Influence of Modified Live Vaccines on Reproductive Performance in Beef Cattle.

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Introduction

Reproductive performance is of critical importance to the profitability of a cow-calf producer and numerous factors (e.g. heifer development, nutrition, cow body condition at calving, bull fertility, environment, etc.) affect reproductive efficiency, but the caveat to reproductive management is the things you do well do not compensate for the mistakes you make. Instead, the mistakes you make cancel out all the things you do well. Thus to have optimal reproductive efficiency we need to evaluate the details and how they can impact efficiency. One of these details that has the potential to create significant losses is infectious diseases. Infectious diseases affecting reproduction can create losses all throughout the reproductive cycle by decreasing ovulation rates, fertilization rates, embryonic survival rates, and fetal survival rates. Thus the cow-calf industry spends millions of dollars a year to vaccinate cows against diseases that can impact reproductive efficiency. It is important to realize that vaccination of all individuals within a population does not mean that each individual becomes immune to the agent in question. Individual animal responses to vaccine are subject to biological variation, in which a few animals respond extremely well to the vaccine, a few respond poorly to the vaccine, and most animals respond in an intermediate fashion. Therefore, the goal of a vaccination program is not to render each individual immune to disease; rather it is to stimulate sufficient immunity in a sufficient number of animals such that an epidemic, or widespread outbreak, does not occur, and all vaccine programs should be designed with appropriate guidance from your local veterinarian.

Infectious Diseases Affecting Reproduction:

Two of the diseases that are often vaccinated for are viruses (Bovine Viral Diarrhea and Infectious Bovine Rhinotracheitis or bovine herpesvirus 1). Both of these viruses can impact reproductive performance through decreased conception rates and embryonic/fetal losses.

Bovine Viral Diarrhea (BVD) virus

Evidence of exposure to BVD virus is widespread throughout cattle herds in the United States and the world. The reproductive effects of BVD possibly surpass its other effects in economic importance, when the occurrence of persistently infected animals is factored in. Signs of BVD in the cow herd depend on the stage of gestation in which the cow or heifer is infected. Early gestation infection results in low conception rates due to early embryonic death. Infection in mid-gestation may result in the formation of

persistently infected calves, which occurs as a result of infection during a period of fetal development (roughly between 40 and 120 days of gestation) in which the fetus is differentiating its own cells from foreign materials. The result is a calf that has incorporated the virus into its own body and sheds high levels of virus persistently throughout its lifetime. Later infections may result in congenital defects, late-term abortions, or the birth of congenitally infected calves, which are weaker and more prone to illness than normal calves. BVD virus is spread through many body fluids including saliva, respiratory secretions, and feces. The virus does not persist in the environment but can survive long enough to be transmitted via infected equipment, needles, and palpation sleeves.

Infectious Bovine Rhinotracheitis (IBR, "Red-nose")

IBR virus is also termed BHV-1, or "bovine herpesvirus 1." Being a herpes virus (in the same family as viruses causing cold sores in people), it has a propensity to become "latent" or dormant in nerve clusters in the throat area or lower spine, and can re-activate during times of stress. Because of this, any animal exposed to IBR in the past could potentially shed the virus to susceptible animals. IBR is shed and transmitted in nasal secretions and aerosols from infected animals. In addition to its effects on the respiratory tract, IBR virus affects reproduction by its effects on the ovaries, uterus, and developing embryo or fetus. The result can be infertility or early embryonic death, but in addition, IBR is one of the most frequently diagnosed viral causes of late-term (5^{th} to 9^{th} month of gestation) abortions.

Types of Vaccine

Modified-live virus (MLV) vaccines stimulate the immune system by actively infecting host cells. In general, these types of vaccines are considered to be more cross-reactive and broader in their immune system stimulation (antibody production and cell-mediated immunity), exhibit longer duration of effect and provide more flexibility in timing of administration. Modified live virus vaccines also carry with them the potential to revert to virulence and inflict the damage they are designed to prevent. Inactivated virus vaccines (IVV) are safe to use in a wide variety of circumstances, yet carry the general considerations that their effects are less broad and of shorter duration compared to MLV vaccines (Kelling, 2007).

Impact of Vaccination against IBR and BVD on Reproductive Performance

The question is often asked; can the time and labor involved in heifer development be reduced by vaccinating heifers at the start of the synchronization protocol?

The effects of vaccination on estrus synchronization and conception are variable. A study in which the vaccination history was not reported and titer concentrations were not determined indicated that vaccination with a MLV at time of the start of a synchronization protocol (day -9, with AI on day 1 to 5) did not impact estrous response or pregnancy success (Stormshak et al., 1997). In another study, animals were vaccinated with a MLV vaccine at least two times prior to synchronization protocol (the second dose being administered at day -90 prior to peak breeding day). The heifers were then

revaccinated either at -40 d or -3 d prior to peak breeding (three doses total) and no differences in conception rates were observed (Bolton et al., 2007). However, several studies have reported negative impacts on pregnancy success by vaccinating naïve heifers with a MLV around time of breeding (Miller et al., 1989; Chiang et al., 1990; Miller, 1991; Perry et al., 2013).

Naïve Animals

Decreases in fertility by vaccination of naïve heifers around the onset of standing estrus are likely mediated through negative effects on corpus luteum (CL) function (Van der Maaten and Miller, 1985; Smith et al., 1990), with the hypothesis that the virus can get inside large dominant follicles and disrupt the formation and development of the corpus luteum. However, recently developed estrous synchronization or fixed-time AI protocols in heifers and cows try to control follicular development by inducing ovulation at the start of the synchronization protocol; therefore, insemination should occur on the second ovulation after the start of the protocol (Lamb et al., 2010; Grant et al., 2011). Therefore, a recent study investigated the effect that vaccinating naïve heifers with either a Modified Live Vaccine (MLV) or inactivated virus vaccine (IVV) at the time of the first induced ovulation of a fixed-time AI synchronization protocol has on changes in hormone production, estrous cycle length, and pregnancy success (Perry et al., 2013).

In this study, no control heifers (nonvaccinated) experienced an abnormal estrous cycle following AI. An abnormal estrous cycle was defined as an estrous cycle less than 15 d (concentrations of P4 decreased to < 1 ng/mL prior to day 15 after AI) or concentrations of P4 never increased above 1 ng/mL. Heifers vaccinated 36 and 8 days before AI with an IVV (ViraShield® 6VL5HB) experienced 10% (2/21) abnormal cycles and heifers vaccinated 8 days before AI with an IVV (ViraShield® 6VL5HB) experienced 14% (1/7) abnormal cycles. There was no difference between these groups (P = 0.72), and both were similar to the control group (P = 0.31 and 0.22, respectively). A greater percentage of heifers vaccinated with a MLV 8 days before AI (BoviShield Gold® FP 5 VL5) had abnormal estrous cycles [38% (8/21)] compared to control heifers (P = 0.02). In addition, bulls were with the heifers for only14 d following AI, thus heifers only had one chance to conceive unless they experienced an abnormal estrous cycle. Of the heifers that experienced an abnormal estrous cycle, 100% of heifers vaccinated 36 and 8 days before AI with an IVV (2/2) and heifers vaccinated 8 days before AI with an IVV (1/1) conceived during the breeding season. However, only 38% of heifers vaccinated with a MLV 8 days before AI (3/8) conceived during the return cycle.

When heifers that conceived following an abnormal estrous cycle were considered open to allow comparison of conception rates following the synchronization protocol, pregnancy rates were similar (P = 0.52) between control heifers [90% (9/10)] and heifers vaccinated 36 and 8 days before AI with an IVV [81% (17/21)]. Both control and heifers vaccinated 36 and 8 days before AI with an IVV had greater pregnancy rates compared to heifers vaccinated with a MLV 8 days before AI [33% (7/21); P < 0.01 and < 0.01, respectively]. Pregnancy rates for heifers vaccinated only 8 days before AI with an IVV [71% (5/7)] were intermediate. They were similar to control (P = 0.32) and heifers

vaccinated 36 and 8 days before AI with an IVV (P = 0.59), but tended (P = 0.08) to be greater than heifers vaccinated with a MLV 8 days before AI.

Thus, it has been well established that vaccination of naïve heifers with a MLV around time of breeding has negative impacts on corpus luteum development and on pregnancy success (Miller et al., 1989; Chiang et al., 1990; Miller, 1991) even when utilizing a synchronization protocol that induces ovulation of the dominant follicle at the start of the protocol (Perry et al., 2013). 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 during the second service following vaccination (Chiang et al., 1990; Perry et al., 2013), and in some heifers infected with BHV-1 at or near estrus, normal estrous cycles were delayed for up two months (Miller and Van der Maaten, 1985). Furthermore, BVDV antigen has been detected in the ovary up to 30 d post-vaccination [(Grooms et al., 1998) although the impact of this finding is not clear.

Previously Vaccinated Animals

The same effect of abnormal luteal function that occurs following vaccination of naïve animals has not been reported when previously vaccinated heifers were

Table 1. Impact of vaccine on luteal function and pregnancy success in naïve animals.

Vaccine	Abnormal luteal function	AI Pregnancy Success (%)	Pregnancy Success (%) to second service	
1 dose Modified Live	8/21 (38%)[b]	7/21 (33%)[b]	3/8 (38%)	
1 dose Inactivated	1/7 (14%)[a]	5/7 (71)[ab]	1/1(100%)	
2 doses Inactivated	2/21 (10%)[a]	17/21 (81%)[a]	2/2 (100%)	
Saline	0/10 (0%)[a]	9/10 (90%)[a]	-----	

Means within a column having different superscripts are different [ab]P < 0.05
Adapted from Perry et al., 2013

vaccinated with a MLV (Spire et al., 1995). Few studies have attempted to measure the effect of vaccinating well vaccinated (non-naïve) beef animals (Stormshak et al., 1997; Bolton et al., 2007), and one deficiency in these studies is the lack of true control (non-vaccinated animals) 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 (Walz et al., 2015b). In another recent study (Walz et al., 2015a), heifers were vaccinated with either a MLV or inactivated vaccine 40 and 10 d prior to a 45 d breeding season (n = 30) or 61 and 31 d prior to a 45 d breeding season (n = 30). Among heifers vaccinated 40 and 10 d prior to breeding, heifers vaccinated with the inactivated vaccine had a 20% greater pregnancy success compared to MLV vaccine, and heifers vaccinated at 61 and 31 d prior to breeding with an inactivated vaccine had a 15% greater pregnancy success compared to heifers vaccinated at 61 and 31 d prior to breeding with a MLV vaccine. However, in this study

animal numbers were small, limiting their ability to detect small differences in pregnancy success. Another recent study (Walz et al., 2017), reported a 20% decrease in pregnancy success between heifers vaccinated with 2 doses of

MLV compared to heifers vaccinated with 2 doses of saline, but again the animal numbers were small (n = 60 and 15; respectively). However, with the large numerical

Table 3. Impact of BVD and IBR challenge following vaccination with either a MLV or IVV.

Vaccine	Abortions following BVD and IBR challenge (%)	Detection of BVDV in fetuses and/or calves	Detection of IBR in fetuses and/or calves	Detection of BVD and/or IBR in fetuses and/or calv
Modified Live	3/23 (13%)[a]	2/23 (9%) [a]	2/23 (9%) [a]	4/24 (17%) [c]
Inactivated	1/22 (5%)[a]	0/22 (0%) [a]	0/22 (0%) [a]	0/22 (0%) [d]
Saline	11/15 (73%)[b]	14/15 (93%) [b]	8/15 (53%) [b]	15/15 (100%) [b]

Means within a column having different superscripts are different [a,c,d vs b]$P < 0.01$, [cd]$P = 0.045$
Adapted from Walz et al., 2017

differences noted between those vaccinated with a MLV vaccine and non-vaccinated controls in these two studies, the question arises, does vaccination 30 days prior to the start of an AI breeding season negatively influence breeding season pregnancy success? Therefore, a study was conducted to examine the differences in pregnancy success between beef females vaccinated with either a MLV (BoviShield Gold® FP 5 L5 HB) vaccine or an inactivated (ViraShield® 6 L5 HB) vaccine 30 days before the breeding season, with sufficient power to detect a difference of less than 10 % in pregnancy success between groups (9 herds with 1436 animals) (Perry et al., 2016).

Conception rates to the fixed-time AI tended to differ between MLV treated animals and IVV treated animals ($P = 0.055$), but control animals were intermediate with no difference in conception rates between MLV and Control ($P = 0.21$) or between IVV and Control ($P = 0.49$). When pregnancy was determined on day 56 of the breeding season (AI conceptions plus 1 return estrus) conception rates in the IVV group were greater ($P = 0.01$) compared to the MLV group. Animals treated with MLV also had

Table 2. Impact of vaccine on pregnancy success among previously vaccinated animals.

Vaccine	AI Conception (%)	Day 56 Pregnancy Success (%)	Breeding Season Pregnancy Success (%)	Early Embryo Los (%)
Modified Live	40.0 ± 4^{a}	88.9 ± 2^{c}	95.2 ± 2^{c}	2 ± 1
Inactivated	46.5 ± 4^{b}	93.2 ± 2^{d}	98.0 ± 1^{d}	2 ± 1
Saline	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]$P \leq 0.01$
Adapted from Perry et al., 2016

decreased pregnancy success compared to the Control ($P \leq 0.01$), but there was no difference between IVV and Control. Following the breeding season, pregnancy success

was similar between MLV and Control (P = 0.34) as well as between the Inactivated and Control (P = 0.14), but there was still a difference between MLV and IVV (P = 0.01).

It is commonly thought that IVV provide some protection against these viruses, but the same level of protection as a MLV is not achieved (Zimmerman et al., 2007; Rodning et al., 2010). However, a recent publication reported that heifers vaccinated with a MLV prior to their first breeding season and then vaccinated with a Chemically Altered/Inactivated vaccine CA/IV (CattleMaster Gold FP5) before their second breeding season had similar levels of abortions following both a BVD and IBR challenge as animals vaccinated with a MLV (Bovi-Shield Gold 5 FP) before their second breeding season (Walz
et al., 2017).

Therefore, with CattleMaster Gold FP5's ability to protect the fetus from abortion and virus, a field study was conducted to examine the differences in pregnancy success between beef females vaccinated with either a MLV (BoviShield Gold® FP 5 L5 HB) vaccine or a CA/IV (CattleMaster Gold FP5) vaccine between 27 and 89 days before the breeding season, with sufficient power to detect a difference of less than 10 % in pregnancy success between groups (10 herds with 1565 animals) (Perry et al., 2017).

Table 4. Impact of vaccine and timing of vaccine on pregnancy success among previously vaccinated animals.

Vaccine	AI Conception (%)	Breeding Season Pregnancy Success (%)	Breeding Season Pregnancy Success (%)
Modified Live	52.0%[a]	95.2 ± 2	95.2 ± 2
Chemically Altered/Inactivated	60.0%[b]	96.4 ±1	96.4 ±1
27 to 30 days	52%[a]		
30 to 37 days	52%[a]		
38 to 89 days	64%[b]		

Means within a column having different superscripts are different [ab]P < 0.05
Adapted from Perry et al., 2017

Conception rates to AI were greater in the CA/IV vaccine group compared to the MLV vaccine group (P = 0.05; 60% vs 52%). Furthermore, interval from vaccination with either vaccine until AI also influenced conception rates (P = 0.02). Animals vaccinated 27 to 30 d prebreeding and animals vaccinated 30 to 37 days prebreeding had similar (P = 0.98; 52% and 52%) conception rates; however, both were decreased compared to animals vaccinated 38 to 89 d prebreeding (P < 0.03; 64%). There was no treatment by interval interaction (P = 0.79), indicating at all three intervals conception rates to the CA/IV vaccine were increased compared to the MLV. Furthermore, there was no effect of treatment (P = 0.18) or treatment by interval interaction (P = 0.17) on breeding season pregnancy rates. In summary, vaccination of well-vaccinated beef cows and heifers with a MLV vaccine pre-breeding (28 to 89 d) decreased AI conception rates compared to a CA/IV vaccine.

Conclusions

So where do these studies leave us on the impact of virus vaccines on reproductive success? Vaccines against infectious reproductive diseases are valuable tools in the prevention of these diseases, as outbreaks of these diseases can be potentially devastating to a beef herd. This emphasizes the importance of proper vaccination of females before they enter the breeding herd.

However, evidence is growing that MLV versions of these vaccines can have negative effects on reproductive management in well managed herds. Studies utilizing different pre-breeding vaccination protocols and intervals indicate that MLV vaccines, even when given at labeled pre-breeding intervals, may negatively affect reproductive parameters compared to cattle vaccinated with inactivated vaccines. In light of this research, it appears the choice of pre-breeding vaccine product type and timing is one to carefully consider. Important to this consideration is the level of exposure that a given herd may have, as none of these large prebreeding studies were carried out in the face of disease challenge and do not address the question of protection in the face of an infectious reproductive disease exposure. Future research will help determine how to strike the best balance between appropriate disease protection and minimizing harmful effects from the vaccines themselves. It is reasonable to expect that striking this balance will be different for each individual cattle operation, making it imperative that cattle producers consult their veterinarian and weigh all available information when making decisions about pre-breeding vaccinations in their herds.

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