Bovine Viral Diarrhea (BVD): Review for Beef Cattle Veterinarians

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Abstract

Characteristics of bovine viral diarrhea virus (BVDV), such as its genetic diversity and ability to induce a persistently infected (PI) carrier state, make its control a challenge. A systematic control program that utilizes diagnostic testing strategies to identify PI cattle, vaccination to increase fetal protection from infection, and biosecurity to reduce the risk of exposure to infected animals is necessary for control of BVD.

The primary reservoir for BVDV is PI cattle. If a herd has had recently confirmed PI calves, or if the history strongly suggests the presence of PI calves, then all calves, replacement heifers, bulls, and non-pregnant dams without calves should be tested for PI status. Positive cattle should be removed prior to the start of breeding. Because of the low prevalence of herds with PI animals, whole-herd screening protocols for herds at low risk for PI cattle may not be justified. Several strategies short of whole-herd screening can be employed to monitor herds for the presence of PI cattle.

Biosecurity to reduce the risk of exposure to BVDV should also be implemented. Replacement heifers and bulls should be tested and confirmed PI-negative prior to the start of breeding. If a pregnant animal is purchased, she should be segregated until both dam and calf are confirmed PI-negative. Fence line contact with neighboring herds should be avoided during early gestation unless they also have a strict biosecurity program in place. Vaccination to reduce the risk of fetal infection in the event of exposure to a BVDV-shedding animal is an integral part of a biosecurity program.

Résumé

Les caractéristiques particulières du virus de la diarrhée virale bovine (BVDV), telles que sa diversité génétique et l'induction d'un état d'infection permanente (PI), en font un virus difficile à contrôler. Afin de contrôler le BVD, il est nécessaire d'avoir un programme systématique de contrôle incluant un volet stratégie de dépistage diagnostic des bovins infectés de manière permanente, un volet vaccination pour accroître la protection des fœtus contre l'infection et enfin un volet biosécurité pour réduire le risque d'exposition aux animaux infectés.

Les bovins PI constituent le principal réservoir du BVDV. Dans le cas d'un troupeau présentant des cas confirmés de veaux PI ou si l'on soupçonne fortement la présence de veaux PI, il est suggéré de tester tous les veaux, les génisses de remplacement, les taureaux et les vaches non gravides sans veaux pour le statut d'infection permanente. Les bovins positifs devraient être retirés avant le début de la période de reproduction. Compte tenu de la faible prévalence des troupeaux avec des bovins PI, des protocoles de dépistage au niveau du troupeau pour les troupeaux à faible risque pour ce type d'infection ne sont pas toujours justifiables. Plusieurs stratégies de dépistage n'impliquant pas tout le troupeau peuvent être utilisées pour surveiller les troupeaux pour la présence de bovins PI.

Un volet biosécurité devrait aussi être mis en place pour réduire le risque d'exposition au BVDV. Les génisses de remplacement et les taureaux devraient être testés et avoir un statut négatif à l'infection permanente avant la reproduction. Si un animal gravide est acheté, il faudrait l'isoler jusqu'à ce que le statut négatif d'infection permanente soit déterminé pour la vache et son veau. Il faudrait aussi éviter les contacts près des clôtures avec des vaches d'autres troupeaux durant la période initiale de gestation à moins qu'un programme de biosécurité ne soit aussi en place dans ces troupeaux. La vaccination est une partie intégrale d'un programme de biosécurité pour réduire le risque d'infection des fœtus dans le cas d'une exposition à un animal excrétant des BVDV.

Introduction

Management and control of bovine viral diarrhea virus (BVDV) infection in cattle herds must consider two methods of transmission: postnatal horizontal infection and gestational vertical infection from a viremic dam to her fetus.[57] Postnatal infection results in a transient infection that is usually mild or subclinical, but can result in severe disease in seronegative cattle exposed to a virulent strain of the virus.[33,46] In addition, postnatal horizontal infection can lead to vertical transmission of BVDV if a susceptible pregnant dam becomes viremic following horizontal exposure, and subsequently infects her fetus.

The primary reservoir for and source of BVDV are cattle persistently infected (PI) with BVDV, with transiently infected cattle considered a less important source. Persistently infected animals are more efficient transmitters of BVDV than transiently infected animals because they secrete higher levels of virus for a longer period of time. After a short incubation period, transiently infected animals become viremic and virus may be shed in body secretions and excretions from days 4 to 15 post-infection.[14,26] In contrast, PI animals usually have a very high and persistent viremia, and BVDV is shed throughout life from virtually all secretions and excretions including nasal discharge, saliva, semen, urine, tears, milk, and to a lesser extent, feces.[4,10,11,71] Fetuses, placentae and fetal fluids from BVDV-induced abortions can also contain BVDV. Horizontal transmission of BVDV to seronegative cattle has been shown to occur after only one hour of direct contact with a single PI animal.[80] Over-the-fence contact with a PI animal from a neighboring herd can also introduce BVDV into a susceptible herd.[60,74]

Transiently infected cattle are considered far less efficient at transmitting the virus to susceptible animals.[58,64,65] However, seroconversion among assembled cattle without the presence of PI animals indicates that transmission from transiently infected animals does occur, although spread is considered to be slower.[57,61] Horizontal transmission of the virus from either persistently or transiently BVDV-infected animals to susceptible cattle in direct contact may be via inhalation or ingestion of virus-containing body fluids.[26] In addition, air transmission over short distances seems likely; however, when cattle are housed at greater distances from PI animals, the spread of infection is slow or absent.[83]

Clinical effects of BVDV in beef cattle

Even mild or subclinical infections of susceptible breeding females can cause conception failure and may cause early embryonic loss, abortion or vertical fetal infection in pregnant, susceptible females. The immune status of the dam, stage of gestation, and the viral biotype are important factors in determining the result of vertical infection. Transplacental infection occurs with high efficiency during the pregnancy of seronegative dams.[23,56] However, naturally acquired immunity is considered to provide good, but not necessarily complete, protection against fetal infection.[67] Fetal infection can lead to early embryonic death, abortion, congenital defects, the birth of PI calves, or the birth of normal calves.[1] Fetal infection early in the gestation of seronegative dams with a cytopathic biotype of BVDV will result in abortion. However, fetal infection with a noncytopathic biotype of BVDV will result either in abortion or, in a certain percentage of infections, survival of a calf that is immunotolerant to and persistently infected with that noncytopathic strain of BVDV. Persistently infected cattle are the result of *in utero* exposure to the noncytopathic biotype of BVDV prior to the development of a competent fetal immune system.[16,56] Age at immune competence in the face of BVDV exposure is variable and has been reported to range from 90 to 125 days.[16,56,75] If PI fetuses survive to term, they are continually infected, but immunotolerant to the homologous BVDV.[26,75] In addition to BVDV causing conception failure and abortion, reproductive efficiency can be decreased due to fatal congenital defects following fetal infection between 100 and 150 days of gestation.[26] Teratogenic lesions associated with fetal infection with BVDV include microencephaly, cerebellar hypoplasia, hydranencephaly, hydrocephalus, hypomyelination of the spinal cord, cataracts, retinal degeneration, optic neuritis, microphthalmia, thymic aplasia, hypotrichosis, alopecia, brachygnathism, growth retardation and pulmonary hypoplasia.[1]

BVDV reservoir and transmission

In beef herds, suckling calves are commonly in contact with the breeding herd during early gestation, prior

to the time the bovine fetus develops a competent immune system. As a result, PI suckling calves are considered to be the primary source of BVDV infection in breeding herds causing decreased pregnancy percentage, pregnancy loss, pre-weaning mortality and the induction of PI calves in the next generation.[26,56,85]

Although mortality of PI calves prior to weaning has been reported to be very high due to fatal congenital defects and secondary infections that cause enteritis, pneumonia and arthritis,[55,56] 17 to 50% of PI calves may reach breeding age.[2,6,39] Persistently infected females of breeding age are not only a source of horizontal transfer of BVDV, but will always produce a PI calf themselves.[41,55]

The result of introduction of a PI animal into a beef herd with a confined breeding and calving season depends on the timing of the introduction relative to the breeding season and the immunologic status of the herd during early gestation. Even in the absence of vaccination, the number of PI animals and the amount of BVDV infection in a herd seems to be self-limiting.[40] A likely scenario for a BVDV-exposed herd is an initial peak of disease, followed by low-level chronic reproductive losses in subsequent months and years. If a PI animal enters the herd either by birth or by introduction near the start of the breeding season, a high percentage of the herd may not be immunologically protected to the degree necessary to prevent viremia, conception failure, abortion, or fetal infection. Once the PI animal is in contact with the breeding herd for a sufficient time period, the majority of the herd is likely to become infected and seroconvert. Seropositive animals are less likely to have BVDV-associated reproductive failure compared to seronegative animals. Even if no intervention steps are taken, the number of susceptible females the following year will likely be greatly decreased and the number of abortions and infected fetuses (both persistently infected and immunocompetent) is expected to decrease. A model developed by Cherry et al[17] indicates that in continuous calving dairy situations, the proportion of PI animals in the herd will reach an equilibrium of about 0.9 to 1.2% in herds with no BVDV control procedures.[17]

Estimates of the prevalence of PI animals in the general cattle population have been reported to range between 0.13% and 2.0%.[8,41,43,85] Differences in reported prevalence may be due to the population tested, the country/continent where the population was located and/or the diagnostic tests utilized. Persistent infection has a clustered distribution, which means a few herds may contain several persistently infected cattle but most herds contain only non-PI cattle.[7] Clustering of multiple PI animals in a herd is due to exposure of numerous susceptible dams to a PI or transiently infected source of noncytopathic BVDV prior to day 125 of gestation.

Diagnostic tests for the identification of cattle persistently infected with BVDV

Cattle persistently infected with BVDV can be identified by virus isolation from whole blood (buffy coat) or other tissues, microtiter virus isolation (ImmunoPerioxidase Monolayer Assay; IPMA) from serum, immunohistochemistry (IHC) staining of viral antigen in skin biopsies, antigen-capture enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) methods.[25]

Virus isolation

Persistently infected animals produce an exceptionally large number of BVDV particles that can be isolated from virtually any tissue. Virus isolation is considered to be very specific for BVDV infection; however, colostral antibodies may temporarily reduce the amount of free virus in the serum of young calves and make the test less sensitive.[10,47,68] In the presence of sufficient passively acquired BVDV antibodies, virus from PI calves cannot be detected in serum or whole blood by virus isolation. However, once maternal antibodies begin to wane, BVDV can be demonstrated repeatedly. Maternal antibodies had disappeared and BVDV could be isolated by six weeks of age in all four calves in one study,[10] and by eight weeks of age in all 11 PI calves in another study.[68] A few PI calves will develop neutralizing antibodies to heterologous BVDV strains which may cross-react with the PI strain and can clear the virus from serum. Therefore, in some PI cattle, virus isolation will only be possible from white blood cell samples, rather than serum.[10] Virus isolation methods are labor intensive and take several days to complete. An additional shortcoming is that virus isolation may not differentiate between transiently infected animals and PI animals, unless positive cattle are re-tested and remain positive at a later date (i.e. three weeks later).

Immunohistochemistry

An IHC test for BVDV infection using a skin biopsy sample, such as that obtained with ear notch pliers, identifies PI animals but usually not transient BVDV infections.[66] Transiently infected animals may have internal organ tissue samples that are IHC positive. However, when skin samples were evaluated, transiently infected animals either had no staining, or staining was confined to the epidermal keratinocytes and follicular ostia, in contrast to PI cattle with antigen-positive staining cells in all layers of the epidermis, all levels of hair follicles, and the hair bulb.[66] If the animal is very valuable, or if history and clinical examination are not consistent with a diagnosis of being PI, positive results should be confirmed with a second test

three weeks after the first. The IHC test is suitable for herd screening because samples can be taken from cattle of any age, sample collection is simple, the samples are stable for transport and handling, and the test is both sensitive and specific for BVDV PI cattle.[3,27,66] In addition, use of a modified live BVDV vaccine did not cause false positive IHC results of skin biopsies when testing for PI animals.[24]

Polymerase chain reaction

Polymerase chain reaction testing for BVDV infection is more rapid than virus isolation and can detect virus in antigen-antibody complexes.[10] Polymerase chain reaction tests are sensitive and protocols are available to differentiate between BVDV genotypes. However, a single BVDV positive blood sample tested by PCR does not allow the diagnostician to differentiate between viremia from a postnatal acquired infection and viremia due to being PI. Because PCR tests can identify minute amounts of virus, this test can be used in pooled samples of blood or milk in surveillance programs. Because PCR is able to detect a transient viremia present 3 to 10 days following vaccination with a modified live virus (MLV) BVDV vaccine, interpretation of PCR results must consider timing of vaccination with MLV products.[49]

Serology

Although PI cattle are usually seronegative to BVDV once maternal antibodies have cleared, an immune response can be elicited to a heterologous strain.[10] Presumably, this response can follow either natural or vaccine exposure. Residual maternal antibodies in the serum of young PI calves can cause a false-negative diagnosis if relying on the presence of serum neutralizing antibody to rule-out PI status. In addition, some cattle in both vaccinated and unvaccinated herds are seronegative, making serology alone unsuitable for identification of PI animals.[8,41,85]

Diagnostic testing strategies to identify PI calves

Because the PI animal is an important reservoir and transmitter of BVDV, control programs must first identify and remove these animals from the breeding herd. Exposing a breeding herd to PI cattle is likely to cause transient BVDV infections of susceptible cows, and the subsequent vertical transmission of BVDV to their fetuses if pregnant. To prevent contact with pregnant cows, PI animals should be removed prior to the start of the breeding season. In order to find and remove PI cattle prior to the start of the breeding season, all calves, all replacement heifers, all bulls, and all non-pregnant dams without calves (due to not be-

coming pregnant, aborting, or calf mortality) must be tested for PI status.[45] Any female that is pregnant at the time the herd is tested should be isolated from the breeding herd and kept isolated until her calf is tested and found to be negative.

If a herd has had recently confirmed PI calves, or if the history strongly suggests the presence of PI calves, the *a priori* assessment of PI prevalence is fairly high. This makes the predictive value of a single positive test high enough to conclude that the individual is a PI and that the herd has PI animals present, and therefore a second confirmatory test may not be justified. In contrast, if the diagnostician has no *a priori* evidence of PI prevalence greater than the range of 0.3 to 0.5% reported for US beef herds, the predictive value of a positive test is low and a different confirmatory test may be advisable before making conclusions about the individual and herd. Once a calf is identified as PI, it should be euthanized or removed for slaughter and the dam should be tested. Most dams of PI calves are not PI themselves, and if confirmed as non-PI, can re-enter the breeding herd because naturally acquired immunity is considered to be good protection from future fetal infections.[67] Dams identified as a PI should be slaughtered immediately.

In most whole herd testing situations, IHC testing of skin samples is the test of choice because it can be accurately performed on animals of any age, and a single sample is all that is usually needed. Other tests can be used for confirmatory testing following presumptive positive results from IHC when the history or clinical presentation does not concur with a diagnosis of PI. Using virus isolation or PCR to identify PI cattle requires a second test at least three weeks following any positive samples to differentiate between transient viremia and PI with BVDV.

Monitoring herds for BVDV PI risk

The cost of initiating a BVDV PI whole-herd screening protocol on a farm or ranch is significant. Because of the low prevalence of herds with at least one PI animal, veterinary practitioners may not be economically justified to initiate whole-herd screening protocols to find PI cattle in herds at low risk for the presence of PI cattle or herds that cannot gain significant market price advantage for selling groups of cattle that have been tested and determined to be free of PI individuals.[51,85] However, if ranch history raises the suspicion of presence of PI cattle in the herd, or if significant marketing advantages exist, a protocol to screen the herd can be defended based on its likelihood to improve or protect economic return.[51] Several strategies can be employed to monitor herds for their risk of having PI cattle present.

Use of production records and laboratory evaluation of moribund and dead calves

The minimal level of surveillance for every herd should include monitoring herd fertility (early breeding season pregnancy proportion, pregnancy per insemination proportion, and total pregnancy proportion), neonatal calf morbidity and mortality proportions, and weaning proportions. Because of the negative effect of the presence of PI calves in a breeding herd on measures of reproductive efficiency, the presence of physical abnormalities at birth and calf survivability to weaning, an unacceptable level of these clinical presentations increases the risk that BVDV is a problem in the herd and increases the likelihood that whole-herd screening for PI cattle will be economically rewarding.[42] In many situations, pregnancy rate drops significantly at the time of conception of the oldest PI animal, and about six months later calf mortality increases. However, using production records alone lacks sensitivity for identifying herds with PI animals because the clinical indications of PI presence may be less noticeable in some outbreaks.[42] The clinical signs and time sequence following introduction of BVDV infection into different herds varies considerably due to the different proportions of susceptible animals in the critical period of pregnancy and different virulence among BVDV strains.[40]

In addition to monitoring production records, minimal surveillance should include necropsy examination of as many aborted fetuses, stillborn calves and calves that die pre-weaning as possible, with whole blood submitted for determination of BVD viremia, and serum submitted for serologic evidence of infection. In addition, moribund calves from clusters of pneumonia, neonatal scours, or septicemia outbreaks that are not easily explained by sanitation or other problems should also be tested for BVDV exposure and PI status. If all perinatal and pre-weaning mortalities are examined for BVDV antigen via IHC and found to be negative, it is not likely that PI animals are present in the herd. As the percentage of mortalities necropsied and tested declines, the ability to detect the presence of PI calves declines. The presence of PI animals in the herd will be established by a single confirmed IHC-positive skin sample. The presence of PI animals is not ruled out and may be considered likely if few moribund or dead cattle are tested and found to be IHC negative, but other tests indicate the presence of viremia, or serology indicates recent BVDV infection and the possibility of contact between PI animals and the moribund or dead sample animals.

The advantage of utilizing production measures and necropsies to determine if herds have either a high or low risk for the presence of BVDV PI animals is that minimal expense is involved, and these management strategies are useful for monitoring other disease and production problems. This level of monitoring is probably appropriate in herds with no evidence of PI animals and at low risk of PI introduction.[51] The disadvantage is that at least one PI animal is allowed in the herd before production losses are identified, and production losses will continue for at least one year after intervention is initiated.

Use of pooled samples for PCR testing

Herd monitoring for the introduction of PI animals can also be accomplished with pooled whole blood or serum samples for PCR testing. By pooling samples, the expense of screening herds with a low prevalence of PI animals is minimized. The polymerase chain reaction is well suited to pooled-sample testing for the presence of BVDV PI animals because it is sensitive enough to detect minute amounts of virus. A single PI animal was detectable in pools of 200 to 250 negative samples.[62] Animals contributing to pools with negative results are all assumed to be non-PI, whereas positive pools may contain samples from PI animals or transiently viremic animals. If the initial pool is PCR-positive, it must be split and retested to differentiate viremic and nonviremic animals. Once the viremic animals are identified, they must be classified as transiently infected or PI with either a subsequent PCR, virus isolation, or IPMA test in three weeks, or via IHC testing of a skin sample.

The best size of the initial pool is determined by the balance between the cost savings of having large numbers of individuals represented in negative pools and few individuals represented in positive pools that require further diagnostics. If pool size is too large, there is an increased chance that any single pool will test positive, requiring additional testing to identify the few truly viremic individuals in the pool. If the samples are grouped in unnecessarily small pools, the cost benefit of pooling samples is lost to the large number of negative pools tested for each positive pool identified.[62] Muñoz-Zanzi et al developed a simulation model to determine that the economically optimum sample size depends on prevalence of true positives in the population. For a PI prevalence of 0.5 to 1.0%, the optimum number of samples in an initial pool is 20 to 30, using a described re-pooling strategy for test-positive initial pools.[62] As prevalence increases the least-cost initial pool size decreases.[62]

If whole blood or serum samples are collected for pooled PCR testing from all suckling calves prior to the start of the breeding season, PI cattle can be identified and removed before contact with pregnant females, thereby eliminating the opportunity for a PI animal within the herd to cause reproductive failure and to cre-

ate more PI animals in the next calf crop. Screening for PI animals at a later time, such as weaning, is discouraged. If samples are taken at weaning, although PI cattle can be removed from the herd, those continuously viremic animals were in contact with pregnant females throughout much of gestation and can cause reproduction and production losses, including the creation of PI calves in the next calf crop.

Use of serologic evaluation of sentinel animals

Herd surveillance of dairy herds has been described using sentinel animals. Pillars *et al* found that serologic evaluation of unvaccinated six- to 12-month-old heifers for both type-I and type-II BVDV to test for the presence of a high serum neutralizing titer had a sensitivity of 66% and specificity of 100% for detecting herds that have PI cattle present.[70] The authors stressed that neutralizing antibody titers be determined for both type-I and -II to avoid false negative classifications.[70] Herds identified as containing PI animals could then utilize other diagnostic tests to identify individual PI animals for removal. In countries that have BVDV control programs that do not allow the use of vaccination, a similar strategy to identify herds with PI cattle has been investigated. This strategy is based on the fact that in unvaccinated herds, there are significantly more antibody-positive animals, especially in young stock, in herds with PI animals than in herds without PI animals.[38] However, because of the variable percentage of antibody-positive animals in herds without PI animals, it was not possible to predict the presence of PI animals in dairy herds in The Netherlands using this method.[86]

Use of annual whole-herd testing

Certain high biosecurity herds, such as herds selling or developing replacement breeding animals, may elect to undergo a high level of surveillance even in the absence of evidence that PI animals are present. This high level of biosecurity may be important to their marketing plan or may indicate a high value placed on avoiding the small, but real risk of introducing BVDV virus into the herd with subsequent negative reproductive, health and marketing consequences. The first year that a beef herd adopts this strategy, all suckling calves, all females that were bred that failed to present a calf on test-day, all replacement heifers, and all bulls should be tested. If any calf is confirmed as a PI animal, its dam should be tested as well. In subsequent years, only suckling calves and any purchased animals need to be tested. If pregnant animals are purchased, the dam should be tested prior to or at arrival, and the calf should be tested immediately after birth. In beef herds with a confined breeding season, this testing must occur before the start of the breeding season to ensure that no PI animals are in contact with pregnant females during gestation. Heifer development operations should test every heifer prior to or at arrival at the facility.

Following the identification and removal of PI animals from a herd, testing of all suckling calves should be done for one or more breeding seasons to ensure the complete accounting for PI animals. Because no test or testing strategy is perfectly sensitive, and because risk factors involved in the initial introduction may still be present, a vigilant monitoring system is wise until a high confidence for PI-free status is achieved.

Other potential sources of BVDV

Bulls (PI and transiently infected)

Male PI calves will occasionally be selected for use as breeding bulls. The amount of BVDV excreted in the semen of persistently infected bulls is very high (10^4-10^6 $TCID_{50}$/ml).[72] When BVDV is infused into the uterus at the time of breeding, seronegative cattle exhibit a significant reduction in conception rate, but seropositive animals may not be adversely affected.[84] BVDV-contaminated semen is an efficient horizontal transmitter of disease from bull to cow.[69] If PI bulls are used for natural service, the cows may conceive when immunity has developed, resulting in the birth of normal (non-PI) calves.[2,55] If PI bulls are used for AI, all or most seronegative females bred with the semen will become infected with BVDV, although most will not produce a PI calf.[58]

Although some evidence exists for BVDV to cause latent infections, particularly in gonads and accessory sex glands, recrudescence and excretion in immune-competent animals has not been shown to be involved in the epidemiology of the disease to date.[12,48,82] Although PI bulls will shed BVDV in semen for prolonged periods of time, virus excretion in semen from transiently infected bulls was confined to days 10-14 following experimental infection, and the virus titer in semen of transiently infected bulls was much lower than for PI bulls.[69]

Embryo transfer

Embryo transfer is a potential route of transmission of BVDV. If the embryo recipient is PI, vertical transmission to the transferred embryo will occur with the creation of a PI fetus.[11] Although there is no evidence to suggest that BVDV is present inside the embryos of viremic females, the virus can be present on the intact zona pellucida of PI and transiently infected females, and the virus is present at high levels in the uterine environment of PI donors.[77] Established washing procedures will remove contaminating virus, but if these procedures are not followed, BVDV from the collection fluids or virus present on the zona pellucida can be horizontally transferred to a susceptible recipient

cow.[76,77] BVDV infection of the recipient cow and embryo can also occur if BVDV-contaminated fetal serum is used in the embryo transfer process, or if contaminated liquid nitrogen is in direct contact with embryos.[5,76]

Other ungulate species (domestic and wildlife)

Other ungulate species may be potential sources of BVDV to susceptible cattle herds. Transmission of BVDV between sheep and cattle has been demonstrated, but the importance of this transmission has not been established.[15] BVDV has also been isolated from pigs, but again, the importance of pigs as a source of the virus to susceptible herds is not established.[52,79] Serologic and virus isolation evidence indicates that deer in both North America and Europe can be infected with BVDV.[21,28,63,81] However, the existence of PI deer has not been demonstrated, and cattle are assumed to be the source of BVDV infection for free-ranging ruminants.

Fomites

Fomites may serve in the transmission of BVDV from PI cattle to susceptible animals. A 19-gauge needle was able to infect susceptible cattle with BVDV when used IV within three minutes of drawing blood from a PI animal.[32] Nose tongs were able to infect susceptible cattle with BVDV when used for 90 seconds within three minutes of being used in a PI animal.[32] Transfer of BVDV from a PI heifer via a common palpation sleeve caused infection in susceptible heifers.[50]

No evidence has been presented that insects are a source of BVDV transmission in field outbreaks. However, a role is possible because BVDV has been isolated from non-biting flies (*Musca autumnalis*) collected from the face of a PI animal. Experimental BVDV transmission between a PI animal and susceptible animals occurred when 50 biting flies fed on the PI animal for five minutes, and 15 minutes later fed on susceptible animals.[32,78]

Vaccination to control BVDV-induced disease and production loss

In addition to removal of PI reservoirs, it is theorized that BVDV transmission to and within the herd can be reduced with an appropriate vaccination program. To date, using information from *in vitro* studies and limited field trials, one can only make empirical recommendations regarding what constitutes an effective vaccination program to limit postnatal and gestational BVDV transmission.

In vitro *evidence of vaccine effects*

In vitro work indicated large variations in the vaccine-induced virus neutralizing titers of individual colostrum-deprived calves vaccinated with two doses (21 days apart) of an inactivated BVDV vaccine or a modified live, temperature-sensitive BVDV vaccine. In spite of the variation in titers, serum from each animal was capable of neutralizing a wide range of antigenically diverse European and American isolates of BVDV, including genotypes I and II.[34,35] Other work has shown that administration of a single dose of a modified live BVD vaccine stimulated an antibody response in seronegative cows that was detectable for at least 18 months. These antibodies were able to cross-neutralize 12 antigenically diverse strains of BVDV.[20]

Colostral immunity and vaccination of young calves

Adequate intake of colostrum from BVDV seropositive dams can provide protection from clinical disease in young calves.[19,73] BVDV vaccination of young calves has also been demonstrated to reduce clinical disease and mortality compared to colostrum-deprived, unvaccinated calves when experimentally challenged.[19] Calves that did or did not receive colostral antibodies to BVDV that were vaccinated at 10 to 14 days of age with a single dose of MLV vaccine that contained a type-I BVDV isolate were protected from clinical disease when experimentally challenged with a virulent type-II BVDV 21 days after vaccination. In contrast, calves that did not receive colostral antibodies to BVDV, and did not receive the MLV vaccine, suffered severe clinical disease and required euthanasia.[19] Clinical scores were not significantly different between seropositive vaccinated and seropositive unvaccinated calves after viral inoculation. Most of the vaccinated calves seronegative prior to vaccination did not have measurable serum antibody response 21 days following vaccination at the time of experimental BVDV inoculation, even though these calves were protected from clinical disease.[19] Similarly, Ridpath *et al* demonstrated that an active protective response was mounted in young calves in the presence of colostral-derived passive immunity that were experimentally challenged with virulent BVDV, even though serum antibody titers had decayed to low levels.[73] Cortese *et al* and Ridpath *et al* concluded that serum antibody titers are an inadequate measure of vaccine or natural protection.[19,73]

Ability of vaccines to provide fetal protection

The benefit of preventing clinical disease in vaccinated cattle exposed to BVDV is inadequate in the management and complete control of the disease because infection is perpetuated from one generation to the next through infection of the fetus. Cowherd vaccination programs are primarily designed to prevent fetal infection, which is immunologically more difficult than protection from clinical disease. In order to prevent fetal infection, vaccination of an exposed herd would have to prime the immune system to effectively neutralize circulating virus before it can cross the placenta and cause fetal in-

fection. Evidence from earlier work, as well as recently reported trials, indicate that vaccination provides some protection of the fetus when the dam is experimentally challenged, but protection does not extend to 100% of fetuses of exposed dams.

Efficacy of maternal vaccination to provide fetal protection when dams were experimentally challenged ranged from 25 to 100% for inactivated vaccines,[13,37,59] and from 58 to 92% for modified live vaccines.[9,18,22] Dams have measurable levels of anti-BVDV antibody following vaccination and fetal protection appears to be improved by vaccination, making a planned vaccination program important for BVDV control. However, a sufficient amount of virus is able to escape inactivation by circulating antibodies in some dams to cause transplacental infection, abortion and the development of persistent fetal infection, making vaccination programs alone inadequate to control BVDV.[9,13,18]

Control programs to limit losses due to BVDV

The primary goals of BVDV control in breeding herds are to prevent fetal infection in order to eliminate BVDV-associated reproductive losses (thereby preventing the birth of PI calves), and to reduce losses from transient BVDV infections.[36] Cattle that have been infected with BVDV after birth and recovered appear to be protected from clinical disease following subsequent exposure to the virus even if they are seronegative.[73] Animals seropositive due to natural exposure are also considered to have a degree of protection from future fetal transmission of the virus, but the protection may not be complete. While vaccination does provide some protection from fetal infection, the herd level protection is not likely to be complete. As a result, BVDV control is generally achieved by a combination of removal of PI cattle, vaccination, and a biosecurity system that prevents the introduction of PI animals into the herd and minimizes contact with potentially viremic cattle or wildlife.[44]

Removal of PI animals

Herds should be monitored to determine the risk that one or more PI cattle are present. If the presence of PI cattle is confirmed or strongly suspected, a whole-herd screening protocol should be undertaken to identify and remove PI individuals. A second whole-herd screening the following year may be advisable in some herds where risk of continued fence-line or other exposure to PI animals is high.

Biosecurity to prevent herd exposure to PI animals

Biosecurity to prevent herd exposure to PI or transiently infected animals is important, especially after the removal of PI cattle, because with the removal of PI BVDV shedders, the percentage of naturally protected seropositive animals in a herd decreases.[44] All replacement heifers and bulls that enter the breeding herd, whether raised or purchased, should be tested and confirmed to be non-PI prior to the start of breeding. If a pregnant animal is purchased, it should be segregated from the breeding herd until both the dam and the calf are confirmed PI-negative. Fence-line contact with neighboring cattle should be managed so that stocker cattle are not adjacent to the breeding herd during early gestation, and other cowherds are not adjacent unless they also have a strict biosecurity and vaccination program in place.

Vaccination as a component of biosecurity

Biosecurity also involves application of a vaccination protocol to reduce the risk of fetal infection in the event of cowherd exposure to a viremic and shedding animal. Live, replicating vaccines (MLV) have inherent properties that may enable them to stimulate more complete protection against transplacental infection.[44] For that reason, one recommendation is to vaccinate unstressed, healthy heifers with MLV vaccine. Vaccine administration should be timed so that a protective immune response coincides with the first four months of gestation. This is done to maximize the potential for adequate immunity to protect against fetal infection and reproductive failure or the birth of PI calves. In heifers not previously vaccinated, the primary series should consist of two administrations. The first dose should be given when the heifers are six months of age or older, and the second dose should be given two months before breeding. Beef cows should be revaccinated annually before breeding according to label directions.[44]

Control program for BVDV in stocker/feedlot operations

Because pregnancy is not a common or desirable component of stocker and feedlot operations, vertical transmission and reproductive losses due to BVDV are not a concern. However, BVDV viremia or seroconversion has been associated with respiratory disease outbreaks in feedlot situations.[29,30,52] Persistently infected cattle are a primary source of BVDV transmission to in-contact susceptible cattle during marketing, trucking, and while in feeding pens and pastures.[31] This has been shown to have an impact on health performance of susceptible penmates and cattle in adjacent pens.[53] Vaccination is currently the primary control intervention for BVDV in stocker and feedlot operations. Screening cattle for the presence of PI individuals prior to purchase or at arrival has not been adequately evaluated for economic return. The economic return will depend on prevalence of PI cattle, sensitivity and specificity of the test used, and economic cost of the disease to the operation.

Conclusions

Bovine viral diarrhea virus has important characteristics, such as its genetic diversity and ability to induce a persistently infected carrier state, that make its control in cattle populations a challenge. A systematic control program that utilizes diagnostic testing strategies to find and remove PI cattle, vaccination to increase fetal protection from infection, and biosecurity to reduce the risk of exposure to animals persistently (or transiently) infected with the virus is necessary for control of BVD.

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