

BVD/BHV 1 Vaccination and Reproduction: What's New?

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Bovine viral diarrhea virus (BVD) and bovine herpes virus 1 (BHV1) are both well-known reproductive pathogens. Vaccination against these pathogens has been a substantial component of control programs for many years. The body of published literature concerning the impact of vaccination against BVD and BHV1 on reproductive performance is substantial and a complete review of that literature is beyond the scope of this document. Fortunately several recent reviews of this body of literature are available and the reader is referred to those publications for more detailed analysis of the published literature.¹⁻⁶ Even though vaccines against BVD and BHV1 have been used for many years, controversy still exists over the most appropriate use of inactivated/killed virus (KV) or modified live virus (MLV) vaccines at various times in the production cycle. The purpose of this document is to provide a brief review of that controversy and provide an update based on the results of recent published studies. Manufacturer trade names of vaccines may be mentioned when appropriate for making specific comparisons but this document should not be viewed as an endorsement or criticism of any particular product. Any mention of specific products will be based directly on the results of published studies.

Efficacy or KV versus MLV vaccines

It is generally accepted that MLV vaccines promote a faster, longer lasting, more robust immune response when compared to KV vaccines. This premise is generally based on the fact the MLV vaccines replicate within the host and therefore more closely mimic a natural infection. There is widely held belief that MLV vaccines stimulate a stronger cell mediated immunity (CMI) response than killed vaccines, again based on the fact that MLV vaccines replicate within the host. That being said, studies have demonstrated the ability to KV vaccines to induce a CMI response^{7,8} and provide protection from viral challenge.⁹

When considering the reproductive losses prevented by vaccination, the primary concerns are abortion caused by BHV1 and abortion or the development of persistently infected (PI) calves caused by BVD. The use of KV vaccine (Virashield 6) against BHV1 has demonstrated the ability to protect against abortion when heifers are challenged intravenously with virulent BHV1.¹⁰ In that study, 14/14 (100%) control heifers aborted while only 3/21 (14.3%) vaccinated heifers aborted. Grooms et al.¹¹ demonstrated the ability of a vaccine containing killed BVD-1 and BVD 2 (Cattlemaster GOLD FP 5L5) to provide protection from the development of PI calves when pregnant heifers were challenged by natural exposure to PI cattle. In that study, 14/14 (100%) fetuses from non-vaccinated controls were PI while only 4/15 (26.7%) fetuses from vaccinated heifers were PI. In a very recent study, Walz et al.¹² investigated the ability of three commercially available KV vaccines to provide protection against BVD challenge when pregnant heifers were exposed to PI cattle. In this study, PI occurred in 13/30 (43%) heifers vaccinated with Cattlemaster FP 5, in 27/29 (93%) heifers vaccinated with Virashield 6 L5 HB, in 18/30 (60%) heifers vaccinated with Triangle 10, and in 15/15 (100%) of non-vaccinated controls.

Numerous studies have demonstrated the ability of MLV vaccines to protect against reproductive losses to BVD and BHV1. Grooms et al.¹³ vaccinated heifers twice prebreeding with Express FP5 and subsequently challenged them by exposure to PI cattle and cattle acutely infected with BHV1. One vaccinated heifer aborted but the fetus was not evaluated and 4 of 10 control heifers aborted. BVD was detected in 0/19 (0%) calves from vaccinated heifers and in 10/10 (100%) fetuses/calves from non-vaccinated controls. BHV1 was not isolated from any fetuses/calves in this study. In an abstract presented at AABP, DeRoos et al.¹⁴ described a study in which Titanium 5 L5 provided 89% protection against BVD type 1 challenge and 91% protection against BVD type 2 challenge. Zimmerman et al.¹⁵ reported the effects of vaccination with Express FP 5 VL5 one year prior to intranasal challenge with BVD type 1b and BVD type 2a. Fetuses from all vaccinated heifers were protected from BVD infection. In the BVD type 1b challenge, 15/18 (83.3%) control fetuses were PI. In the BVD type 2a challenge, 21/22 (95.5%) control fetuses were PI. In a related study, Zimmerman et al.¹⁶ reported the effects of vaccination with Express FP5 VL5 either 8 months or 13 months prior to intravenous challenge with BHV1. In the heifers challenged 13 months after vaccination 1/13 (7.7%) fetuses was positive for BHV1 by virus isolation and polymerase chain reaction (PCR). In the heifers vaccinated 8 months prior to challenge, 3/19 (15.8%) fetuses were positive for BHV1 via virus isolation and 5/19 (26.3%) were positive

via PCR. In the non-vaccinated controls, 7/19 (36.8%) fetuses were positive for BHV1 via virus isolation and 18/19 (94.7%) were positive via PCR. Xue et al. reported a study investigating the ability of Vista 5, which contains BVD type 1a and BVD type 2 to protect against PI when heifers are challenged intranasally by BVD type 1b. Heifers received a single dose of vaccine prior to breeding. In the vaccinated group, 1/40 (4.3%) fetuses was PI while 20/20 (100%) of the fetuses from non-vaccinated controls were PI.

Studies reporting the results of both MLV vaccines and KV vaccines are uncommon. Rodning et al. reported the results of a study comparing three commercial vaccines for the ability to protect fetuses from PI following exposure of pregnant heifers to PI cattle. All vaccinates received 4 doses of vaccine between weaning and breeding. Two vaccinate groups received MLV vaccine (Bovishield Gold FP 5 or Pyramid 5) and the KV vaccine group received Virashield 6. In the non-vaccinated controls, 10/10 (100%) fetuses were PI. In the Virashield group, 2/18 (11.1%) fetuses were PI. None of the fetuses from either MLV vaccine group were PI. Results between vaccine groups and controls were statistically different while results between vaccine groups were not statistically significant.

Trying to sort through the results of numerous vaccine studies can be overwhelming. The publication of review studies with meta-analyses are very helpful for that purpose. Newcomer et al.¹ published a recent meta-analysis of studies investigating BVD vaccination. The results of that analysis indicate that vaccination against BVD reduces the risk of abortion by approximately 45% and the risk of fetal infection by approximately 85%. The use of MLV vaccines provided better protection against abortion and fetal infection compared to KV vaccines but the use of any vaccine was significantly better than no vaccination. A similar meta-analysis investigating BHV1 vaccination has been published more recently.² Evidence from that study indicates that BHV1 vaccination provided a 60% reduction in abortion risk compared to non-vaccinated controls. Both MLV vaccines and KV vaccines significantly reduced abortion risk due to BHV1.

Safety of MLV Vaccines

While it appears that MLV vaccines offer superior protection against reproductive loss in some situations, there are significant concerns about the use of MLV vaccines in some circumstances. The primary concerns with safety revolve around negative impacts of BHV1 on the ovary near the time of breeding and the risk of abortion when MLV vaccines are administered to pregnant animals.

Vaccination near Breeding

When heifers become viremic with BHV1 near estrus, infection of the developing corpus luteum (CL) can lead to CL necrosis, altered progesterone production and decreased fertility. There is a relatively large body of literature supporting these findings. Detailed review of this earlier literature is beyond the scope of this document but Chase et al.⁴ published a recent review on the safety of BHV1 MLV vaccines and the reader is referred to that publication for more detail. More recently, Perry et al.¹⁷ investigated the impact of vaccination with KV (Virashield 6 VL5HB) and MLV (Bovishield GOLD FP5 VL5) at the start of estrus synchronization. Heifers that were seronegative for BHV1 and BVD types 1 and 2 received Virashield 30 and 8 days prior to breeding, Virashield 8 days prior to breeding only, Bovishield 8 days prior to breeding or saline placebo. Heifers vaccinated with the MLV vaccine had lower pregnancy rates and a higher risk of abnormal estrus cycles compared to heifers that received the KV vaccine. It should be noted that this is an extra-label use of the MLV vaccine. The evidence is clear that viremia, either from natural infection or vaccination with MLV vaccine, near the time of estrus, can have a negative impact on fertility. The presence of cytopathic BVD in the ovary following vaccination has been documented¹⁸ but the significance is less well understood compared to that of BHV1.

The impact of MLV vaccination near breeding in previously vaccinated or exposed animals becomes less clear. All of the studies referenced above were performed in seronegative heifers. In recent years, studies investigating the impact of vaccination in previously vaccinated animals have been published. Walz et al.¹⁹ reported a study in which seronegative heifers were vaccinated with Express FP5 VL5 two days after the initial detected estrus. Heifers were vaccinated again 30 days later which corresponded to 10 or 30 days prior to synchronized natural breeding. Control heifers were vaccinated on the same schedule with a product containing leptospira and campylobacter antigens but not viral antigens (Citadel VL5). No significant reproductive impacts were detected based on interestrus interval,

proportion of heifers exhibiting estrus within 5 days of synchronization, serum progesterone concentration, pregnancy rate and pregnancies within the first 5 days of the breeding season. Neither BVD nor BHV1 were detected in fetal and ovarian tissues harvested between 44 and 62 days of gestation. It is difficult to directly compare the results of viral assays on ovarian tissue with the studies referenced above because the interval from vaccination to tissue collection was much longer. Walz et al.²⁰ also published a similar study in primiparous dairy cows in which cows were revaccinated with MLV vaccine (Express FP 10) or KV vaccine (Triangle 10) 17 days prior to the onset of a double ov-synch program. All cows had received four doses of MLV vaccine as calves or heifers. No differences were detected in pregnancy rate, serum progesterone concentrations, or BVD antibody titers. Cows receiving KV vaccine did have higher titers to BHV1 at the time of timed artificial insemination (TAI). Perry et al.²¹ reported the results of a large field trial to evaluate the impact of MLV and KV vaccine use on reproductive success. In that study, 1436 cows and heifers, all previously vaccinated with MLV, received either MLV vaccine or KV vaccine prebreeding according to label directions. All animals then underwent synchronized TAI with subsequent bull exposure. Conception rates to TAI were not different between MLV (40.0±4%) and controls (43.3±4%) or between KV (46.5±4%) and controls. The difference between MLV and KV tended toward significance ($p=0.055$). Pregnancy rate 56 days after AI was less for MLV (88.9±2%) than KV (93.2±2%) and controls (92.5±2%). Overall breeding season pregnancy success for MLV (95.2±2%) and controls (96.4±1%) or KV (98.0±1%) and controls were not different. Overall pregnancy rate between MLV and KV were different ($p=0.01$). The proportion of females calved by day 12 and day 30 of the calving season were similar between MLV and controls and between KV and controls. The proportion tended to be greater for KV compared to MLV ($p=0.09$).

Vaccination During Pregnancy

Vaccination of naïve pregnant heifers or cows with MLV vaccines poses a significant risk of abortion.²² Beginning in 2003, multiple MLV vaccines received a label for use in pregnant cows provided that the cows were vaccinated prior to pregnancy with the same vaccine and that they have been vaccinated within the past 12 months. The process by which these labels were achieved has been scrutinized in a recent review.⁴ In order to achieve the label claims, safety studies were conducted in large numbers of animals at various stages of gestation.²³ This study consisted of an intensive safety study and a larger field trial. The intensive study compared seronegative controls to animals vaccinated prebreeding with Bovishield FP4 L5. All cattle were then vaccinated with MLV vaccine between 160-220 days of gestation. For control heifers seronegative to BHV1, 6/11 (55%) aborted due to BHV1 while 0/59 previously vaccinated heifers aborted. The live calves born to the remaining controls were negative for pre-colostral antibody to BHV1. Thirteen BVD seronegative controls delivered live healthy calves. Of those calves, 9/12 (75%) had pre-colostral antibodies to BVD. All 59 previously vaccinated heifers delivered live calves and 58 of those calves were negative for pre-colostral antibodies to BVD. One calf nursed before sampling. In the larger field study, 1422 cows were vaccinated prebreeding with Bovishield FP4 L5. Controls received no further vaccination while the remaining cows received MLV vaccine during the first, second, or third trimester. There was no difference in abortion rate between any of the groups in the study. Currently at least 4 companies have MLV vaccine products labeled for use in pregnant cows. Review of those product labels reveals that each product label claim for use in pregnant cows is supported by studies similar to the one described above by Ellsworth.²³

It appears from reviewing the literature that most of the concerns about abortion subsequent to MLV vaccination revolve around the BHV1 component of the MLV vaccines. There have been reports of abortions occurring following MLV vaccination even when label directions are followed.²⁴ A review by O'Toole et al.²⁵ describes ten episodes of BHV1 abortion following vaccination with MLV vaccine. In all of the described cases, the BHV1 isolated was consistent with common vaccinal MLV BHV1 isolates based on methodology described by Fulton et al.²⁶ Using the same methodology, other studies have identified consistency between BHV1 isolates from vaccines with BHV1 isolates causing a variety of clinical syndromes.^{27,28} Interestingly, almost all of these cases occurred in the state of Wyoming. In a review²⁹ of data from 5 veterinary diagnostic labs from 2000-2011, Gould et al. reported a slight increase in the incidence of BHV1 positive abortions but they were unable to associate the increase with the use of MLV vaccines during pregnancy based on the available data.

Vaccination of Calves Nursing Pregnancy Cows

In addition to the specific label requirements for use in pregnant cows, MLV vaccines also have specific instructions for use in calves when those calves are nursing pregnant cows. The labels require that the cows receive the same MLV vaccine according to label directions prior to the vaccines being used in nursing calves. The concern is that the vaccinated calves will shed vaccinal MLV virus and expose the cows who are already pregnant again, thereby putting the pregnancy at risk if the cows do not have adequate immunity to prevent viremia. Kleiboeker et al. reported a lack of detectable shedding following vaccination of calves with Express 5. In this study, 18 seronegative calves were vaccinated and then co-housed with 4 seronegative pregnant cows for 42 days. Most vaccinated calves developed a transient viremia but virus could not be detected in nasal swabs assessed via PCR. Additionally, the 4 seronegative cows remained seronegative throughout the study. It appears that vaccination of nursing calves with MLV vaccine carries minimal risk of significant exposure of their pregnant dams.

Recommendations for Veterinarians and Producers

It is difficult to reach a concise conclusion regarding the use of MLV vaccines and the risk of reproductive loss. Although the use of MLV vaccines according to label directions appears to carry a low level of risk, there is still risk and losses may occur in some situations. Killed virus vaccines carry a much wider safety margin but appear to offer questionable protection, particularly against the development of BVD persistently infected calves.¹² The ideal vaccine may be one that contains a killed BHV1 fraction and a MLV BVD fraction but such a vaccine is not currently available. A genetically modified, temperature sensitive BVH1 is available in the Cattlemaster product line. The BVD in this product line is killed. This BHV1 only replicates in the cooler temperatures of the nasal passages and therefore does not pose a risk to the reproductive system. This vaccine line is labeled to protect against the development of PI calves but its performance was inadequate in the recent study by Walz et al.¹² Another possibility would be the use of MLV vaccines prebreeding in heifers to establish a strong immune response and then provide annual revaccination with the temperature sensitive BHV1 found in the Cattlemaster product line. This scenario was tested in a recent study by Walz et al.³⁰ In this study, 75 seronegative heifers were used. Thirty heifers were vaccinated twice prebreeding with Bovishield GOLD FP 5. The remaining 15 heifers remained as non-vaccinated controls. Half of the vaccinated heifers were revaccinated during their first pregnancy with Bovishield GOLD FP5. The other half were revaccinated with Cattlemaster GOLD FP5 during their first pregnancy (these were termed the combined vaccine group or CV). During their second pregnancy, all cows were exposed to 6 PI calves for 16 days. One week after PI exposure, the vaccinates were revaccinated with the same vaccine as before. Later in the second pregnancy, all cows were challenged via intravenous BHV1 challenge. In the MLV group, 3/23 cows aborted and fetal infection with BVD or BHV1 occurred in 4/23 calves. In the CV group, 1/22 cows aborted and fetal infection occurred in 0/22 calves. In the control group, abortion occurred in 11/15 cows and fetal infection occurred in 15/15 calves. The results from the vaccinated groups were significantly different from the control group but not from each other. A more recent study by Perry et al.³¹ investigated the effects of Bovishield GOLD FP5 L5 and Cattlemaster GOLD FP5 administered prebreeding in previously vaccinated beef cows and heifers. The prebreeding vaccines were administered 27 to 89 days prebreeding. The CV group had higher conception to AI than the MLV group (60% vs 52%, respectively). Overall breeding season success was not different between the groups. They also found that vaccination less than 30 days prebreeding reduced overall breeding season success compared to when vaccines were given 30-37 days prebreeding regardless of the vaccine used. These studies demonstrate that annual revaccination with MLV vaccine or CV vaccine during pregnancy in previously vaccinated heifers or cows may be a viable and safe option for control of BVD and BHV1 associated reproductive losses.

Conclusions

As mentioned above it is difficult to draw concrete conclusions regarding the safe use of MLV vaccines in breeding animals. It is well established that MLV vaccines induce a more rapid, stronger immune response compared to KV vaccines but that KV vaccines have a wider safety margin than MLV vaccines. Based on the literature reviewed here, it appears that while the use of MLV vaccines does carry some risks, those risk are relatively small. The risk of using MLV vaccines must be weighed against the comparatively stronger immune response produced by MLV vaccines. There is also clear evidence that using KV vaccines provides better protection than not using vaccines at all. Determining which option

is best will require assessment of the disease challenge risks on each farm along with the goals and risk tolerance of each producer.

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