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Safety of Vaccination with an Inactivated or Modified Live Viral Reproductive Vaccine When Compared to Sterile Saline in Beef Cows

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Abstract

A two year study involving nine herds of well-vaccinated cows and heifers (n=1436) was conducted to evaluate whether a pre-breeding inactivated or MLV reproductive vaccine administered per label instructions had negative impacts on conception rates or calving distribution compared to a non-vaccinated control (saline) group. Within herd, cows were blocked by parity and calving date and randomly assigned to receive one of the three treatments: 1) MLV, 2) Inactivated) or 3) saline. No pre-vaccination screening for prior response to vaccination was performed and no monitoring for reproductive diseases occurred during the study. All females were synchronized with the 7-day CO-Synch + CIDR protocol and artificial inseminated (AI) at the appropriate time after CIDR removal (cows 60 to 66 hrs; heifers 52 to 56 hrs). Cows remained separated from bulls for at least 10 days after AI. Pregnancy success and fetal age were determined on day 28 after AI, and > 30 days after the breeding season. Data were analyzed using the GLIMMIX procedure in SAS with herd as a random variable. Since this was a safety study, primary comparisons were made between the saline control group and each vaccination group. Days postpartum influenced conception rates with heifers and short postpartum cows having decreased conception rates compared to cows that were further postpartum ($P < 0.05$). There was no difference in conception rates to AI between MLV and Control groups ($P = 0.21$; 40.0 ± 4% vs 43.3 ± 4%) or between Inactivated and Control groups ($P = 0.49$; 46.5 ± 4% vs 43.3 ± 4%). At 56 days after AI, MLV animals (88.9 ± 2%) had decreased pregnancy success compared to both the Inactivated (93.2 ± 2%) and Control groups (92.5 ± 2%, $P \leq 0.01$) however, breeding season pregnancy success was similar between MLV and Control groups ($P = 0.34$; 95.2 ± 2% vs 96.4 ± 1%) as well as between the Inactivated and Control groups ($P = 0.14$; 98.0 ± 1% vs 96.4 ± 1%). When cumulative calving distribution was evaluated, the proportion of females that calved by day 12 and 30 of the calving season were similar between MLV vaccine and Control groups ($P > 0.30$) and between the Inactivated and Control groups ($P > 0.30$). In summary, treatment of well-vaccinated beef cows and heifers with a MLV or Inactivated reproductive vaccine 30 days pre-breeding resulted in similar pregnancy rates and calving distributions as non-vaccinated Controls.

Keywords: Modified-live; Inactivated; Vaccine; Reproductive success

Introduction

Vaccinating female beef cattle with a modified live virus (MLV) has been an effective tool for reducing the risk of reproductive failure and fetal loss due to infections with *Bovine Viral Diarrhea virus* (BVDV) and *Bovine Herpesvirus* (BHV-1) infections. [1-4] Inactivated virus vaccines, while providing some protection, have not demonstrated the same levels of reproductive protection [2,5]. However, vaccination of naïve heifers with a MLV vaccine around the onset of standing estrus has been shown to have negative effects on corpus luteum (CL) function [6, 7] and pregnancy success [8]. The effect on luteal function was not seen in previously vaccinated heifers [9]. This negative impact on pregnancy success has been reported on not only first service conception rates, but also on a low percentage of animals conceiving on second service [8, 10], and in some heifers infected with BHV-1 at or near estrus, normal estrous cycles could be delayed for up to two months [11]. Furthermore, BVDV antigen has been detected in the ovary up to 30 days post-vaccination [12] although the impact of this finding is not clear.

The effects of vaccination on estrus synchronization and conception rates are highly variable. Animals vaccinated with a MLV vaccine at least two times prior to synchronization protocol (second dose administered 90 days prior to peak breeding day), and then vaccinated again 40 or 3 days prior to peak breeding (three doses total) resulted in no difference in conception rates between treatments [13]. In an additional study in which the vaccination history was not reported and titer concentrations were not determined, heifers were vaccinated with a MLV vaccine either 30 or 9 days prior to the start of the AI breeding program with no differences in estrous response or pregnancy success between treatments [14]. A recent study compared MLV to inactivated vaccine in naive heifers reported non-significant differences in pregnancy success between treatments [15]. These heifers were vaccinated with either a MLV or inactivated vaccine 40 and 10 days prior to a 45 day breeding season (n = 30) or 61 and 31 days prior to a 45 day breeding season (n = 30).

Among heifers vaccinated 40 and 10 days prior to breeding, heifers vaccinated with the inactivated vaccine had a 20% greater pregnancy success compared to MLV vaccine, and among heifers vaccinated at 61 and 31 days prior to breeding with an inactivated vaccine had a 15% greater pregnancy success compared to heifers vaccinated at 61 and 31 days prior to breeding with a MLV vaccine. The same study showed no impact on reproductive parameters in BHV-1 sero-positive heifers [15].

In the previously mentioned study animal numbers were small, limiting the ability to detect small differences in pregnancy success. However, with the large numerical differences noted between those vaccinated with a MLV vaccine and non-vaccinated controls, the question arises, does vaccination 30 days prior to the start of an AI breeding season negatively influence breeding season pregnancy success? Therefore, the objective of the present study was to examine the differences in pregnancy success between beef females vaccinated with either a MLV vaccine or an inactivated vaccine when compared to a non-vaccinated control group, with sufficient power to detect a difference of less than 10 % in pregnancy success between groups.

Materials and Methods

Animals

Protocols were reviewed and approved by both the South Dakota State University and the North Dakota State University institutional animal care and use committees. All animals were managed according to herd standard operating procedures utilizing routine animal husbandry procedures.

Well vaccinated mature post-partum beef cows and beef heifers (n = 1436) in seven unique herds over 2 years (Table 1) were vaccinated according to the label (30 days prebreeding) with 1) a modified live vaccine 2) an inactivated vaccine, or 3) saline (non-vaccinated control; Figure 1). Prior to year 1 all cows had previously received Bovi-Shield GOLD® FP® 5 L5 HB annually prior to the start of the breeding season. In year 1, cows were grouped by parity, stratified by calving date and randomly assigned to one of the three treatments. In year 2, animals in herds 5 and 6 received the same treatment as in year 1.

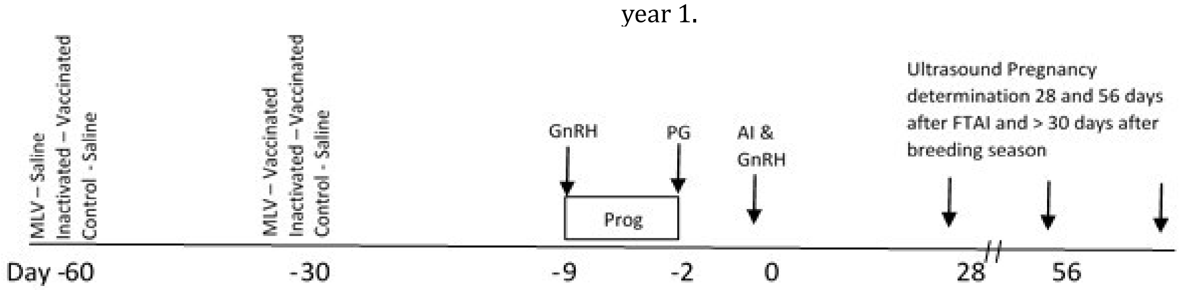

Figure 1. Timeline for synchronization events and vaccination. PG-Prostaglandin F-2alpha (Lutalyse); Prog-Progesterone (EAZI-BREED™ CIDR® implants); GnRH-Gonadotropin releasing hormone; AI- Artificial Insemination

In both years, all animals were synchronized with the 7-day CO-Synch + CIDR protocol and artificially inseminated at the appropriate time after CIDR removal (cows 60 to 66 hours;

Herd	Year	Treatment	No. of Animals	Age (Range)	DPP[1] (Range)	AI[2] (%)	56 day[3] (%)	Season[4] (%)
1	1	MLV	50	5.8 (3 to 13)	77 (33 to 127)	54.0%	90.0%	96.0%
1	1	Inactivated	50	5.2 (3 to 11)	77 (34 to 101)	62.0%	92.0%	100%
1	1	Control	51	5.5 (3 to 13)	75 (37 to 99)	64.7%	82.3%	96.1%
2	1	MLV	48	6.2 (3 to 13)	79 (33 to 99)	47.9%	85.4%	95.8%
2	1	Inactivated	49	5.8 (3 to 13)	76 (29 to 97)	46.9%	89.8%	100%
2	1	Control	49	5.9 (3 to 13)	76 (31 to 97)	49.0%	95.9%	95.9%
3	1	MLV	29	2	103 (67 to 120)	41.3%	62.0%	86.2%
3	1	Inactivated	30	2	102 (67 to 123)	73.3%	90%	96.7%
3	1	Control	29	2	102 (67 to 121)	41.4%	79.3%	96.6%
4	1	MLV	50	heifers	N/A	36%	84%	92%
4	1	Inactivated	49	heifers	N/A	34.5%	85.7%	93.8%
4	1	Control	50	heifers	N/A	30%	88%	86%
5	1	MLV	67	6.9 (5 to 11)	86 (49 to 107)	32.8%	76.1%	94.0%
5	1	Inactivated	65	7.0 (5 to 11)	87 (50 to 108)	29.2%	76.9%	95.3%
5	1	Control	63	7.1 (5 to 11)	86 (52 to 104)	38.1%	73.0%	85.7%
6	1	MLV	71	3 (2 to 4)	97 (45 to 128)	60.6%	80.3%	91.5%
6	1	Inactivated	71	3 (2 to 4)	97 (53 to 127)	60.6%	88.7%	95.8%
6	1	Control	72	3 (2 to 5)	97 (58 to 129)	62.5%	95.8%	98.6%
7	2	MLV	32	heifers	N/A	50.0%	50.0%	87.5%
7	2	Inactivated	32	heifers	N/A	59.4%	65.6%	90.6%
7	2	Control	32	heifers	N/A	50.0%	53.1%	87.5%
5b	2	MLV	79	6.7 (2 to 11)	63 (34 to 86)	41.8%	45.6%	84.8%
5b	2	Inactivated	57	6.5 (2 to 10)	64 (46 to 93)	49.1%	59.6%	89.5%
5b	2	Control	63	6.6 (2 to 11)	64 (40 to 93)	57.8%	60.9%	89.1%
6b	2	MLV	63	3 (2 to 4)	80 (53 to 102)	52.4%	66.7%	92.0%
6b	2	Inactivated	68	3 (2 to 4)	77 (51 to 99)	55.9%	64.7%	95.6%
6b	2	Control	67	3 (2 to 4)	75 (51 to 97)	49.3%	58.2%	89.6%

[1]Days Postpartum (interval from calving to fixed-time AI)
[2]AI Conception Rate
[3]Percentage of animals pregnant on day 56 of the breeding season
[4]Percentage of animals pregnant at the end of the breeding season

Table 1. Selected characteristics of each herds.

heifers 52 to 56 hours). Cows remained separated from bulls for at least 10 days after AI. Pregnancy success and fetal age were determined by transrectal ultrasonography 28 days after AI (year 1 and 2), 56 days after AI (year 1), and > 30 days after the end of the breeding season (year 1 and 2).

Vaccination

In year 1, mature cows in group 1 were administered their treatment, sterile saline at 60 days prior to fixed-time AI and a commercially available MLV vaccine (Bovi-Shield GOLD FP 5 L5 HB, Zoetis, Parsippany, NJ) containing BHV- 1, BVDV (types 1 and 2), bovine parainfluenza-3, and bovine respiratory syncytial virus, as well as Leptospira canicola, *L. gryppotyphosa, L. hardjo, L. pomona*, and *L. icterohaemorrhagiae* bacterin at 30 days prior to fixed-time AI. Virgin heifers received the same vaccine (Bovi-Shield GOLD FP 5 L5 HB) 60 and 30 days prior to fixed-time AI. Mature cows and virgin heifers in group 2 were vaccinated at 60 and 30 days prior to fixed-time AI with a commercially available inactivated vaccine (Vira Shield® 6+L5 HB, Elanco, Greenfield, IN). The inactivated vaccine contained the following viral fractions: BHV-1, BVDV (types 1 and 2), bovine parainfluenza-3, and bovine respiratory syncytial virus, and the following bacterial fractions: *Leptospira canicola, L. gryppotyphosa, L. hardjo, L. pomona*, and *L. icterohaemorrhagiae*. Cows in group 3 were vaccinated at 60 and 30 days prior to fixed-time AI with sterile saline.

In year 2, virgin heifers, and mature cows in group 1 were vaccinated in the same way as year 1. However, mature cows in group 2 only received a single vaccine at 30 days prior to fixed-time AI.

Synchronization and Breeding

Ten days prior to the start of the breeding season, all animals were administered progesterone as a vaginal insert (EAZI-BREED ™ CIDR® Cattle Insert, Zoetis, Parsippany, NJ) and gonadorelin hydrochloride (GnRH; Factrel® Injection, Zoetis, Parsippany, NJ; Figure 1). Vaginal inserts were removed and the heifers were administered dinoprost tromethamine [Prostaglandin F2-alpha (PGF); Lutalyse® Sterile Solution, Zoetis, Parsippany, NJ] IM on day -3. Artificial insemination occurred at the appropriate time after CIDR removal (cows 60 to 66 hrs; heifers 52 to 56 hrs) and an injection of GnRH was given concurrent with insemination. All females remained separated from fertile bulls for at least 10 days after AI. Pregnancy success and fetal age was determined by transrectal ultrasonography on day 28 after AI (year 1 and 2), 56 days after AI (year 1), and > 30 after the end of the breeding season (year 1 and 2). Presence of a fetal heartbeat was used to determine fetal viability and crown-rump length was used to determine fetal age.

Statistical Analysis

Data were initially analyzed using the GLIMMIX procedure in SAS and included treatment, year, and the treatment by year interaction in the model. There was no treatment by year interaction (P > 0.66) therefore herd was included in the statistical model as a random variable to account for unknown differences between herds/years. Therefore, data were analyzed using the GLIMMIX procedure in SAS and included treatment, day postpartum, and the treatment by day postpartum interaction in the model and using the treatment by herd interaction as the error term. The goal of analyzing the data this way was to enable valid data interpretation across all herds.

Some cows were sold prior to calving for non-reproductive reasons (age, health, and disposition; n = 132). Thus calving data was calculated on cows exposed to breeding with cows sold for non-reproductive reasons removed from the analysis (n = 1304). Data were analyzed using the GLIMMIX procedure in SAS and included treatment, day postpartum, and the treatment by day postpartum interaction in the model and using the treatment by herd interaction as the error term. All data are reported as means ± standard error of the mean.

Results

Synchronization and breeding

Days postpartum influenced conception rates with heifers and short postpartum cows having decreased AI conception rates compared to cows that were further postpartum (P < 0.05; Table 2). At the day 56 pregnancy determination (AI and 1 estrus cycle with the bull) the effect of postpartum interval on pregnancy rates remained, with short postpartum cows (< 80 days post-partum at the start of the breeding season) having decreased pregnancy rates compared to cows that were > 80 days postpartum. After the breeding season, heifers still had decreased pregnancy rates compared to cows that were > 120 days postpartum at the start of the breeding season, but there was no difference in pregnancy rates between any groups of cows.

Days Postpartum	n	AI Conception (%)	Day 56 Pregnancy Success (%)	Breeding Season Pregnancy Success (%)	Early Embryo Loss (%)
Heifers	251	33 ± 4^{a}	90 ± 2^{ab}	94 ± 2^{a}	4 ± 2
< 80	481	35 ± 5^{a}	88 ± 3^{a}	96 ± 2^{ab}	2 ± 1
81 to 100	361	43 ± 4^{b}	92 ± 2^{bc}	96 ± 1^{ab}	1 ± 1
101 to 120	235	50 ± 4^{bc}	93 ± 1^{c}	98 ± 1^{b}	1 ± 1
>120	171	57 ± 4^{c}	91 ± 1^{abc}	98 ± 1^{b}	1 ± 1

Means within a column having difference superscripts are different
^{abc}P< 0.05

Table 2. Impact of Postpartum Interval on Pregnancy Success.

At 56 days after AI, MLV animals had decreased pregnancy success compared to the Control groups (P ≤ 0.01), but there was no difference between the Inactivated and Control group.

Following the breeding season, pregnancy success was similar between MLV and Control (*P* = 0.34; Table 3) as well as between the Inactivated and Control (*P* = 0.14; Table 3). While not intended as a comparison between the two vaccine groups, day 28 conception rates tended to differ between MLV and Inactivated groups (*P* = 0.055) and conception rates in the Inactivated group were greater (*P* = 0.01).

Vaccine	n	AI Conception (%)	Day 56 Pregnancy Success (%)	Breeding Season Pregnancy Success (%)	Early Embryo Loss (%)
Modified Live	489	40.0 ± 4[a]	88.9 ± 2[c]	95.2 ± 2[c]	2 ± 1
Inactivated	471	46.5 ± 4[b]	93.2 ± 2[d]	98.0 ± 1[d]	2 ± 1
Saline	476	43.3 ± 4[ab]	92.5 ± 2[d]	96.4 ±1[cd]	2 ± 1

Means within a column having different superscripts are different
[ab]P = 0.055, [cd]P ≤ 0.01

Table 3. Impact of Vaccine on Pregnancy Success.

Calving

The percentage of cows that calved between day 1 and 12 of the calving season did not differ between MLV and Control groups (*P* = 0.50; Table 4) or between Inactivated and Control groups (*P* = 0.31). There was no difference in the percentage of cows that calved between days 13 to 30 among treatments (*P* > 0.41). Furthermore, there was no difference in percentage of cows that calved after day 30 among treatments (*P* > 0.15). When cumulative calving data was evaluated (Table 4), the percentage of cows that calved by day 30 of the calving season did not differ between MLV and Control groups (*P* = 0.16) or between Inactivated and Control groups (*P* = 0.78). Furthermore, the total percentage of cows that calved did not differ between MLV and Control (*P* = 0.86), but was decreased (*P* ≤ 0.02) in MLV and Control groups compared to Inactivated group.

Vaccine	n	Day 1 to 12	Day 13 to 30	Day >30	Day 1 to 30	Calving Season
Modified Live	489	50.0 ± 4[a]	21.3 ± 4	27.4 ± 6	69.5 ± 4[a]	94.8 ± 2[c]
Inactivated	471	56.0 ± 4[b]	23.5 ± 4	23.2 ± 5	74.4 ± 3[b]	97.3 ± 1[d]
Saline	476	52.4 ± 4[ab]	21.2 ± 3	26.4 ± 5	73.6 ± 4[ab]	95.0 ± 2[c]

Means within a column having different superscripts are different
[ab]P < 0.10, [cd]P ≤ 0.02

Table 4. Impact of Vaccine on Calving Distribution.

Discussion

Days postpartum influenced conception rates with heifers and cows less than 80 days postpartum having decreased AI conception rates compared to cows that were greater than 100 days postpartum. This is similar to other published studies where conception rates were improved among animals with longer postpartum intervals compared to animals with shorter postpartum intervals [16, 17]. Furthermore, there was no difference in AI or breeding season conception rates between animals vaccinated with MLV or saline or between animals vaccinated with an inactivated vaccine and saline. Few studies have attempted to measure the effect of vaccinating well vaccinated (nonnaïve) beef animals [18, 19]. One deficiency in these studies is the lack of true control (non-vaccinated animal) against which to measure conception rates. In this regard, it is difficult to draw a conclusion regarding vaccination timing and its effect on ovarian function and conception rates in well vaccinated animals. A recent study in dairy cattle reported no difference in conception rates between vaccinating previously vaccinated primiparous dairy cows (3 MLV as calves and 1 prebreeding as a heifer) with either a MLV or inactivated vaccine 45 days prior to FTAI [18].

In the present study there was only a significant difference between MLV and saline controls and between MLV and inactivated for the 56 day pregnancy success. The importance of the 56 day pregnancy determination is that this represents cows that will calve during the first 30 days of the calving season; numerous studies have reported that cows that calve early in the calving season are more likely to conceive during the subsequent breeding season, with increased longevity in the herd compared to animals that calve later in the calving season [20-22]. It was surprising that among well vaccinated animals, even though neither treatment group was statistically different from controls, there tended to be a difference in AI conception rates between animals vaccinated with a MLV and an inactivated vaccine. This difference was significant at day 56 and after the breeding season between animals vaccinated with a MLV and an inactivated vaccine. However, the reason for this difference is unknown since a similar difference was not seen between the MLV and controls.

Any discussion on vaccine safety must be coupled with the ability of the various vaccine options to provide reproductive and fetal protection. If disease challenge or the potential of exposure were not of concern then omitting reproductive vaccination would be the ultimate “safe” intervention. However, the benefit of reproductive vaccines in breeding age animals has been shown by multiple studies indicating both better and longer protection when MLV BVDV and BoHV1 vaccines are used [22].

In summary, while vaccination with a MLV vaccine 30 days prebreeding tended to decrease pregnancy success to AI, vaccination with either a MLV or inactivated reproductive vaccine 30 days pre-breeding resulted in similar pregnancy rates and calving distributions as non-vaccinated Controls. The findings suggest that the potential small decrease in reproduction caused by MLV vaccination should be balanced with the increased protection provided by these vaccines when making vaccine decisions.

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