiation between treatments would be possible, both IBR and BVD viruses were used in this challenge study. This challenge method was very effective in creating clinical disease. It approximated the experience of calves arriving at large feed yards during the fall run and it was a fair challenge model to evaluate vaccines.

The ultimate measure of a vaccine's efficacy is its ability to protect under significant challenge. From the results, it is evident that the IBR and BVD virus challenge was significant. The results also indicate that vaccination with either of the tested products was highly effective in limiting morbidity and mortality. Further, the chemically altered virus, MLV, and killed virus vaccine (Treatment I) was shown to significantly reduce morbidity and mortality compared to the all killed virus vaccine (Treatment II).

The differences noted in efficacy between the two vaccine products may result from the immunologic processing of killed virus vaccines versus modified live and chemically altered virus vaccines. There was no significant difference between the serologic response of the two vaccinated groups to IBR and BVD (Table III). This would suggest that both products were able to stimulate a humoral immune (HI) response. The development of a cell mediated immune (CMI) response cannot be documented by these data; however, several things are known about the development of CMI and HI responses.

It is known that cytolytic T lymphocytes (CTL's) are an important part of CMI response to viral infections.[6] Further, the activation of $CD8^+$ CTL's occurs only when it recognizes endogenously synthesized viral antigens associated with a class I Major Histocompatibility Complex (MHC).[6] These viral antigens are produced during viral infection. Live virus vaccines may more closely simulate natural infection than killed virus vaccines.

From the foregoing, it is possible to speculate that the processing of a killed viral antigen is different than the processing of a MLV antigen. Processing of MLV antigens would result in activation of both $CD8^+$ CTL's and $CD4^+$ helper T cells, thereby stimulating both CMI and humoral immunity. This is plausible because MLV vaccines function by infecting cells which would result in endogenous production of viral proteins that would be associated with class I MHC and, therefore, activate $CD8^+$ CLT's. Based on the strong and rapid humoral response, it was evident that both products stimulated $CD4^+$ helper T cells and, therefore, B cells. Processing of the killed virus particles may have resulted primarily in soluble virus protein being associated with class II MHC, with the resultant $CD4^+$ helper T cell activation and subsequent B cell activation leading to a strong humoral response, but only a limited $CD8^+$ CTL response.

Assuming the preceding is correct, the difference seen in clinical response between the treatments could result for the following reasons. The sero-negative calves (Treatment III) were exposed simultaneously to significant levels of IBR and BVD virus without prior sensitization and as a result, severe disease was produced. The cattle vaccinated with the all killed virus product did have good humoral protection to BVD (protection to BVD is believed to be dependent on HI more than CMI[7]), but may not have had as good of protection to IBR because of a limited CMI response (protection to IBR is reported to be closely related to CMI[8]). The cattle that received the chemically altered virus, MLV and killed virus vaccine had good humoral protection to BVD and presumably a better CMI response to IBR, which resulted in the marked overall reduction in severity of clinical disease seen in this group.

Summary

The effect of two virus vaccines on morbidity and mortality in fall weaned feeder calves was evaluated. Treatment I cattle received a multivalent vaccine consisting of chemically altered IBR and PI_3 viruses, a modified live BRSV, an inactivated BVDV, and a bacterin containing 5 Leptospira interrogans serovars (canicola, grippotyphosa, hardjo, icterohaemorrhagiae, and pomona).[a] Treatment II

cattle received an all killed virus IBR-BFD-PI_3-BRSV and a bacterin containing 5 Leptospira interrogans serovars.[b] Treatment III cattle were not vaccinated. Vaccine products were administered per manufacturer's label specifications. All animals were subjected to direct aerosol challenge with virulent IBR and BVD virus 30 days after booster vaccination. The non-vaccinated group was included to provide a measure of the severity of challenge, and to serve as a basis of comparison for the vaccinated groups.

All cattle were sero-negative for IBR and BVD prior to initiation of the study. The two vaccinated groups (Treatment I and II) received primary and booster inoculations prior to virus challenge. The control group (Treatment III) remained sero-negative to IBR and BVD until challenge.

Treatment I calves experienced a morbidity rate of 8% and no mortality. Treatment II calves experienced a morbidity rate of 33% and a mortality rate of 13%. Morbidity and mortality in Treatment III calves were 100% and 58% respectively.

A statistically significant reduction in morbidity and mortality was demonstrated in vaccinated calves versus non-vaccinated calves. A significant reduction in morbidity and mortality was also demonstrated in the calves that received the chemically altered virus, MLV, and killed virus combination vaccine as compared to the calves that received the all killed virus vaccine. This study strongly supports the use of combination virus vaccines for the control of IBR and BVD induced respiratory disease in fall weaned calves.

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[a] *CattleMaster 4+L5™ – SmithKline Beecham Animal Health, 812 Springdale Drive, Exton, PA 19341*

[b] *Triangle 9™ – Fort Dodge Laboratories Inc., 800 Fifth Street N.W., Fort Dodge, IA 50501*

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