

# Effective utilization of vaccination to protect against viral reproductive pathogens

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## Abstract

Bovine viral diarrhea virus (BVDV) and Bovine alphaherpesvirus-1 (BoHV-1) have long been recognized as major causes of reproductive disease in beef and dairy cattle. Enhancing immunity through prebreeding vaccination and annual revaccination of the cowherd provide important contributions to limiting reproductive losses associated with these viral infections and are also important control procedures to limit transmission of these viruses among cattle populations. While providing efficacy, vaccination should also be safe. Safety concerns are often associated with the BoHV-1 fractions, while efficacy concerns are often associated with BVDV fractions of multivalent vaccines. Vaccination against BVDV and BoHV-1 effectively decrease risk of fetal infection, including abortions, birth of persistently infected BVDV carriers, and pregnancy loss. Safety concerns associated with viral vaccines, more specifically modified-live viral vaccines, should not overshadow the protective effects associated with sound vaccination principles and programs.

**Key words:** vaccination, Bovine viral diarrhea virus, Bovine alphaherpesvirus-1, fetal protection

## Introduction

Bovine viral diarrhea virus (BVDV) and Bovine alphaherpesvirus-1 (BoHV-1) are the most important viral reproductive diseases of cattle, resulting in significant economic loss to the beef and dairy cattle industries in North America. Bovine viral diarrhea virus is the prototypic member of the genus *Pestivirus* within the family *Flaviviridae*.<sup>1</sup> The pestiviruses are enveloped, single-stranded, positive-sense RNA viruses. Recently, the genus *Pestivirus* has undergone a change in nomenclature by the International Committee on Taxonomy of Viruses, with new species designations of *Pestivirus A-K*.<sup>1</sup> *Pestivirus A* and *B* now correspond to BVDV 1 and BVDV 2. Within the United States cattle population, there are three major subtypes, BVDV-1a, BVDV-1b, and BVDV-2a, with the BVDV-1b subtype predominating from diagnostic laboratory submissions and PI prevalence studies.<sup>2,3</sup> BVDV employs multiple strategies to ensure survival and successful propagation in cattle, and this includes suppression of the bovine immune system, transmission by various direct and indirect routes, and, perhaps most importantly, induction of persistently infected (PI) cattle that shed and transmit BVDV much more efficiently than other sources. Persistent infection is the key mode by which the virus maintains and perpetuates itself in the cattle population. PI calves are the result of an in utero BVDV infection during the period between the end of the embryonic stage and the development of fetal immunocompetence.<sup>4</sup> Because BVDV is an RNA virus, mutations and substitutions in the genome can be expected during replication, ultimately resulting in genomic and antigenic variation.<sup>5</sup> In contrast, BoHV-1 is a DNA virus (family *Herpesviridae*, subfamily *Alphaherpesvirinae*, genus *Varicellovirus*).<sup>6</sup> Owing to the fact BoHV-1 is a DNA virus, mutations and subsequent genomic

and antigenic variation are of less concern than with BVDV. BoHV-1 employs multiple strategies for survival and propagation in cattle, including hit-and-run and hit-and-stay (latency) strategies.<sup>7</sup> The abortifacient properties of virulent BoHV-1 can become apparent following natural exposure in susceptible cattle, both naïve and immunosuppressed. Classically, the virus is viewed as a late-term abortifacient with the majority of abortions occurring after seven months of gestation.<sup>7</sup> Abortion generally occurs within a few weeks of viral exposure but may be delayed for as long as three to four months post-exposure if viral latency occurs in the placenta. Abortions may be observed in association with signs of respiratory disease although expulsion of the fetus may be delayed for several months.

Many vaccines are available for use in cattle against BVDV and BoHV-1, with the majority of USDA licensed vaccines containing these viruses in combination with other bovine respiratory and reproductive pathogens.<sup>8</sup> For BVDV, vaccines in the United States exist as killed viral (KV) or modified-live viral (MLV) vaccines, with these vaccines being administered parenterally. For BoHV-1, vaccines in the United States exist as KV, MLV, and chemically-altered, temperature-sensitive (TS) MLV. The MLV and TS MLV vaccines are formulated to be given either by parenteral or intranasal routes. Prior to 1995, most BVDV vaccines contained only BVD V1 strains, but because of antigenic diversity and outbreaks of severe clinical disease in association with BVDV 2 strains, MLV and KV vaccines now contain both BVDV 1 and BVDV 2 strains. Advantages and disadvantages of MLV and KV have been described.<sup>8</sup> In general, MLV vaccines are less expensive, induce more rapid immunity, provide longer durations of immunity, induce both humoral and cell-mediated immune responses, are effective against a broader spectrum of viral strains (BVDV), and are better able to decrease the risk of infection of the developing fetus. One noted disadvantage of KV vaccines is that two doses are required for the initial immunization, and a major problem with programs using KV vaccines is the potential lack of compliance among producers by failing to booster the primary series.<sup>9</sup> MLV and KV are generally safe when administered according to the manufacturer's label. However, risk of abortion associated with administration of multivalent MLV vaccines containing BoHV-1 to pregnant cows has been demonstrated.<sup>10,11</sup>

## Vaccine efficacy and vaccination effectiveness

The efficacy of a vaccine is measured in a controlled clinical trial and is based on how many cattle that received the vaccine developed the outcome of interest as compared to a control group. The outcome of interest for both viruses is fetal infection, more specifically abortion/pregnancy loss for BoHV-1 and persistent infection and abortion/pregnancy loss for BVDV. In comparison, vaccine effectiveness is a measure of how well vaccines work in the real world, encompassing the wide variety in cattle

operations and management practices that are present in modern beef and dairy industries. Effectiveness in the real world might differ from efficacy measured in clinical trials because predictions can be difficult when incorporating all the factors that exist in cattle production environments including host factors such as stress and immunosuppression and viral factors such as wide genetic and antigenic diversity of BVDV strain and regional or local prevalence rates of BVDV persistently infected cattle and BoHV-1 latently infected cattle. Efficacy studies are often under controlled conditions, with exposure to the virus at a predetermined time in relation to the vaccines, and in populations that are free of the viruses at the time of vaccination, whereby effectiveness of vaccination would need to consider exposure of virus at differing times or in cattle that are incubating viruses at the time of vaccination. Many other factors also contribute to the effectiveness of vaccination to prevent BVDV and BoHV-1 infections including variability associated with individual farm biosecurity/biocontainment practices, handling and administration of the vaccines, and other variables associated with real-life conditions. Therefore, the veterinarian will often rely on two major pillars for vaccination decision-making which include: 1) efficacy data from controlled clinical trials and/or meta-analyses, and 2) personal clinical experience.

## BVDV vaccine efficacy

When discussing BVDV vaccination efficacy, it is first important to discuss reasonable expectations following vaccination and to remember that disease and infection are not synonymous terms. Although vaccines are an important component to BVDV control, vaccination against BVDV is not 100% efficacious, meaning that no vaccine will prevent all viremias and infections.<sup>4</sup> Thus, identification and elimination of the PI reservoir and biosecurity/biocontainment practices are important components of BVDV control programs. Reasons for lack of efficacy of vaccination against BVDV include factors related to the administration of the vaccine and host response to vaccination. Control of infectious diseases relies upon eliminating pathogen reservoirs and controlling transmission from infected to susceptible animals. Protection against viremia is critical for BVDV vaccine efficacy. To be 100% efficacious, vaccination against BVDV should prevent viremia and dissemination of virus to the uterus and developing fetus. Published studies have demonstrated variable protection rates between 60-100% against fetal infections following BVDV vaccination.<sup>12</sup> Variation in protection is dependent upon whether the vaccine is MLV or KV, the timing of challenge, and upon the degree of homology between the vaccine strains and the challenge strains. Twenty-two studies evaluated the effect of vaccination of heifers and/or cows pre-breeding with a MLV (n = 18) or KV (n = 4) vaccine on clinical protection after experimental BVDV infection during gestation.<sup>12</sup> The time between vaccination and experimental challenge/exposure varied from 70 days to 490 days. These studies reported between 22% and 100% protection against fetal infection, between 82% and 100% protection against abortion, and between 8% and 100% prevention of generation of PI or BVDV-seropositive calves.<sup>12</sup> The higher percentages of protection corresponded to MLV vaccination.<sup>12</sup> The inability of KV vaccines to induce long-lasting humoral protection could explain the higher rates of fetal infection observed in some studies.<sup>13</sup> An opportunity might exist for KV vaccines to be utilized as an immunization booster. Vaccination of heifers with MLV vaccine at weaning and prior to breeding followed by KV vaccination 6 months later (at pregnancy examination) resulted in higher fetal protection rates as compared to heifers that

were administered MLV vaccination at the same times prior to breeding and then again at pregnancy examination.<sup>14</sup> Similarity among vaccine and challenge BVDV strains could also influence clinical protection provided by vaccination. Summary conclusions from a meta-analysis demonstrates that multivalent BVDV vaccines provide better coverage to heterologous strains compared with monovalent vaccines.<sup>12</sup> Additionally, the risk of fetal infection and abortion is lower in cattle vaccinated with MLV vaccines vs. cattle vaccinated with KV vaccines.<sup>12</sup> Since BVDV 1 strains exist more commonly as BVDV 1b in the United States, speculation has arisen that current vaccines which contain BVDV-1a and BVDV 2 do not fully prevent infection with antigenically diverse BVDV-1b strains.<sup>4</sup> An unproven hypothesis is that vaccination utilizing commercial vaccines containing BVDV-1a and BVDV 2 has resulted in a selective advantage of BVDV 1b strains to become the predominant subgenotype in the United States. Further research evaluating antigenic variation among BVDV strains and comparing them to vaccine strains is necessary.

## BoHV-1 vaccine efficacy

Less data are available for assessing BoHV-1 vaccination efficacy in preventing fetal infection when compared to data available for BVDV. In comparison to BVDV where the outcome assessment of PI rate is relevant, abortion risk is the outcome measurement for BoHV-1 vaccine efficacy. A meta-analysis study on BoHV-1 vaccination on prevention of abortion in cattle evaluated 15 efficacy studies, with nine studies evaluating MLV vaccines and six studies evaluating KV vaccines.<sup>15</sup> In summary from all studies included in the meta-analysis, vaccination reduced the risk of abortion by 60% in vaccinated animals compared to unvaccinated controls. Interestingly and contrary to the BVDV meta-analysis, the reduction in risk for abortion was similar between MLV and KV vaccines, although less data and studies were available for BoHV-1 vaccination.<sup>15</sup> Intentional BoHV-1 challenge studies have also been performed in vaccinated pregnant cattle and unvaccinated pregnant cattle, and the routes of challenge have even involved intravenous inoculation of cattle. While this is far from a natural challenge, intravenous inoculation with BoHV-1 is a robust challenge method. Even in these challenge models, protection against abortion is achieved when compared to unvaccinated controls.<sup>15</sup> While the reduction in risk of abortion following BoHV-1 challenge is apparent, an important observation has been that most studies did not have an abortion, indicating that 100% protection is difficult to achieve with vaccination against BoHV-1 abortion.<sup>15</sup>

## Summary

Nothing seems to generate more opinions than which vaccine should be used to vaccinate cattle for protection against BVDV and BoHV-1. Even though controversy exists, vaccination against BVDV and BoHV-1 has proven more effective than no vaccination at all when the vaccines are handled and administered correctly and given to healthy cattle at the appropriate times in the production schedule. In general, currently available vaccines provide protection against clinical disease and greatly reduce the risk of fetal infection in pregnant cattle. Equally important is for veterinarians to recognize the safety concerns associated with administration of MLV vaccines in pregnant cattle or in replacement female cattle in close time proximity to breeding; however, this concern should not transcend the overwhelming protective effects associated with sound vaccination principles.

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