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Bovine Respiratory Disease Vaccination Against Viral Pathogens

Modified-Live Versus Inactivated Antigen Vaccines, Intranasal Versus Parenteral, What Is the Evidence?

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KEYWORDS

• Calves • BRD • Vaccine • Modified-live viral (MLV) • Inactivated ("killed") viral (KV) • Parenteral • IN

KEY POINTS

- Vaccination of beef calves around the time of weaning with multivalent modified-live viral (MLV) vaccines alone or in combination with *Mannheimia haemolytica*/*Pasteurella multocida* bacterins reduces bovine respiratory disease (BRD) morbidity and mortality after weaning.
- It is uncertain if vaccination of young beef calves reduces BRD morbidity and mortality before weaning age.
- There is conflicting evidence of the efficacy of vaccination of young dairy calves with MLV vaccines alone or in combination with *M haemolytica*/*P multocida* bacterins on the reduction of BRD morbidity and mortality.
- The level of specific maternal antibodies from colostrum, the ecosystem of respiratory viruses in each farm, and the degree of homology of field versus vaccine virus strains affect efficacy of BRD vaccination in young beef and dairy calves.

INTRODUCTION

The bovine respiratory disease (BRD) complex is the most important cause of morbidity and mortality in beef and dairy cattle operations.[1] Although respiratory

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disease can affect cattle of any age and stage of production, economic losses associated with BRD occur most commonly in the following calf populations:

1. Beef calves around the time of weaning, between 5 and 8 months of age
2. Preweaning beef calves younger than 5 months of age
3. Dairy calves younger than 3 months of age.

Stress and immunosuppression are important risk factors for the development of BRD in any of these population groups; however, different factors play a role in the presentation of clinical disease in each group. Failure in the transfer of passive immunity, the level and decay of maternal antibodies (MA), commingling, transport/shipping, dietary changes, and biosecurity breaches can influence the presentation of BRD in calves.[2,3] The impact of these factors on individual operations introduce variation in the clinical presentation of BRD in each calf group. Despite this variation, whole-herd vaccination against BRD pathogens is a common practice among producers and veterinarians to minimize calf losses associated with morbidity and mortality.[4,5] Modified-live (MLV) and killed virus (KV) vaccines with different label specifications are commercially available.[6,7] Recently, a meta-analysis of the efficacy of BRD vaccines demonstrated inconsistency of the reduction of morbidity and mortality in calves.[6,7] The lack of evidence of efficacy of vaccination against BRD pathogens may affect the practitioner's decision-making process when developing vaccination protocols for cattle operations. The objective of this article is to perform an assessment of the quality of evidence on whether MLV and inactivated antigen vaccines administered parenterally or intranasally provide similar clinical protection against BRD in different calf groups. "High-quality evidence" was defined as an outcome reported by 3 or more naturally occurring or experimentally induced BRD vaccine efficacy studies that fulfilled all of the following requirements: clear definition of study population, random and clear allocation of treatment groups, clear definition of disease (morbidity and mortality) outcomes, and blinding of evaluators. "Moderate-quality evidence" was defined as an outcome reported by at least one vaccine efficacy study that fulfilled all the previously mentioned requirements, and "low-quality evidence" was defined as failure to fulfill any of the requirements.

Modified-Live Versus Inactivated Virus Vaccination Against Bovine Respiratory Disease. What Is the Evidence?

In general, MLV vaccines induce complete humoral and cell-mediated long-lasting immunity, and fewer doses are required to provide clinical protection.[8–11] In contrast, KV vaccines induce strong humoral responses but less robust cell-mediated immunity and require at least 2 doses 21 days apart to provide protection.[12] Several studies have evaluated the effect of MLV and KV vaccines on the prevention of BRD in calves of different ages, immune status, and production settings.[13–17] Among practitioners, it is thought that MLV vaccines provide better clinical protection against BRD compared with KV[4]; however, selection of vaccination protocols should be based on field (naturally occurring) BRD vaccine-efficacy trials that provide strong evidence on vaccine selection for BRD prevention.[6,7]

Are modified-live virus and killed virus respiratory vaccines similarly effective for providing clinical protection against bovine respiratory disease in weaned beef calves?

The highest economic impact of BRD on the beef industry is associated with morbidity and mortality of calves shortly after weaning.[1] Therefore, a fundamental goal of vaccination of this group of cattle is to reduce the incidence of BRD after arrival to stocker/

feedlot operations. Nine studies evaluated the effect of vaccination with MLV (8 studies) and KV (1 study) vaccines on the natural occurrence of BRD in beef calves after conventional (5–8 months) weaning age.[13,15,16,18–22] MLV and KV vaccines included at least one of the following agents: bovine herpes virus 1 (BHV-1), bovine viral diarrhea virus 1 (BVDV 1), BVDV 2, bovine respiratory syncytial virus (BRSV), bovine coronavirus (BCV), and parainfluenza-3 virus (PI3V). In all studies, vaccination occurred in the transition from weaning to arrival at the stocker/feedlot operation. Significant reduction of morbidity was reported in 75% (6/8) of the studies using MLV vaccination. Further, significant reduction of mortality was observed in 67% (4/6) of studies using MLV vaccination that reported mortality rates. Only one study evaluating the efficacy of KV vaccines reported significant reduction of BRD-associated morbidity and mortality.[21] The introduction of BVDV-2, BCV, *Mannheimia haemolytica* and *Pasteurella multocida* in combination with MLV, and early vaccination (before weaning, before arrival) increased vaccination efficacy.[22] *There is strong and high-quality evidence that vaccination of beef calves around the time of weaning with MLV vaccines alone or in combination with M haemolytica/P multocida bacterin/toxoids is superior to vaccination with KV vaccines in reducing naturally occurring BRD morbidity and mortality after weaning.*

Thirteen studies evaluated the effect of vaccination of beef calves around the time of weaning with MLV or KV vaccines on BRD-associated morbidity and mortality after experimental challenge with respiratory viruses.[12,23–34] In all studies, calves were vaccinated between 5 and 12 months of age, and experimental inoculation/exposure occurred between 3 and 230 days after vaccination. In 11 studies calves were challenged with BVDV; one study used BHV-1 and one study used BRSV as challenge agents. Eleven studies evaluated MLV vaccines and 2 studies evaluated KV vaccines. Significant reduction of BRD morbidity was reported in 82% (9/11) of studies using MLV vaccines. Significant reduction of mortality was reported in 100% (5/5) of MLV vaccination studies that reported mortality rates. In both of the 2 studies using KV vaccines, there was a significant reduction of BRD morbidity but none reported mortality. One study compared the effect of MLV versus KV vaccination in recently weaned beef calves and reported no significant differences on BRD morbidity after challenge with BVDV.[35] A recent study compared the effect of vaccination of beef calves at birth and again at 2 months of age, with 1 of 3 vaccine-combination protocols, MLV/MLV, MLV/KV, or no-vacc/MLV, on clinical protection of calves after experimental challenge with BRSV at weaning. No differences on BRD morbidity and mortality were reported among vaccinated groups.[36] *There is strong and high-quality evidence that vaccination of beef calves with vaccines containing MLV alone or in combination with M haemolytica/P multocida bacterins is superior to KV vaccination for reducing BRD-associated morbidity and mortality after experimental challenge with BVDV, BHV-1, or BRSV.*

Are modified-live virus and killed virus respiratory vaccines similarly effective for providing clinical protection against bovine respiratory disease in preweaning beef calves?

Respiratory disease is the leading cause of death of beef calves between 3 weeks of age and weaning.[37] The proportion of preweaning beef calves affected by BRD is variable among cow-calf operations, with some farms reporting a very high incidence of the disease (~20%) and other farms with no calf-BRD issues at all.[38,39] The goal of vaccination is to reduce the risk of BRD before weaning; however, in this case the presence and level of colostrum-derived immunity at the time of vaccination can play a role in clinical protection as well as interfere with vaccine efficacy. Two studies

reported no effect of vaccination on the natural occurrence of BRD after 4 months of age in calves previously vaccinated with 2 doses of an inactivated BRSV vaccine between 2 and 4 months of age.[14,34] One study reported increased BRD-associated morbidity and mortality on vaccinated calves.[14] The investigators suggested that detrimental priming induced by the inactivated BRSV vaccine could have been responsible for inducing a hypersensitivity reaction after natural exposure to field virus in vaccinated calves. *There is very limited evidence of moderate quality indicating deleterious or no effect of KV BRSV vaccination in reducing naturally occurring BRD morbidity and mortality of young beef calves.*

Three studies evaluated the effect of vaccination (2 studies using MLV vaccines and 1 study using a KV vaccine) of 2.5- to 4-month-old beef calves on BRD-associated morbidity and mortality after experimental challenge/exposure to BVDV.[40–42] Experimental challenge/exposure occurred between 30 and 45 days after vaccination in all studies. No effect of vaccination on reduction of BRD-associated morbidity and mortality was reported in the 2 studies that vaccinated calves with a multivalent MLV vaccine 45 days before BVDV challenge.[40,41] In these studies, MA against BVDV 1 and BVDV 2 at the time of challenge provided protection against respiratory signs in unvaccinated calves. In contrast, the high level of BVDV-specific antibodies observed before challenge in vaccinated calves not only protected against clinical disease but also resulted in greater protection against viremia and BVDV shedding. Results from the third study using a KV vaccine demonstrated reduction of clinical signs associated with acute BVDV infection in calves vaccinated with 2 doses of an inactivated BVDV vaccine 30 days before challenge.[42] *There is limited evidence of moderate quality indicating no effect of MLV vaccination or positive effects of KV vaccination for reducing BRD-associated morbidity and mortality after experimental challenge with BVDV of young beef calves.*

Are modified-live virus and killed virus respiratory vaccines similarly effective for providing clinical protection against bovine respiratory disease in young dairy calves?

BVD is a common cause of morbidity and mortality of young dairy heifers before and after weaning.[5] In contrast to the lower prevalence of preweaning calf pneumonia reported in young beef calves, results from a recent report indicated that overall preweaning dairy heifer BRD-associated morbidity is 22.8%. Similarly, overall preweaning dairy heifer BRD-associated mortality is 19%.[43] The level of interference of colostrum-derived immunity at the time of vaccination can similarly affect clinical protection and efficacy of vaccination in dairy calves. Two studies evaluated the effect of vaccination of dairy calves between 3 days and 6 weeks of age, with single or 2 doses of a multivalent MLV vaccine on the natural occurrence of BRD between 1 and 3 months of age.[17,44,45] Vaccination did not result in significant reduction of naturally occurring BRD morbidity and mortality in any of the studies. One study reported that 21% of the risk of BRD in young dairy calves was the result of failure in the transfer of passive immunity.[46] Calves with a higher colostrum-derived BRSV and IBR antibodies had lower odds of developing signs of BRD compared with calves with lower titers. In another study, calves vaccinated with 2 doses of an intranasal (IN) multivalent MLV vaccine between 3 to 6 days and at 6 weeks of age demonstrated no difference in BRD signs but had less lung consolidation compared with calves vaccinated at 6 weeks, with a single dose of a subcutaneous (SC) MLV vaccine or unvaccinated calves.[45] *There is limited moderate quality evidence indicating that vaccination of young dairy calves with multivalent MLV vaccines is ineffective for reducing naturally occurring BRD morbidity and mortality.*

Seventeen studies evaluated the effect of vaccination of young dairy calves in the presence of different levels of MA with MLV (14 studies) or KV vaccines (3 studies) on reduction of BRD-associated morbidity and mortality after experimental inoculation with respiratory viruses.[9–11,47–63] In all studies, calves were vaccinated between 3 days and 4.5 months of age. Experimental inoculation with respiratory viruses occurred between 5 days and 9 months after vaccination. Six studies used BVDV as the experimental challenge agent; 10 studies used BRSV, and 1 study used BHV-1. Significant reduction of BRD morbidity was reported in 86% (12/14) of studies using MLV vaccines. Significant reduction of mortality was reported in 57% (4/7) of MLV vaccine studies that reported mortality rates. Vaccination in the face of maternal antibodies (IFOMA) and experimental challenge with a homologous BVDV strain provided clinical protection up to 7 months after vaccination in one study.[11] In contrast, in another study vaccination IFOMA and experimental challenge with a heterologous BVDV strain 4.5 months after vaccination did not prevent clinical disease.[50] Colostrum-deprived or seronegative dairy calves vaccinated with a MLV vaccine were clinically protected after experimental challenge with BVDV, BRSV, or BHV-1.[10,50,53]

Significant reduction of BRD-associated morbidity and mortality was reported in only 1 of 3 (33.3%) studies where a KV BRSV vaccine was used to vaccinate calves subsequently challenged with BRSV. *There is robust, moderate-quality evidence that vaccination of young dairy calves with multivalent MLV vaccines is superior to vaccination with KV vaccines for reducing BRD-associated morbidity and mortality after experimental challenge with respiratory viruses. Clinical protection may depend on the level of colostrum-derived immunity at the time of vaccination (seronegative vs seropositive), homology between the vaccine and experimental challenge strains, and time between vaccination and challenge.*

Intranasal Versus Parenteral Vaccination Against Bovine Respiratory Disease. What Is the Evidence?

Numerous studies have demonstrated the inhibitory effects of passive immunity on vaccine-induced immune responses and complete protection against respiratory viruses after parenteral administration of BRD vaccines.[50,64,65] Young calves prime-vaccinated with parenteral MLV vaccines IFOMA do not usually seroconvert. However, there is evidence that they can mount specific T- and B-cell–mediated immune responses that provide variable clinical protection later in life when MA have decayed.[9,11,50,62] Because variability in the transfer of specific passive immunity has been reported in young calves,[66] it becomes challenging to estimate the timing when parenteral vaccination would provide the highest efficacy on protection against respiratory pathogens. Intranasal vaccination is an effective mechanism to induce local mucosal immune priming and immunoglobulin A production IFOMA.[67] Greater mucosal (nasal secretions) and systemic-specific immunity has been reported in calves vaccinated IFOMA intranasally with a MLV BRSV and/or BHV-1 vaccine versus parenteral vaccination.[68] Several studies have demonstrated efficacy of IN vaccination of calves IFOMA on protection against respiratory viruses[53,58,68]; however, few field and experimental challenge studies have compared their efficacy to parenteral vaccines for reducing BRD morbidity or mortality.

Are modified-live virus intranasal and parenteral vaccines similarly effective for providing clinical protection against bovine respiratory disease in young dairy calves?
Only one field study using 468 dairy calves compared the effects of 2 MLV vaccination protocols using IN or SC vaccination on the risk of BRD from 8 to 12 weeks of age.[45]

The vaccination protocol (IN vs SC) did not have an effect on the natural occurrence of BRD. The IN vaccine demonstrated potential to reduce lung consolidation based on ultrasound examination findings and improve growth of calves. *There is very limited moderate quality evidence indicating that vaccination of young dairy calves with neither multivalent MLV IN nor parenteral vaccines is effective in reducing naturally occurring BRD morbidity and mortality.*

Fifteen studies evaluated the efficacy of vaccination of young dairy calves with a multivalent MLV vaccine containing all or some of the following agents: BVDV 1, BVDV 2, BHV-1, BRSV, and PI3V on clinical protection against experimental viral challenge. Six studies used IN MLV vaccines[10,49,52,53,58,60] and 9 used parenteral MLV vaccines (see previous sections in this article). Significant reduction of BRD-associated morbidity after challenge was reported in 83.3% of IN vaccination studies and in 67% of parenteral vaccination studies. Significant reduction of BRD-associated mortality was reported in 75% of both IN and parenteral vaccination studies that reported mortality rates. Maternally derived antibodies affected immune response and clinical protection offered by parenteral MLV vaccination in calves subsequently challenged with BRSV in one study[9]; in contrast, maternal immunity had no effect in calves vaccinated parenterally with an adjuvanted MLV BRSV vaccine and subsequently challenged with BRSV in another study.[63] Similarly, calves vaccinated IFOMA with a parenteral MLV BVDV vaccine and subsequently challenged with a homologous BVDV strain were protected against clinical disease.[9,56,62] Regardless of the level of MA, IN and parenteral vaccination of dairy calves against BRSV resulted in clinical protection when experimental challenge occurred less than 4 months of vaccination.[52,53,63] *There is strong, high-quality evidence that both intranasal and parenteral vaccination of young dairy calves with MLV vaccines result in similar reduction of BRD-associated morbidity and mortality after experimental challenge with respiratory viruses.*

Are modified-live virus intranasal and parenteral vaccines similarly effective for providing clinical protection against bovine respiratory disease in beef calves?

Intranasal or parenteral vaccination of beef calves from cow-calf or feedlot operations with MLV vaccines containing some or all of the following viruses—BVDV 1, BVDV 2, BHV-1, BRSV, BCV, and PI3V—for BRD prevention usually occurs at branding (~2 months of age), around weaning, or at stocker/feedlot arrival. Only 25% of studies (1/4) evaluating MLV IN vaccines reported significant reduction of naturally occurring BRD morbidity in vaccinated calves.[13,19,20,69] In contrast, significant reduction of naturally occurring BRD morbidity in calves vaccinated with a parenteral MLV vaccine was reported in 75% (3/4) of studies (see previous sections in this article).[15,16,18,22] Significant reduction of naturally occurring BRD mortality was reported in 50% (2/4) of parenteral vaccination studies and in 25% (1/4) of IN vaccination studies that reported mortality rates. One study reported a greater reduction of BRD in recently weaned beef calves vaccinated with 2 doses of a parenteral MLV vaccine versus calves vaccinated with a single dose of an IN MLV vaccine.[19] Another study reported no impact on clinical health or mortality of feedlot calves that received a single dose of a MLV IN vaccine when treated the first time for BRD.[69] *There is strong, high-quality evidence that parenteral vaccination of beef calves before or shortly after weaning with MLV vaccines is superior to IN vaccination for reducing naturally occurring BRD-associated morbidity and mortality after arrival to stocker/feedlot operations.*

Fourteen studies evaluated MLV vaccines on the reduction of BRD-associated morbidity and mortality of beef calves after experimental challenge with respiratory viruses (see previous sections of this article). Only 2 studies[36,70] (14.3%) evaluated

intranasal vaccines alone or in a combination protocol with parenteral vaccines. In one study, calves were vaccinated with an IN vaccine containing BHV-1, BRSV, and PI3V and subsequently challenged with BRSV. In the other study, calves were vaccinated with an IN vaccine containing BVDV 1, BVDV 2, BHV-1, BRSV, and PI3V and subsequently challenged with BHV-1. Significant reduction of BRD-associated morbidity and mortality was reported in the BHV-1 challenge study but not in the BRSV challenge study. Significant reduction of BRD morbidity and mortality was reported in 67% and 57% of studies, respectively that used parenteral MLV vaccines in calves that were subsequently challenged with BVDV, BRSV, or BHV-1.[24–29,31–33,35,40,41] Intranasal vaccination of beef calves at 3 to 6 weeks of age and again at 6 months of age with an IN or SC vaccine was associated with reduced BRD morbidity after BHV-1 challenge.[70] Moreover, in this study, the vaccination protocol based on IN priming and IN booster resulted in reduced BHV1 shedding. In addition, vaccination with a single dose of the IN vaccine at 3 to 6 weeks or at 6 months of age with no additional booster was associated with reduction of mortality but not BRD morbidity. In another study, IN MLV vaccination at birth in addition to SC MLV or KV booster at 2 months of age was not different from SC MLV vaccination at 2 months for reducing BRD morbidity after BRSV challenge at weaning.[36] *There is limited, moderate-quality evidence that vaccination of beef calves with parenteral multivalent MLV vaccines is superior to IN MLV vaccines on reducing BRD-associated morbidity and mortality after experimental challenge with BVDV, BHV-1, or BRSV.*

SUMMARY

Assessment of the evidence of efficacy of vaccination of different calf populations with MLV and KV vaccines on the reduction of BRD-associated morbidity and mortality produced the following conclusions:

- There is strong high-quality evidence that vaccination of beef calves at or shortly after weaning with parenteral multivalent MLV vaccines alone or in combination with *M haemolytica*/*P multocida* bacterins is effective for reducing naturally occurring and experimentally induced BRD morbidity and mortality after weaning. The presence of BVDV 1 and BVDV 2 antigens in parenteral multivalent MLV vaccines plays an important role in providing clinical protection against BRD.
- There is limited evidence of efficacy of vaccination of young beef calves (preweaning) with parenteral or IN MLVor KV vaccines in reducing naturally occurring or experimentally induced BRD morbidity and mortality before weaning age. There is an evident need for additional research to determine true effects of vaccination, type of vaccines, and routes of administration in this group of cattle.
- With respect to vaccination of dairy calves for the prevention of BRD, there is a lack of connection between results from naturally occurring and experimentally induced BRD vaccine-efficacy studies. There is limited moderate-quality evidence that vaccination of young dairy calves with parenteral or IN MLV vaccines is ineffective for reducing naturally occurring BRD. In contrast, there is strong evidence that vaccination of young dairy calves with parenteral or IN MLV vaccines is effective providing clinical protection against BRD after experimental challenge with respiratory viruses.
- The level and duration of specific MA against respiratory viruses of calves from individual cow-calf and dairy operations play an important role in providing clinical protection as well as in affecting vaccine efficacy against BRD.

DISCLOSURE

The authors have nothing to disclose.

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