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Review

Vaccination of calves against common respiratory viruses in the face of maternally derived antibodies(IFOMA)

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Abstract

Vaccination of calves in the face of maternal antibodies (IFOMA) often does not result in seroconversion as maternally derived immunity interferes with the activation of adequate antibody responses to vaccination; however, it can prime T and B cell memory responses that protect calves against clinical disease when maternal immunity has decayed. The activation of B and T cell memory responses in calves vaccinated IFOMA varies and is affected by several factors, including age, level of maternal immunity, type of vaccine, and route of administration. These factors influence the adequate priming of humoral and cell mediated immune responses and the outcome of vaccination. The failure to adequately prime immune memory after vaccination IFOMA could result in lack of clinical protection and increased risk of viremia and/or virus shedding.

Keywords: colostrum, maternal, antibody, vaccination, BVDV, BRSV.

Introduction

Viral respiratory pathogens such as bovine viral diarrhea virus 1 and 2 (BVDV1 and BVDV2), bovine herpesvirus 1 (BoHV-1), bovine respiratory syncytial virus (BRSV), and parainfluenza 3 virus (PI3V) play a critical role in the pathogenesis of bovine respiratory disease complex (BRDC) (Van Donkersgoed *et al.*, 1994; Martin *et al.*, 1999; O'Connor *et al.*, 2001). Vaccination against BVDV1, BVDV2, BoHV-1, BRSV, and PI3V is considered a key management strategy to minimize mortality and economic losses associated with BRDC in weaned calves (Peters *et al.*, 2004; Step *et al.*, 2009); A positive correlation between high levels of serum virus-neutralizing antibodies derived from colostrum or vaccination and decreased incidence of BRDC have been previously reported in calves (Moerman *et al.*, 1994; Martin *et al.*, 1999; Fulton *et al.*, 2004); however, higher intensification and specialization of beef and dairy operations may contribute to BRDC which can be seen before weaning (Woolums *et al.*, 2013a). Additionally, changing conditions in climate and the beef market have at times led producers to adopt early weaning practices in beef calves (Rasby, 2007). These factors may prompt farmers to vaccinate calves against BRDC pathogens earlier in life, when maternally derived antibody is still present. For some time it was believed that the presence of maternally derived antibody interfered with the induction of adequate immune responses to vaccination; however, some studies indicate that priming humoral and cell mediated immune responses is possible when vaccinating calves in the face of maternal antibody (IFOMA) (Ellis *et al.*, 1996; Endsley *et al.*, 2004; Patel and Didlick, 2004; Platt *et al.*, 2009).

The magnitude of immunologic responses induced by vaccination IFOMA is variable among calves as it is the degree of clinical protection against viral challenge (Ellis *et al.*, 2001, 2010;

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Patel and Shilleto, 2005; Platt *et al.*, 2009). Factors such as calf age, concentration of maternally derived antibodies, type of vaccine, presence or not of an adjuvant in the vaccine, and route of administration play a critical role in the outcome of vaccination (Brar *et al.*, 1978; Menanteau-Horta *et al.*, 1985; Ellis *et al.*, 2001; Patel and Didlick, 2004; Platt *et al.*, 2009; Stevens *et al.*, 2009; Zimmerman *et al.*, 2009). The ultimate goal of vaccination of calves IFOMA against respiratory viruses is to prevent acute clinical disease and virus transmission. This paper reviews the literature on the subject of vaccination of calves IFOMA to prevent infection and disease due to viral respiratory pathogens common in North America, and follows a similar approach used by a previous article published in 2007 (Woolums, 2007). The objective of this review is to provide evidence-based recommendations on the clinical application of vaccination of calves IFOMA.

Transfer of virus-specific antibodies from colostrum

Virus neutralizing antibodies to BVDV1, BVDV2, BoHV-1, BRSV, and PI3V transmitted through maternal colostrum protect neonatal calves against acute clinical disease during the first months of life (Ridpath *et al.*, 2003; Patel and Didlick, 2004; Peters *et al.*, 2004). However, the higher the titer and longer the persistency of maternal antibodies, the higher the interference of antibody responses induced by vaccination (Munoz-Zanzi *et al.*, 2002; Fulton *et al.*, 2004); low maternally derived antibody titers generate less interference to vaccination (Ellis *et al.*, 2001; Munoz-Zanzi *et al.*, 2002). The duration of maternal antibodies to respiratory viruses such as BVDV1, BVDV2, BoHV-1, BRSV, and PI3V depends mostly on the initial titer absorbed from maternal colostrum (Kirkpatrick *et al.*, 2001; Munoz-Zanzi *et al.*, 2002); however, the range of maternal antibody titers to respiratory viruses after colostrum intake is highly variable among calves (Kirkpatrick *et al.*, 2001; Fulton *et al.*, 2004; Chamorro *et al.*, 2014). In one study the initial range of maternal antibody titers in 60-day-old calves varied from 0 to 935 for BoHV-1, 16 to 16,384 for BVDV1a, 8 to 8192 for BVDV1b, 0 to 8192 for BVDV2, and 0 to 4096 for BRSV (Fulton *et al.*, 2004). In a recent study, the coefficients of variation of initial ranges of viral antibody titers derived from maternal colostrum in a group of 2-day-old calves were 28.03% for BVDV1, 37.4% for BVDV2, 24.98% for BRSV, and 43.49% for BoHV-1 (Chamorro *et al.*, 2014).

High variation in the level of maternally derived immunity to respiratory viruses could affect the uniformity of ages at which calves become seronegative to each virus and therefore can affect responses to vaccination IFOMA. In one study, the standard deviation (SD) of the mean time to reach seronegative status to BVDV1, BVDV2, BoHV-1, BRSV, and PI3V in calves that received maternal colostrum at birth varied from 37 to 116 days (Kirkpatrick *et al.*, 2001). Another study reported an 18–53-day variation in the mean time to reach seronegative status to the same viruses in calves that received maternal colostrum or a colostrum replacer at birth (Chamorro *et al.*, 2014). These results indicate that differences in antibody response to vaccination IFOMA should be expected as commonly some calves will have higher and others lower antibody titers to respiratory viruses at vaccination at any time point (Kirkpatrick *et al.*, 2001; Munoz-Zanzi *et al.*, 2002).

Immunologic responses induced by vaccination IFOMA

A common way to evaluate response to vaccination is seroconversion (Kelling *et al.*, 1990; Kirkpatrick *et al.*, 2008). Seroconversion is defined as a 4-fold or greater increase in serum antibody titers to a specific infectious agent and has been used to evaluate responses to vaccination in calves (Brar *et al.*, 1978; Kelling *et al.*, 1990). The absence of seroconversion following vaccination of young calves could be interpreted as vaccine failure; however, previous research demonstrated that protection against acute clinical disease caused by BVDV and BRSV can be observed in the absence of seroconversion in calves vaccinated IFOMA (van der Sluijs *et al.*, 2010; Stevens *et al.*, 2011). Vaccination IFOMA does not usually result in seroconversion but anamnestic antibody responses at a second dose of vaccine were reported in some studies (Brar *et al.*, 1978; Menanteau-Horta *et al.*, 1985). Additionally, an increased persistence of maternal antibodies (reduced decay rate likely resulting from increased antibody production) and development of specific-lymphocyte proliferative responses have been reported in calves vaccinated IFOMA (Ellis *et al.*, 1996; Fulton *et al.*, 2004).

In previous studies, 28–84-day-old calves vaccinated IFOMA with MLV and KV containing BVDV1, BoHV-1, PI3V, and BRSV did not seroconvert to initial vaccination; however, at a second dose of the same vaccine given 32–112 days later, anamnestic antibody responses were observed (Menanteau-Horta *et al.*, 1985; Kaeberle *et al.*, 1998). In a more recent report, a low proportion of calves vaccinated with a multivalent MLV vaccine at 67 days of age seroconverted to BVDV1, BVDV2, BoHV-1, and BRSV; however, a reduced rate of decay of maternally derived antibodies and anamnestic antibody responses were observed at a second vaccination 123 days later (Kirkpatrick *et al.*, 2008). In another study, age at vaccination (15 vs. 45 days) influenced the mean time at which calves became seronegative to BVDV1 and BVDV2. Depending on the initial level of maternally derived BVDV1 and BVDV2 antibodies, vaccinated calves reached seronegative status earlier or later in life. When calves had an initial BVDV1 titer >512 or a BVDV2 titer >32, no effect of vaccination was observed; however, when BVDV1 titers were <512 and BVDV2 titers <32, vaccination increased the time at which calves became seronegative to each virus (Munoz-Zanzi *et al.*, 2002). Another study reported a reduced rate of decay of maternal antibodies after vaccination of calves with a multivalent KV vaccine at 60 and then again at 155 days of age. The rate of seroconversion after vaccination at 60 days was minimal; however, the mean half-life of specific maternal antibodies to BVDV1, BVDV2, BoHV-1, and PI3V was increased (Fulton *et al.*, 2004).

Another study reported that maternally derived antibodies to BVDV1, BRSV, BoHV-1, and PI3V decayed similarly until 140

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days of age in calves vaccinated parenterally with a multivalent MLV vaccine at 2 or 70 days of age; however, calves vaccinated at 70 days of age had a higher mean BVDV1 antibody levels between 70 and 147 days after vaccination compared with calves vaccinated at 2 days of age (Woolums *et al.*, 2013b). These and previous results suggest that age and level of maternal immunity at vaccination influence the induction of antibody responses in calves vaccinated IFOMA. The level of maternal antibodies that interferes with seroconversion is not uniform and varies among viral pathogens. In one study, 84-day-old calves with a BVDV1 titer of 35 seroconverted to vaccination with a MLV vaccine; however, calves with BoHV-1 titers <16 did not seroconvert (Menanteau-Horta *et al.*, 1985). Another study reported that calves with a BVDV1 titer between 8 and 16 seroconverted to vaccination with a multivalent MLV vaccine; however, BVDV2 titers between 4 and 8 prevented seroconversion to BVDV2 (Kirkpatrick *et al.*, 2001). In the same study, any titer of maternal antibodies to BRSV or PI3V prevented seroconversion in vaccinated calves. Fulton *et al.* (2004), reported that a maternal antibody titer of 128 for BVDV1a, 32 for BVDV1b, 128 for BVDV2, 32 for BRSV, and 20 for BoHV-1 interfered with seroconversion to vaccination with a multivalent KV vaccine. Downey *et al.* (2013), demonstrated that calves with a maternally derived BVDV2 antibody titer of 8.24 or higher did not seroconvert to vaccination with a MLV vaccine at 130 days of age.

Intranasal vaccination has been described as an effective way to overcome interference exerted by maternal antibodies. A recent study reported that calves vaccinated at 2–3 days of age with an intranasal multivalent MLV vaccine and a booster with the same vaccine 35 days later did not seroconvert to vaccination but had an increase in IgA specific to BVDV and BoHV-1 in nasal secretions. In the same study, cell-mediated immune responses (interferon (INF)-γ) were not detected in serum or nasal secretions of vaccinated calves (Hill *et al.*, 2012). Another study reported no differences in BoHV-1-specific IgA levels in nasal secretions or cell mediated responses by peripheral blood mononuclear cells to BVDV1, BRSV, and BoHV-1 in calves vaccinated intranasally with a multivalent MLV vaccine at 2 or 70 days of age when compared with unvaccinated controls (Woolums *et al.*, 2013b).

Response in calves vaccinated IFOMA and subsequently challenged with live viruses

Reduction of clinical signs of disease have been reported in calves inoculated with a virulent BVDV2 strain or vaccinated with KV and MLV vaccines containing BVDV1, BVDV2 and BRSV in the presence of maternal immunity and subsequently challenged with BVDV2 or BRSV (Ridpath *et al.*, 2003; Patel and Didlick, 2004; Zimmerman *et al.*, 2006; Woolums, 2007). Priming of specific T cell memory responses following vaccination has been suggested as the main source of clinical protection of BVDV2-challenged calves (Endsley *et al.*, 2003; Platt *et al.*, 2009; Stevens *et al.*, 2011). Additionally, some reports suggest that the presence of a vaccine adjuvant could aid in the induction of cell-mediated immune responses that result in clinical protection in calves vaccinated IFOMA and subsequently challenged with BVDV2 (Zimmerman *et al.*, 2009; Stevens *et al.*, 2009); Protection provided by vaccination IFOMA would ideally also prevent viremia and virus shedding, in addition to clinical disease (Thurmond *et al.*, 2001; Peters *et al.*, 2004). However, some studies failed to demonstrate complete clinical protection or significant reduction of viremia and nasal shedding in calves vaccinated IFOMA with different vaccines containing BVDV1, BVDV2, and BRSV and subsequently challenged with virulent BVDV2 or BRSV (Ellis *et al.*, 2001, 2010; Stevens *et al.*, 2011).

Failure to induce anamnestic antibody responses to vaccination and subsequent challenge with BVDV2 could result in a higher proportion of calves with viremia and nasal shedding (Stevens *et al.*, 2011); however, differences in specific humoral and cell-mediated immune responses induced by BVDV vaccines containing different biotypes (cytopathic vs. non-cytopathic) and genotypes (BVDV1 vs. BVDV2) could be expected (Lambot *et al.*, 1997; Palomares *et al.*, 2014). Some reports suggest that while cytopathic (CP) BVDV strains commonly present in vaccines induce higher Th1-type cell mediated responses, non-cytopathic (NCP) BVDV strains commonly found in the field induce higher Th2-type humoral responses (Lambot *et al.*, 1997; Rhodes *et al.*, 1999). In contrast, a recent study reported that inoculation of calves with a virulent NCP BVDV2 resulted in similar expression of Th1- and Th2-type cytokines in tracheobronchial lymph nodes (Palomares *et al.*, 2014). Other studies indicate that in general, higher BVDV1, BVDV2, and BRSV antibody titers in response to vaccination IFOMA result in decreased viremia and nasal shedding after BRSV and BVDV2 challenge (Vangeel *et al.*, 2007; Chamorro *et al.*, 2015).

Most of the experimental research has used BVDV1 and BVDV2 to evaluate protection of calves against viral challenge following vaccination IFOMA. Vaccination of 5-week-old calves with a multivalent MLV vaccine containing BVDV1 and BVDV2 and challenged 3.5 months later with BVDV2 resulted in protection against clinical disease, prevention of viremia, and reduction of leukopenia (Zimmerman *et al.*, 2006). Another study demonstrated that calves inoculated IFOMA with live strain of BVDV2 between 2 and 5 weeks of age were protected against clinical disease at 7–9 months of at a second challenge with BVDV2 (Ridpath *et al.*, 2003). Endsley *et al.* (2003), reported that calves exposed to a live strain of BVDV2 at 2–5 weeks of age develop BVDV2-specific CD4, CD8, and γ/δ T cells and anamnestic antibody responses at challenge with BVDV2. In the same study, calves vaccinated at 7 weeks of age with a KV or multivalent MLV vaccine containing BVDV1 and BVDV2 developed anamnestic antibody responses to BVDV2 at second vaccination at 14 weeks of age; however, in this study the KV vaccine failed to induce T-cell responses specific to in vaccinated calves.

Although the studies described above showed that vaccination IFOMA can protect calves against clinical disease following BVDV2 challenge, the practice is not always effective. Failure to provide clinical protection and reduction of viremia

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has also been reported in calves vaccinated IFOMA. In one study, 10–14 day-old calves vaccinated with a MLV vaccine containing BVDV1 were not protected at challenge with BVDV2, 4.5 months after vaccination. Sixty six percent of vaccinated calves in this study had to be euthanized due to severity of clinical disease (Ellis *et al.*, 2001). In the same study, 10–14 day-old calves deprived from passive immunity to BVDV1 and BVDV2 and also vaccinated, seroconverted to vaccination, had less viremia, and were protected against challenge. Another study demonstrated that vaccination of calves at 3 days of age with a multivalent non-adjuvanted MLV vaccine containing BVDV1 and BVDV2 resulted in clinical protection and reduction of mortality at 7–9 months of age when calves were challenged with BVDV2; however, in this study 80% of calves vaccinated IFOMA became viremic after challenge (Stevens *et al.*, 2011). A more recent study reported that calves from 1 to 2, 4 to 5, and 7 to 8 weeks of age vaccinated IFOMA, with a multivalent MLV vaccine containing BVDV1 and BVDV2, developed BVDV1- and BVDV2-specific T-cell-mediated responses and were clinically protected after challenge with BVDV2 at 12 weeks after vaccination; however, only calves vaccinated at 4–5 and 7–8 weeks developed anamnestic antibody responses to BVDV1 and BVDV2 after challenge. Cell-mediated responses to BRSV, BoHV-1, or PI3V after vaccination were not detected in any of the calves (Platt *et al.*, 2009).

Protection against challenge with BRSV in calves vaccinated (parenterally or intranasally) IFOMA has also been reported. In one study, 2-week-old calves vaccinated parenterally at 2 and 6 weeks with a KV BRSV vaccine demonstrated significantly less signs of disease and reduced viral shedding after challenge at 10 weeks of age. Although anamnestic antibody responses were not observed, vaccinated calves demonstrated a slower rate of decay of maternal BRSV antibodies compared with controls (Patel *et al.*, 2004). When a third dose of the same vaccine was given at 18 weeks of age, anamnestic antibody responses were induced. Another study reported that 2-week-old calves vaccinated parenterally with a KV BRSV vaccine and challenged 21 days later did not develop anamnestic antibody responses; however, vaccinated calves were protected against severe clinical disease and had increased BRSV-specific IFN-γ production in peripheral lymphocytes 1 week after challenge (van der Sluijs *et al.*, 2010).

Intranasal (IN) vaccination of calves with MLV vaccines containing BRSV has produced mixed results. Woolums *et al.* (2004), reported that 4 to 6-week-old calves vaccinated IFOMA with an IN MLV vaccine and challenged at 8 weeks of age with BRSV had reduced clinical signs of disease following challenge. In this study, anamnestic antibody responses were not induced in vaccinated calves; however, IFN-γ production was increased in lymphocytes from lymphoid bronchial tissue. Another study reported that 3 to 8-day-old calves vaccinated IN with a MLV BRSV vaccine were not completely protected against challenge with BRSV at 4.5 months of age (Ellis *et al.*, 2010). In this study, vaccinated calves demonstrated similar levels of virus shedding and similar lung lesions compared with controls. Additionally, antibody responses in serum and nasal secretions were not different between vaccinated and unvaccinated calves. Intranasal or subcutaneous (SC) vaccination of 3 to 8-day-old BRSV-seronegative calves challenged with BRSV 21 days after vaccination resulted in clinical protection; however, significant antibody responses or production of IgA in the upper respiratory tract were not detected after challenge (Ellis *et al.*, 2010). In a similar study 2 to 9-week-old calves were vaccinated with a single component IN MLV BRSV vaccine, calves were protected at challenge 8 days after vaccination and had increased concentrations of IgA and IFN-α in nasal secretions. Additionally, vaccinated calves developed anamnestic antibody responses following BRSV challenge when a 2 dose of vaccine was administered 21 days later (Ellis *et al.*, 2007).

Field trials of vaccination IFOMA and prevention of bovine respiratory disease

The best way to evaluate the efficacy of vaccination of calves IFOMA against natural infection with respiratory viruses is through well-designed field trials. Unfortunately, the inability to control the occurrence of natural disease and other logistic complications under field conditions limit publication of these types of studies. A previous study described the efficacy of vaccination of calves at 3 and 5 weeks of age with a MLV BRSV vaccine and a *Mannheimia haemolytica* leucoctoxin/*Histophilus somni* bacterial extract to reduce a high incidence of BRDC in calves from a farm where BRSV and *M. haemolytica* had been previously isolated. The proportion of calves treated for BRDC as determined by the owner was higher in calves that did not receive any vaccine (34%) compared with calves that received both vaccines (15%) (Van Donkersgoed *et al.*, 1994). In another study on a dairy heifer rearing operation, calves were vaccinated IFOMA at 15 days of age with a multivalent KV vaccine containing BVDV1 and at 45 days of age with a multivalent MLV vaccine containing BVDV1. Exposure to BVDV measured as proportion of calves that seroconverted to BVDV1 was reduced in vaccinated calves. Additionally, it was estimated that vaccination prevented 48% of BVDV1 transmission among calves from 4 to 9 months of age (Thurmond *et al.*, 2001). A recent trial involving 2874 dairy calves reported that vaccination of calves with a multivalent MLV vaccine containing BVDV1, BVDV2, and BRSV at 21 days, 28 days, or both did not reduce incidence of BRDC during the first 3 months of life (Windeyer *et al.*, 2012); however, the median calf age for BRDC treatment was 30 days and 44% of the cases of BRDC occurred before completion of the vaccination protocol.

Clinical recommendations based on current research

Experimental trials evaluating the efficacy of vaccination IFOMA against common respiratory viruses in young calves indicate that immunological responses and clinical outcome following vaccination are variable and could be influenced by several factors. However, research evaluating the response of calves vaccinated prior to experimental challenge with BVDV2 or BRSV provides

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the basis for some clinical recommendations that may be helpful in planning vaccination programs for young calves:

- A single dose of a multivalent MLV vaccine containing BVDV1, BVDV2 and/or BRSV administered parenterally or intranasally to calves that received maternal colostrum and are older than 2 weeks can offer some degree of clinical protection against challenge by these viruses later in life when maternal antibodies have disappeared.
- A single dose of a KV vaccine containing BVDV1, BVDV2 and/or BRSV administered parenterally to calves that received maternal colostrum and are older than 2 weeks could offer clinical protection after challenge; however, the administration of a second dose after 4 weeks is recommended.
- Parenteral or intranasal administration of KV or MLV vaccines containing BVDV1, BVDV2, and/or BRSV to calves younger than 2 weeks with high levels of maternally derived antibodies may not be useful, as vaccination might not result in clinical protection after challenge later in life.
- Parenteral or intranasal administration of MLV vaccines containing BVDV1, BVDV2, and/or BRSV to calves deprived of specific maternal immunity due to failure to receive an adequate volume of good quality colostrum effectively primes B- and T-cell responses and can offer clinical protection to calves after challenge.

Conclusions

Vaccination of young calves IFOMA against BVDV1, BVDV2, and BRSV has been demonstrated to prime humoral and cell mediated immune memory responses that provide different degrees of protection against viral challenge with BVDV2 and BRSV. Factors such as age at vaccination, level of maternally derived immunity, route of administration, presence or not of a vaccine adjuvant and type of vaccine could affect immune responses of calves vaccinated IFOMA. Vaccination of calves with high levels of maternally derived antibody to BVDV1 and BVDV2 has been demonstrated to activate specific T-cell memory responses to these viruses and provides protection against clinical disease; however, activation of BVDV1- and BVDV2-B cell memory responses might not be optimal in the presence of high levels of maternally derived immunity, and B-cell memory responses may be necessary to increase antibody production and prevent BVDV viremia and virus shedding.

Prevention of clinical signs of disease and reduction of viremia and virus shedding are the most important outcomes of vaccination IFOMA. However, current research on vaccination IFOMA against respiratory viruses such as BVDV1, BVDV2, and BRSV suggests that calves that fail to increase antibody levels after vaccination and to develop anamnestic antibody responses after BVDV2 or BRSV challenge might have a higher risk of developing viremia and viral shedding. Failure to prevent or reduce viral shedding at challenge with BVDV2 and BRSV could increase the risk of virus transmission and affect overall calf-herd health. Further research that clarifies how vaccination IFOMA can most effectively be used to not only prevent clinical disease, but also to prevent viral shedding, could help veterinarians and farmers better prevent disease in groups of calves.

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