CATTLE HEALTH MANAGEMENT CONFERENCE

VACCINATION TO PROTECT PREGNANCY AGAINST BVDV: BALANCING SAFETY AND EFFICACY

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INTRODUCTION

Bovine viral diarrhea virus (BVDV) has long been recognized as a major cause of reproductive and respiratory diseases in cattle, resulting in significant economic loss to the beef cattle and dairy cattle industries throughout the world. *Bovine viral diarrhea virus* is the prototypic member of the genus *Pestivirus* within the Family *Flaviviridae*. The pestiviruses are enveloped, single-stranded, positive-sense RNA viruses.[1] Historically, the genus *Pestivirus* contained four recognized species which include the two genotypes of BVDV (BVDV-1 and BVDV-2), *Classical swine fever virus* and *Border disease virus*. Genetically distinct pestiviruses which had not been designated as unique species included Giraffe virus, Bungowannah virus, Pronghorn virus, and HoBi-like 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. *Pestivirus* A-D correspond to the classic four species, BVDV 1, BVDV 2, classical swine fever virus, and border disease virus, respectively, while Pestivirus E-K correspond to pronghorn antelope pestivirus (E), Bungowannah virus (F), giraffe pestivirus (G), Hobi-like pestivirus (H), Aydin-like pestivirus (I), rat pestivirus (J), and atypical porcine pestivirus (K), respectively. A part of the logic for this new classification scheme is the knowledge that not all BVDV strains are host restricted to cattle. Similar to many RNA viruses, mutations can occur within BVDV genomes leading to genetic, antigenic and pathogenic variation. BVDV exists as a quasispecies, which are different but closely related mutant viral genomes subjected to continuous competition and selection. Nucleotide sequence differences are the most reliable criteria for differentiation of BVDV species. Subgenotypes of BVDV are described within BVDV-1 and BVDV-2 species, twelve among BVDV-1 viruses (BVDV-1a through BVDV-1l) and two among BVDV-2 viruses (BVDV-2a and BVDV-2b). 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, accounting for 78% of bovine persistent infections in one North American study.

Strains of BVDV can be also be further subdivided into cytopathic (CP) or noncytopathic (NCP) biotypes based upon their effect on cultured cells, with CP strains causing vacuolation and death of cultured cells. The effect of the virus in cultured cells does not correlate with virulence, as NCP BVDV are associated with cases of severe clinical disease, and only NCP strains of BVDV have been demonstrated, both naturally and experimentally, to induce persistent infection. The NCP biotype predominates in the cattle population, accounting for approximately 90% of BVDV isolates. The NCP biotype is often the source for CP strains, which arise by mutations and recombination in the NCP strain. Since CP strains are incapable of resulting in persistent BVDV infections, these strains have become common as vaccine strain candidates.

BVDV infection in cattle may result in a wide spectrum of clinical manifestations ranging from subclinical to fatal disease. Clinical manifestations associated with BVDV are dependent upon the interplay of host factors, environmental stress levels, and viral factors.[2] 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 considered by many the most important aspect of BVDV infection as this 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 of fetal development from gestation day 45 to gestation day 125 which is the gestational period bracketed by the end of the embryonic stage and the development of fetal immunocompetence.[3] Infecting biotype is important to the development of persistent infection. While infection with either biotype is capable of causing fetal death, only NCP strains are associated with persistent infection.[4] All genotypes and subgenotypes of BVDV appear to be capable of causing PI's. Successful control of BVDV in cattle herds requires a multidimensional approach, involving vaccination, biosecurity and identification of BVDV reservoirs.[5] Because PI cattle are the main source of transmission within and between beef and dairy cattle herds, most of recent research assessing BVDV vaccination efficacy has focused on prevention of fetal infection and the generation of PI offspring.

AVAILABLE VACCINES

Many BVDV vaccines are available, and the majority of USDA licensed vaccines contain BVDV in combination with other bovine respiratory and reproductive pathogens. Prior to 1995, most BVDV vaccines contained only BVDV1 strains, but because of antigenic diversity and outbreaks of severe clinical disease in association with BVDV 2 strains, modified-live and inactivated vaccines containing both BVDV1 and BVDV2 strains are now widely available and more routinely used. Predominance of the BVDV-1b strains in North America is noteworthy because most vaccines licensed and marketed in the United States contain BVDV-1a and BVDV-2 strains (**Table 1**).

Table 1. Current BVDV vaccines. (MLV = modified-live viral; KV = killed viral; cp = cytopathic**)**

Vaccine	Manufacturer	Formulation	BVDV 1a strain	BVDV 2 strain
Express 5	Boehringer Ingelheim Vetmedica, Inc. (BIVI)	MLV	Singer (cp)	296 (cp)
Pyramid 5	BIVI	MLV	Singer(cp)	5912 (cp)
Bovishield Gold 5	Zoetis	MLV	NADL (cp)	53637 (cp)
Titanium 5	Elanco	MLV	C24V (cp)	296 (cp)
Vista 5 SQ	Merck	MLV	Singer (cp)	125A (cp)
MasterGuard 5	Elanco	KV	C24V (cp)	125c (cp)
Triangle 5	BIVI	KV	Singer (cp)	5912 (cp)
CattleMaster Gold FP	Zoetis	KV	5960 (cp)	53637 (cp)
ViraShield 6	Elanco	KV	K22 (cp) GL760 (ncp)	TN131 (ncp)

Advantages and disadvantages of BVDV modified-live viral vaccines and inactivated vaccines have been described.[6] Modified-live and inactivated vaccines have been shown to be safe when administered according to the manufacturer's label. In general, modified-live viral vaccines are believed to more effective since they induce both humoral and cell-mediated immune responses. One disadvantage of inactivated BVDV vaccines is that two doses are required for the initial immunization, and a major problem with programs using inactivated vaccines is the widespread lack of compliance among producers by failing to booster the primary series.[7]

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 prevention and control, they are not 100% efficacious, meaning that no vaccine will prevent all infections from occurring.[8] Reasons for lack of efficacy of vaccination against BVDV are many, and include factors related to the administration of the vaccine and factors related to the ability of the host to respond to the vaccine. Control of any infectious disease relies upon eliminating the reservoirs of the pathogen and limiting transmission from infected individuals to susceptible animals. Development and implementation of herd health programs that involve vaccination and biosecurity to limit exposure of pregnant cattle to PI cattle are important for success of control. Protection against viremia is the true measure of BVDV vaccine efficacy. To be truly efficacious, vaccination against BVDV should protect against viremia to prevent dissemination of virus throughout the host, including preventing infection of target cells of the reproductive tract that result in fetal infection. In the past decade, the focus for vaccine efficacy has shifted from protection against clinical disease to protection against fetal disease or infection. Published studies indicate the protection against fetal infections following BVDV vaccination varies anywhere from 60-100%. This wide degree of variation depends upon whether the vaccine is inactivated or modified-live, the timing of challenge, and upon the degree of homology between the vaccine strains and the challenge strains. Fetal protection studies have been performed evaluating commercial vaccines containing only BVDV 1 strains and commercial vaccines containing both BVDV 1 and BVDV 2 strains. From published studies, it would appear that protection is superior when animals are challenged with strains from the same genotype. Since BVDV 1 strains exist more commonly as BVDV 1b in the United States, there has been great concern by the BVDV research community that current vaccines containing BVDV 1a and BVDV 2 do not fully prevent infection and viremias when animals are exposed to antigenically diverse BVDV 1b strains.

MEASUREMENTS OF VACCINE EFFICACY

The requirements for vaccine licensure in the United States were first described within the Code of Federal Regulations (CFR) 113.311 for 'Bovine virus diarrhea vaccine" (MLV) and 113.215 "Bovine virus diarrhea vaccine, Killed virus." These licensing documents describe the requirements for immunogenicity. To summarize from the CFR113.311 guidelines for modified-live BVDV viral vaccines (http://edocket.access.gpo.gov/cfr_2003/9cfr113.311.htm), immunogenicity was determined by testing for neutralizing antibodies in 20 vaccinated calves as compared to 5 unvaccinated calves. Efficacy was determined by challenging the calves with virulent BVDV two to four weeks after vaccination. A BVDV vaccine is considered immunogenic if 19 of the 20 vaccinated develop an antibody response (>1:8 titer), with efficacy being defined as vaccinates not developing leukopenia where 4/5 unvaccinates did.

These early licensing requirements did not address efficacy related to reproductive disease or reproduction-related label claims. The vaccine claims for protection of the fetus against BVDV were described in the Center for Veterinary Biologics Public Notice 02-19 (http://www.aphis.usda.gov/animal_health/vet_biologics/publications/notice_02_19.pdf). The label claims for BVDV reproductive effects are divided into claims for fetal protection and claims for abortion (maternal and/or fetal causes). Here, the label claims are type-specific, i.e. BVDV 1 or BVDV 2 protection. Supporting data for the label claim is performed according to Veterinary Services Memorandum 800.202.

Three categories for label claims are: 1) aids in the prevention of abortion, 2) aids in the prevention of persistently infected calves, and 3) aids in the prevention of fetal infection or aids in the prevention of fetal infection including persistently infected calves. Most clinical trials evaluating vaccine efficacy are performed with the goal of achieving efficacy claims for the prevention of persistently infected calves. These studies are characterized by vaccination prior to breeding, then challenging the pregnant cattle between days 75-90 of gestation, and finally testing the fetuses on or after 150 days of gestation. Virus isolation procedures are performed on fetal tissues, and those fetuses from which BVDV is isolated are considered to be persistently infected.

Protection from clinical disease

Initially, the effectiveness of BVDV vaccination was focused on limiting clinical disease due to BVDV infection. Numerous studies have demonstrated the ability of vaccination to protect against overt clinical disease associated with BVDV, and many trials have investigated the ability of commercially available BVDV vaccines in protecting against the high virulent BVDV 2 strains isolated from outbreaks of severe peracute BVD in the late 80's and early 90's. Experimental[9,10] and field data[11] indicate vaccination with either inactivated or modified-live BVDV vaccines are effective at reducing or obviating clinical disease. In addition, modified-live viral vaccines containing BVDV 1 strains are effective at limiting or preventing clinical disease when vaccinated animals are subsequently challenged with a virulent BVDV 2 strain.[12,13] Protection from clinical disease is important for stocker/backgrounder and feedlot operations, and immunity to BVDV has been demonstrated to be protective against bovine respiratory disease complex. Preconditioning cattle by vaccinating cattle against BVDV prior to an expected exposure (commingling and shipping) reduces the effects of exposure of cattle to BVDV.

Prevention of fetal infection

For the reproductive herd, vaccination against BVDV should protect against viremia to prevent dissemination of virus throughout the host, including preventing infection of the reproductive tract and fetus. In the past decade, the focus for vaccine efficacy has shifted from protection against clinical disease to protection against fetal infection. Published studies indicate the protection against fetal infections following BVDV vaccination varies, with influences by use of inactivated or modified-live vaccine, the timing of challenge, and the degree of homology between vaccine and challenge strains. In general, most experimental studies indicate significant, although incomplete, protection against fetal infection using modified-live viral vaccines,[14-17] and partial protection using inactivated viral vaccines.[18,19] The genotype of the challenge strain is important, and fetal protection is superior when animals are challenged with strains from the same genotype.[17]

An important observation regarding all of the fetal protection studies so far is that although protection may not be 100%, the level of protection is superior to that observed when proper vaccination is not utilized as evidenced by higher rates of PI animals in unvaccinated cattle. Recently, cattle PI with BVDV have been used for the challenge exposure of vaccinated and control cattle in BVDV vaccine efficacy studies evaluating fetal protection.[16,18-20] These types of studies provide a more natural and rigorous challenge method.

Within the United States cattle population, there are three major subtypes, BVDV1a, BVDV1b, and BVDV2a, with the BVDV1b subtype predominating from diagnostic laboratory submissions and PI prevalence studies, accounting for 78% of bovine persistent infections in one North American Study.[21] Because of the finding of higher isolation rates for BVDV 1b strains and the fact that commercial vaccines for BVDV contain BVDV 1a and/or BVDV 2a strains, logic would dictate that challenge experiments should be performed using cattle PI with BVDV 1b strains. Two clinical trials have evaluated commercial modified-live viral vaccines in their efficacy in preventing fetal infections.[14,16] Like previous studies, these studies have demonstrated that modified-live BVDV vaccines provide significant (85-96%), although incomplete, protection against fetal infection.

VACCINATION STRATEGIES

Designing a vaccine program is critical in helping to control BVDV associated losses and giving producers a sense of security. In general, vaccines do not fail; vaccination programs fail. Timing of vaccination is a critical issue. Providing young calves with immunity can help reduce disease and death associated with BVDV infections. Timing of vaccination has been performed to co-incide with the decay of colostral antibodies, which may occur as early as a few weeks to as long as 8 months of age. Recent research has demonstrated that vaccination of young calves that possess colostral antibodies can result in an immune response that provides protection against clinical BVD later on in life.

Vaccination programs aimed at preventing reproductive losses may have different timing than vaccination programs aimed at preventing losses associated with clinical disease, such as pneumonia in weaned calves. Maximizing immunity during the early periods of gestation is most likely to reduce BVDV-associated reproductive losses. This is achieved through the use of prebreeding vaccination and boostering. The use of a modified-live viral vaccine at 1 month prior to breeding has been recommended to the point of being indisputable. However, vaccinating or using booster vaccines in the early lactation period of dairy cows (15-45 days in milk) can be an immunological challenge for cows due to negative energy balance. Delaying vaccination until after this period may provide better immunity.

SUMMARY

Nothing seems to generate more opinions regarding BVDV than what vaccine is the best to control BVDV, and in fact, choices and opinions are many. Even though controversy exists, most everyone believes that when vaccines are given correctly, at appropriate times, to healthy cattle, they are better than not vaccinating at all. In general, currently available vaccines provide adequate protection against clinical disease. Prevention of infection in pregnant animals is the ideal measure of vaccine efficacy.

REFERENCES

1. Ridpath JF. Bovine viral diarrhea virus: Diagnosis, management and control. Ames, IA: Blackwell Publishing; 2005:65.
2. Baker JC. **Vet Clin North Am Food Anim Pract** 1995;11:425.
3. McClurkin AW, et al. **Can J Comp Med** 1984;48:156.
4. Harding MJ, et al. **Am J Vet Res** 2002;63:1455.
5. Walz PH, et al. **J Vet Intern Med** 2010;24:476.
6. Fulton RW. Bovine viral diarrhea virus: Diagnosis, management and control. Ames, IA: Blackwell Publishing; 2005:209.
7. Rauff Y, et al. **J Am Vet Med Assoc** 1996;209:1618.
8. Grooms DL, et al. **Bovine Practitioner** 2009;43:106.
9. Dean HJ, Leyh R. **Vaccine** 1999;17:1117.
10. Cortese VS, et al. **J Am Vet Med Assoc** 1998;213:1312.
11. Carman S, et al. **J Vet Diagn Invest** 1998;10:27.
12. Kelling CL, et al. **Am J Vet Res** 2007;68:788.
13. Makoschey B, et al. **Vaccine** 2001;19:3261.
14. Xue W, et al. **Vaccine** 2011;29:4657.
15. Brock KV, et al. **Vet Ther** 2006;7:27.
16. Leyh RD, et al. **Am J Vet Res** 2011;72:367.
17. Ficken MD, et al. **J Am Vet Med Assoc** 2006;228:1559.
18. Grooms DL, et al. **Am J Vet Res** 2007;68:1417.
19. Rodning SP, et al. **Theriogenology** 2010;73:1154.
20. Ellsworth MA, et al. **Vet Ther** 2006;7:295.
21. Fulton RW, et al. **J Am Vet Med Assoc** 2006;228:578.