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# Comparison of the BVDV, BHV-1, and BRSV Anamnestic Response to Modified-live or Inactivated Vaccines in Calves Previously Vaccinated with a Modified-live Virus Vaccine

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**Abstract**

The objective of this study was to compare the serological responses in cattle initially vaccinated with a modified-live virus (MLV) vaccine containing infectious bovine rhinotracheitis (IBR) virus, parainfluenza-3 ($PI_3$) virus, bovine viral diarrhea virus type 1 (BVDV1), bovine viral diarrhea virus type 2 (BVDV2), and bovine respiratory syncytial (BRS) virus antigens, and subsequently re-vaccinated with either the same MLV vaccine or an oil-adjuvanted, inactivated vaccine containing the same viral antigens.

A group of 145 nursing calves received a MLV vaccine containing IBR, $PI_3$, BVDV1, BVDV2, and BRSV at one to two months of age. The calves were re-vaccinated with the same MLV vaccine at weaning, three-and-a-half months later. Approximately five months later, 45 of these animals were randomly selected and assigned to one of three treatment groups. Twenty calves received an oil-adjuvanted, inactivated vaccine (IBR, $PI_3$, BVDV1, BVDV2, BRSV); 20 received the same MLV vaccine that they had received as calves (IBR, $PI_3$, BVDV1, BVDV2, BRSV); and five controls received the MLV sterile diluent.

Following final vaccination, the animals receiving the oil-adjuvanted, inactivated vaccine had the highest titer response ($P<0.05$) for IBRV, BRSV, BVDV1, and BVDV2.

**Keywords:** bovine, vaccination, virus vaccine, anamnestic response

**Résumé**

L'objectif de cette étude était de comparer les réactions sérologiques chez des bovins vaccinés initialement avec un vaccin à virus vivants modifiés (MLV) contenant des antigènes du virus de la rhinotrachéite infectieuse bovine (IBR), du virus para-influenza de type 3 ($PI_3$), du virus de la diarrhée virale bovine de type 1 (BVDV1), du virus de la diarrhée virale bovine de type 2 (BVDV2) et du virus respiratoire syncitial bovin (BRSV), et subséquemment revaccinés avec soit le même type de vaccin ou soit un vaccin inactivé avec adjuvant huileux contenant les mêmes antigènes viraux.

Un groupe de 145 veaux allaitants ont reçu le vaccin MLV avec IBR, $PI_3$, BVDV1, BVDV2 et BRSV à un ou deux mois d'âge. Les veaux ont été revaccinés avec le même vaccin MLV au sevrage trois mois et demi plus tard. Approximativement cinq mois plus tard, 45 de ces veaux ont été choisis aléatoirement et ont reçu l'un des trois traitements suivants : (1) vaccin inactivé avec adjuvant huileux (IBR, $PI_3$, BVDV1, BVDV2, BRSV, n = 20), (2) le même vaccin MLV que les veaux avaient reçu préalablement (IBR, $PI_3$, BVDV1, BVDV2, BRSV, n = 20), et (3) le diluant stérile du vaccin MLV (n = 5). Après la dernière vaccination, les veaux ayant reçu le vaccin inactivé avec adjuvant huileux avaient les titres les plus élevés contre les virus IBRV, BRSV, BVDV1, et BVDV2 ($P<0.05$).

## Introduction

Practitioners have many options when designing vaccination protocols for clients that precondition calves. There are many "vaccine recommendations," but little research available to indicate the true effectiveness of vaccine timing or ideal protocols for use in young calves. Vaccination protocols that use combinations of different vaccines, containing different virus strains, should theoretically expose the immune system to a wider range of viral antigens, resulting in better protection. The utility of this practice remains to be proven.

The booster or anamnestic response following re-vaccination of animals can be limited.[1] Up to 40% of animals fail to mount an anamnestic response to bovine

viral diarrhea virus (BVDV) vaccine 140 days after initial vaccination with a modified-live virus (MLV) vaccine.[3] This is thought to result from a combination of cell-mediated immunity stimulated by previous vaccination and circulating antibody which limits replication of vaccine virus. Inactivated vaccines contain a high antigenic mass protected by adjuvant, and may not be affected by circulating antibody or cell-mediated immunity.[1] An inactivated vaccine may be more effective to booster a MLV vaccine because it can provide a more consistent humoral immune response resulting in higher antibody levels than produced by MLV vaccine.[1]

Several studies have examined the effect of using an inactivated vaccine as a booster following primary immunization with a MLV viral vaccine for potential control of bovine respiratory disease.[4,5,8] Grooms *et al*[4] examined the use of various combinations of inactivated or MLV vaccines against infectious bovine rhinotracheitis (IBR) virus, bovine viral diarrhea (BVD) virus, parainfluenza-3 ($PI_3$) virus, and bovine respiratory syncytial (BRS) virus. The use of MLV and inactivated BVDV vaccine in a priming and booster vaccination series was equally as effective for stimulating virus-neutralizing antibody titers as two doses of MLV vaccine.[4] Reber *et al*[8] found that the MLV/MLV and MLV/inactivated groups developed significant serum neutralization titers to the BVDV1 strains, and low crossover titers were also developed to the BVDV2 strain.[8] Kerkhofs *et al*[5] compared four vaccination protocols based on inactivated and commercially available MLV marker vaccines for IBR. Cellular and humoral immune responses were highest in calves that received at least one injection of inactivated vaccine. Calves receiving one dose of inactivated vaccine as a booster vaccination shed significantly less challenge virus than calves vaccinated only with MLV vaccine.[5] Although all three studies indicated that vaccination with inactivated vaccine was effective following initial vaccination with MLV vaccine, all re-vaccinations were done 21 to 32 days after administration of a vaccine. In this study, the effects of administering an inactivated vaccine five months after the second dose of MLV vaccine was evaluated.

## Materials and Methods

*Animals*

The trial was conducted at the Western Beef Development Centre, Trumunde Farm in Lanigan, Saskatchewan. Calves were crossbred Angus born on the farm, and had grazed on pasture at the farm, or at Patlow pasture in northeast Saskatchewan during that summer. A total of 145 calves, 1-2 months old, were administered a combination IBR, $PI_3$, BVDV1, BVDV2, BRSV MLV vaccine[a] prior to turnout on summer pasture on June 12 or June 13, 2002, and again three-and-a-half months later when weaned on October 1, 2002. After weaning, the calves were backgrounded in confinement pens at the Trumunde Farm.

In February 2003 (five months later), 45 calves were randomly selected from the group of 145. Test animals were assigned a computer-generated random number and allocated to one of three treatment groups: 1) control group (n=5); 2) inactivated vaccine group (n=20); and 3) MLV group (n=20).

*Animal Housing and Care*

Test animals were weighed and commingled prior to the start of the trial and remained commingled for the duration of the trial. They were housed in a feedlot-style background lot with open-air, dirt floor pen, porosity fence windbreak, and a center-facing alley with a concrete feed bunk. Health status of test animals was observed and recorded daily.

*Treatment*

Calves were administered the following products 148 days post-weaning, which was also 148 days since they had received their second vaccination:

- Group 1–control group (n=5). Calves were administered 5 mL of sterile water subcutaneously (SC).
- Group 2–inactivated vaccine group (n=20). Calves were administered an inactivated, adjuvanted bovine respiratory viral vaccine[b] (IBR, $PI_3$, BVDV1, BVDV2, and BRSV) SC in the neck.
- Group 3–MLV group (n=20). Calves were administered MLV bovine respiratory viral vaccine[a] (IBR, $PI_3$, BVDV1, BVDV2, BRSV) SC in the neck.

*Sample Collection and Analysis*

Animals were weighed and allocated to treatment group on day 142 post-weaning. Blood samples were collected immediately prior to vaccination on day 148 post-weaning (trial day 0). Serum was harvested and frozen until submitted for analysis. At 169 days post-weaning (trial day 21), animals were weighed, and a 21-day post-vaccination blood sample was collected. Serum was harvested, frozen, and submitted to Prairie Diagnostic Services in Saskatoon, Saskatchewan, to determine the ELISA titer for IBR and BRSV, and serum neutralization titers for BVDV1 and BVDV2.

*Statistical Analysis*

Data were analyzed by an independent statistician.[c] All statistical analyses were performed using SAS. The level of significance was set at $P<0.05$.

All comparisons were made using a least squares analysis of variance procedure that accounts for the

unequal sample sizes in comparisons where this is a factor. The analyses and resulting significance tests were conducted on the logarithm of the titer value. The geometric means were back-transformed to the original scale for presentation in the tables that follow.

## Results

*Vaccine Reactions and Weight Gain*

There were no adverse reactions following vaccination. None of the animals were treated for any medical condition during the course of the trial. There were no differences in average daily gain among treatment groups (Table 1).

*Serological Responses*

Controls were sentinel animals used to monitor inadvertent exposure to naturally occurring strains of virus (Table 2). There was no statistical difference for the control group between day 0 and day 21 for any of the viruses. Controls exhibited a slight decline in mean antibody titers between day 0 and day 21 for each fraction.

*BVDV1 and BVDV2*

Although there were statistical differences at day 0 between the control group and the other two groups, the smaller group size of the control group and outliers with titers greater than 13,000 (MLV group with two outliers and inactivated group with three outliers for BVDV1; inactivated with two outliers for BVDV2) also skewed the average between the groups (Table 2). The titer in the inactivated group increased significantly from 1,821 on day 0 to 11,958 on day 21, a 6.57-fold increase in BVDV1 titer following vaccination compared to 1.39 for calves vaccinated with MLV vaccine ($P<0.05$; Table 3). Using a covariate analysis to adjust for the effect of the existing titer on day 0 on the response to vaccination at day 21, the BVDV 1 titer was significantly higher for calves in the inactivated vaccine compared to the group administered MLV vaccine ($P<0.05$; Table 4). Similar results were seen with BVDV2. The titer in calves vaccinated with inactivated vaccine increased significantly from 1,631 to 14,073 (Table 2). This was an 8.63-fold increase compared to a 6.74-fold increase in the MLV group (Table 3). Using a covariate analysis to adjust for the effect of the existing titer on day 0 on the response to vaccination at day 21, the BVDV2 titer was significantly higher in calves receiving inactivated vaccine compared to those vaccinated with MLV vaccine ($P<0.05$; Table 4). An additional analysis using titer ranking of the day 21 titers indicated the inactivated group was clustered together at the higher titers while calves in the MLV group were clustered in the lower titers (Figure 1).

*IBR*

Calves in the inactivated group had a significant increase in IBR titer over those receiving MLV vaccine. The titer in the inactivated group increased from 14 to 98 (Table 2), which was a 6.74-fold increase compared to a 2.92-fold increase in the MLV group ($P<0.05$; Table 3). Using a covariate analysis to adjust for the effect of existing titer on day 0 on the response to vaccination at day 21, the IBR titer was significantly higher for the inactivated vaccine group compared to the group that received MLV vaccine ($P<0.05$; Table 4).

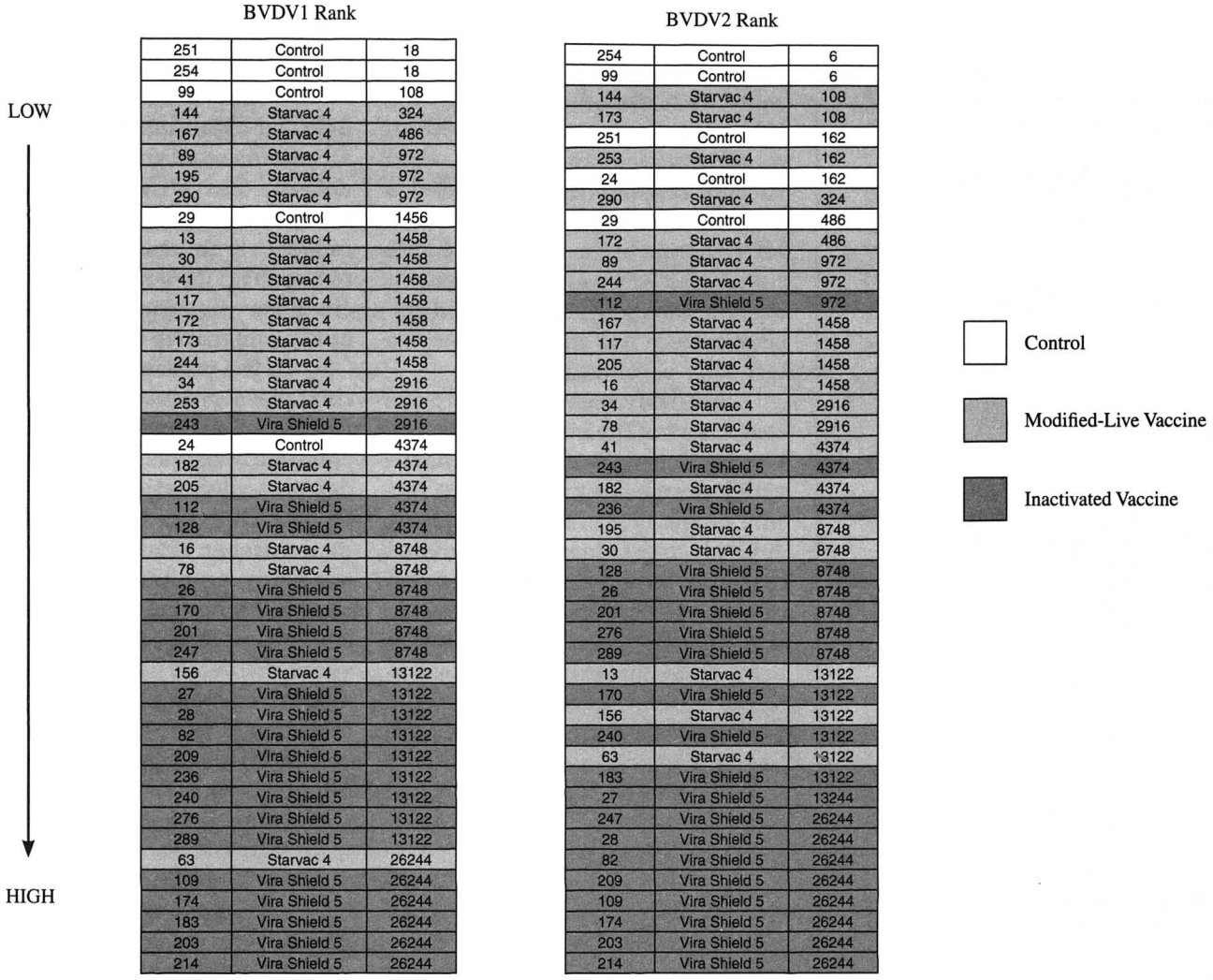
**Table 1.** Initial weight, feedlot entry weight, and average daily gain of control calves, calves vaccinated with modified-live virus (MLV) vaccine, or inactivated virus vaccine.

| | Control | MLV vaccine | Inactivated vaccine |
|---|---|---|---|
| No. calves | 5 | 20 | 20 |
| Initial weight (lb) | 727.6 | 756.2 | 746.7 |
| Feedlot entry (lb) | 780.0 | 808.5 | 799.3 |
| ADG (lb/day) | 1.87 | 1.87 | 1.88 |

**Table 2.** Geometric mean antibody titers* for BVDV1, BVDV2, IBR, and BRSV in control calves, calves vaccinated with modified-live virus (MLV) vaccine, or inactivated virus vaccine.

| Vaccine treatment | Day | BVDV1 | BVDV2 | IBR | BRSV |
|---|---|---|---|---|---|
| Control | 0 | 280[a] | 66[a] | 16 | 43 |
| Control | 21 | 186 | 54 | 15 | 38 |
| MLV | 0 | 1,595[b] | 266[a] | 24 | 43 |
| MLV | 21 | 2,223 | 1,689 | 69 | 58 |
| Inactivated | 0 | 1,821[b] | 1,631[b] | 14 | 34 |
| Inactivated | 21 | 11,958 | 14,073 | 98 | 118 |

*Day 0 values in the same column with different superscripts are significantly different ($P<0.05$).




| BVDV1 Rank | | |
|---|---|---|
| 251 | Control | 18 |
| 254 | Control | 18 |
| 99 | Control | 108 |
| 144 | Starvac 4 | 324 |
| 167 | Starvac 4 | 486 |
| 89 | Starvac 4 | 972 |
| 195 | Starvac 4 | 972 |
| 290 | Starvac 4 | 972 |
| 29 | Control | 1456 |
| 13 | Starvac 4 | 1458 |
| 30 | Starvac 4 | 1458 |
| 41 | Starvac 4 | 1458 |
| 117 | Starvac 4 | 1458 |
| 172 | Starvac 4 | 1458 |
| 173 | Starvac 4 | 1458 |
| 244 | Starvac 4 | 1458 |
| 34 | Starvac 4 | 2916 |
| 253 | Starvac 4 | 2916 |
| 243 | Vira Shield 5 | 2916 |
| 24 | Control | 4374 |
| 182 | Starvac 4 | 4374 |
| 205 | Starvac 4 | 4374 |
| 112 | Vira Shield 5 | 4374 |
| 128 | Vira Shield 5 | 4374 |
| 16 | Starvac 4 | 8748 |
| 78 | Starvac 4 | 8748 |
| 26 | Vira Shield 5 | 8748 |
| 170 | Vira Shield 5 | 8748 |
| 201 | Vira Shield 5 | 8748 |
| 247 | Vira Shield 5 | 8748 |
| 156 | Starvac 4 | 13122 |
| 27 | Vira Shield 5 | 13122 |
| 28 | Vira Shield 5 | 13122 |
| 82 | Vira Shield 5 | 13122 |
| 209 | Vira Shield 5 | 13122 |
| 236 | Vira Shield 5 | 13122 |
| 240 | Vira Shield 5 | 13122 |
| 276 | Vira Shield 5 | 13122 |
| 289 | Vira Shield 5 | 13122 |
| 63 | Starvac 4 | 26244 |
| 109 | Vira Shield 5 | 26244 |
| 174 | Vira Shield 5 | 26244 |
| 183 | Vira Shield 5 | 26244 |
| 203 | Vira Shield 5 | 26244 |
| 214 | Vira Shield 5 | 26244 |

| BVDV2 Rank | | |
|---|---|---|
| 254 | Control | 6 |
| 99 | Control | 6 |
| 144 | Starvac 4 | 108 |
| 173 | Starvac 4 | 108 |
| 251 | Control | 162 |
| 253 | Starvac 4 | 162 |
| 24 | Control | 162 |
| 290 | Starvac 4 | 324 |
| 29 | Control | 486 |
| 172 | Starvac 4 | 486 |
| 89 | Starvac 4 | 972 |
| 244 | Starvac 4 | 972 |
| 112 | Vira Shield 5 | 972 |
| 167 | Starvac 4 | 1458 |
| 117 | Starvac 4 | 1458 |
| 205 | Starvac 4 | 1458 |
| 16 | Starvac 4 | 1458 |
| 34 | Starvac 4 | 2916 |
| 78 | Starvac 4 | 2916 |
| 41 | Starvac 4 | 4374 |
| 243 | Vira Shield 5 | 4374 |
| 182 | Starvac 4 | 4374 |
| 236 | Vira Shield 5 | 4374 |
| 195 | Starvac 4 | 8748 |
| 30 | Starvac 4 | 8748 |
| 128 | Vira Shield 5 | 8748 |
| 26 | Vira Shield 5 | 8748 |
| 201 | Vira Shield 5 | 8748 |
| 276 | Vira Shield 5 | 8748 |
| 289 | Vira Shield 5 | 8748 |
| 13 | Starvac 4 | 13122 |
| 170 | Vira Shield 5 | 13122 |
| 156 | Starvac 4 | 13122 |
| 240 | Vira Shield 5 | 13122 |
| 63 | Starvac 4 | 13122 |
| 183 | Vira Shield 5 | 13122 |
| 27 | Vira Shield 5 | 13244 |
| 247 | Vira Shield 5 | 26244 |
| 28 | Vira Shield 5 | 26244 |
| 82 | Vira Shield 5 | 26244 |
| 209 | Vira Shield 5 | 26244 |
| 109 | Vira Shield 5 | 26244 |
| 174 | Vira Shield 5 | 26244 |
| 203 | Vira Shield 5 | 26244 |
| 214 | Vira Shield 5 | 26244 |

**Figure 1.** Comparison of titer stratification for BVDV1 and BVDV2.

**Table 3.** Fold-change in antibody titer* for BVDV1, BVDV2, IBR, and BRSV.

| Treatment | BVDV1 | BVDV2 | IBR | BRSV |
|---|---|---|---|---|
| Control | 0.66[a] | 0.82[a] | 0.93[a] | 0.89[a] |
| MLV | 1.39[a] | 6.34[b] | 2.92[b] | 1.35[b] |
| Inactivated | 6.57[b] | 8.63[b] | 6.74[c] | 3.43[c] |

*Values in the same column with different superscripts are significantly different ($P<0.05$).

**Table 4.** Antibody titers adjusted for titer at day 0** for BVDV1, BVDV2, IBR, and BRSV.

| Treatment | BVDV1 | BVDV2 | IBR | BRSV |
|---|---|---|---|---|
| Modified-live virus (MLV) vaccine | 2262 | 2422 | 69 | 55 |
| Inactivated vaccine | 11,754** | 9,632** | 105** | 123** |

**Differences between treatments are significantly different ($P<0.05$) for each fraction.

*BRSV*

The inactivated group had a significant increase in BRSV titer over calves in the MLV group. The inactivated group titer increased from 34 to 118 (Table 2), which was 3.43-fold compared to a 1.35-fold increase in the MLV group ($P<0.05$; Table 3). Using a covariate analysis to adjust for the effect of existing titer at day 0 on the response to vaccination at day 21, the BRSV titer was significantly higher for the inactivated vaccine compared to the MLV vaccine ($P<0.05$; Table 4).

## Discussion

In this study, where calves were vaccinated earlier with a MLV vaccine, a single dose of an oil-adjuvanted, inactivated viral vaccine consistently stimulated a greater antibody response than a MLV vaccine in the presence of high circulating antibody levels against all four viruses. This occurred approximately five months after the last MLV vaccination.

Antibody response is only one component of the immune response. Vaccinating with either an inactivated vaccine or a modified-live vaccine in the face of high circulating antibody may induce a cell-mediated response, which was not measured in this trial. In an earlier study of IBR vaccines,[5] cellular and humoral immune responses were highest in calves that received at least one injection of inactivated vaccine. Calves receiving one dose of inactivated vaccine as a booster or two doses of inactivated vaccine shed significantly less challenge virus than calves vaccinated only with MLV vaccine. Similarly, Muylkens *et al*[7] reported that using a MLV vaccine as a priming injection and boostering with an inactivated IBR vaccine was the most efficacious for reducing virus excretion following challenge.

An increased immune response when using an inactivated booster vaccine has been reported in other studies. Grooms *et al*[4] examined preconditioning programs assigning calves to one of nine vaccine regimens, each consisting of inactivated or MLV bovine herpes virus-1, BVDV, $PI_3$, and BRSV vaccines. The use of MLV and inactivated BVDV vaccine in a priming and booster series at a 21-day interval was equally as effective in stimulating virus-neutralizing antibody titers as were two doses of MLV vaccine.[4] Reber *et al*[8] compared the BVDV titer response using three prime/boost vaccination strategies at a 14-day interval: inactivated vaccine followed by an inactivated booster; MLV vaccine followed by a MLV booster; and a MLV vaccine followed by an inactivated booster; all vaccines contained IBR, BVDV1, and $PI_3$. The MLV/MLV and MLV/inactivated groups developed significant serum neutralization titers to the BVDV1 strain, low BVDV2 crossover titers, and a T-cell mediated proliferative response.[8]

In the present study, the inactivated vaccine was administered five months after the last MLV vaccination, whereas there was a 21-day post-vaccination interval in the Grooms study[4] and a 14-day interval in the Reber study.[8] In the present study, an anamnestic response occurred when an inactivated vaccine was used as a booster in calves vaccinated with a MLV vaccine five months earlier. This finding offers more flexibility to veterinarians and producers as they develop vaccination protocols.

Other studies have looked at using an inactivated vaccine for the priming dose, and a MLV vaccine for the booster. One study evaluated the antibody response to inactivated and MLV multivalent vaccines administered at 35 days-in-milk to cows vaccinated semiannually. Titer levels in the inactivated/MLV group were higher than saline controls and the group vaccinated with only inactivated vaccine.[2] Similar increases were not seen with MLV IBR and BRSV. The researchers commented that "a vaccination strategy of priming with killed vaccine followed by a MLV booster may achieve titer levels not found with either vaccine type alone."[2] Similar serological outcomes were reported by Grooms *et al*.[4]

Vaccinating calves with a combination of MLV and oil-adjuvanted, inactivated vaccines may induce a greater humoral response than using either vaccine type alone. Higher titers to BVDV, BRSV, and bovine coronavirus on arrival at the

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feedlot have been shown to be associated with a reduced risk of undifferentiated bovine respiratory disease and increased weight gain.[6]

## Conclusion

Animals vaccinated with oil-adjuvanted, inactivated vaccine five months after vaccination with a MLV vaccine had a higher titer response ($P<0.05$) for IBR, BRSV, BVDV1, and BVDV2 than calves boostered with MLV vaccine. No difference in average daily gain was seen among treatment groups.

Based on this trial, vaccinating backgrounded calves with an oil-adjuvanted, inactivated vaccine may reduce BRD morbidity. Studies utilizing challenge with BVD or IBR viruses are needed to determine if a greater serological response correlates with increased protection against BRD in cattle production systems.


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## Endnotes

[a]Starvac 4Plus™, Novartis Animal Health Canada Inc., Mississauga, Ontario

[b]Vira Shield® 5, Novartis Animal Health US, Inc., Greensboro, NC

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