Bovine Viral Diarrhea Virus-Associated Disease in Feedlot Cattle

Bob L. Larson, DVM, PhD, ACT, ACVPM-Epi, ACAN
Professor, Coleman Chair Food Animal Production Medicine
Department of Clinical Sciences
College of Veterinary Medicine
111B Mosier Hall
Manhattan, Kansas 66506
(785)532-4257
Rlarson@vet.ksu.edu

Key Words: Bovine viral diarrhea virus, feedlot cattle, immunosuppression, vaccination, screening test

Key Points:

- Bovine Viral Diarrhea virus (BVDv) has immunosuppressive and direct effects that interact with other risk factors to impact the likelihood and severity of bovine respiratory disease complex (BRDC) in feedlot cattle.
- Vaccination of feedlot cattle against BVDv antigens is commonly practiced in North American feedlots and a relatively small amount of research data supports this intervention as being effective to reduce the likelihood or severity of BRDC.
- Several tests are available to determine if cattle are persistently infected (PI) with BVDv and these tests have high sensitivity and specificity.
- Because of the low prevalence of feedlot cattle PI with BVDv, many positive test results are false-positive.
- Selection of the optimum strategy to use available tests for PI status depends on having an accurate estimate of the cost of PI cattle to feedlot production.

Synopsis: Bovine viral diarrhea virus is associated with BRDC and other diseases of feedlot cattle. Although occasionally a primary pathogen, BVDv's impact on cattle health is most importantly through the immunosuppressive effects of the virus and its synergism with other pathogens. The simple presence or absence of BVDv does not result in consistent health outcomes because BVDv is only one of many risk factors, including other pathogens and numerous metabolic, immunologic, and physiologic factors that contribute to disease syndromes of feedlot cattle. Current interventions available to veterinarians providing services to feedlot operations to address BVDv involve: vaccination at feedlot arrival or earlier in beef cattle production, the use of testing for persistent infection (PI) status and either euthanasia or segregation of test-positive animals to remove this important BVDv reservoir, and other animal husbandry and health interactions to limit concurrent or serial disease risk factors. All of these

interventions have limitations and the optimum strategy for their uses to limit the health, production, and economic costs associated with BVDv have to be carefully considered for optimum cost-effectiveness.

Disclosures: During the past five years, Dr. Larson has materially participated in research funded through a variety of sources including: Kansas State University Department of Clinical Sciences, the United States Department of Agriculture, the National Cattlemen's Beef Association, Merck Animal Health, Zoetis Animal Health, and CEVA Biomune. He has performed consulting or training activities for: Alpharma Animal Health, Bayer Animal Health, Boehringer-Ingelheim, Elanco Animal Health, IDEXX, Merck Animal Health, Merial, Novartis Animal Health, and Zoetis Animal Health.

Introduction

Bovine viral diarrhea virus (BVDv) refers to a heterogeneous group of viruses that belong to two different species, BVDv1 and BVDv2, within the pestivirus genus of the Flavivirus family.[1] Bovine viral diarrhea viruses are further subclassified as cytopathic and noncytopathic based on their activity in cultured epithelial cells, with noncytopathic BVDV predominating in nature.[1] These viruses are associated with a number of feedlot cattle diseases; primarily bovine respiratory disease complex (BRDC) and to a lesser frequency, digestive tract disease.

BVDv and Bovine Respiratory Disease Complex (BRDC)

Bovine respiratory disease complex is an important disease of cattle and is causally-associated with a number of identified and suspected risk factors, including infection with BVDv.[2-4]. While, BVDv alone (uncomplicated by co-infection or serial-infection with other agents) has been demonstrated to cause respiratory infection and signs of clinical BRDC in experimental challenge-studies [6,7], reviews of numerous studies have concluded that BVDv association with BRDC is most importantly due to suppression of the immune system and synergism with other pathogens.[7-10]

Immunosuppression associated with BVDv infection

Brakenbury et al.[7], summarized evidence that infection with BVDv results in immunosuppression in the absence of clinical signs of primary BVDv-induced disease. Experimental studies found that acute infections with BVDv enhanced susceptibility to infection with bovine herpes virus 1,[11] and case reports have linked concurrent

infections with other BRDC-associated pathogens with BVDv infections.[12] Subsequent experimental studies showed healthy cattle exposed to BVDv responded differently to a challenge with *Mannheimia haemolytica* than calves not previously exposed to BVDv.[13]

Ridpath et al., [8] reviewed available literature and concluded that the immunosuppression that accompanies acute BVDv infections results from a combination of outright lymphoid cell death [14,15] and reduced function in remaining lymphoid cells.[10] Although the mechanism remains undefined, infection with either high- or low-virulence BVDV, results in the reduction of circulating lymphocytes [14-16] and the depletion of lymphoid tissue.[17,18] The difference in pathology between high- and low-virulence BVDV strains is in the extent of cell death or loss, with reduction of circulating lymphocytes and lymphoid depletion being significantly higher following infection with highly virulent BVDv.[8]

Peterhans et al.[9] and Chase et al.[10] summarized the literature relating to the immune response to BVDv and reported that in addition to reducing lymphoid cell numbers, BVDv infections impair the function of cells associated with both the acquired and innate immune systems. The interactions resulting in immune suppression are complex and components of the innate immune response that are reported to be suppressed in response to BVDv infection include interferon production, phagocytosis, chemotaxis, and microbiocidal killing. On the acquired immune side, changes such as down-regulation of MHC II and IL-2 that suppress T-helper cell response and apoptosis of T and B cells in lymphoid tissue are critical immunosuppressive mechanisms.[10]

Persistently Infected (PI) cattle as the most important reservoir for BVDv

Creation of cattle PI for BVDv

Several pathogens associated with important diseases of cattle are able to establish a persistent infection (PI) state, but the method by which BVDv creates a PI state is unique. Rather than evading the adaptive immune response of an immune-competent animal, noncytopathic BVDv is able to establish PI by invading the fetus early in its intrauterine development - prior to the development of a competent immune response, thus establishing immunotolerance which is specific for the persisting viral strain.[9]

Even mild or subclinical infections of susceptible breeding females can cause conception failure, early embryonic loss, abortion, or vertical fetal infection. Fetal infection can lead to early embryonic death, abortion, congenital defects, the birth of PI calves, or the birth of normal calves. The immune status of the dam, the stage of gestation at the time of infection, and the viral biotype are important factors in determining the result of vertical infection. Transplacental infection occurs with high efficiency of seronegative dams;[19,20] however, naturally acquired immunity is considered to provide good, but not necessarily complete, protection against fetal infection.[21] Fetal infection early in the gestation of susceptible dams with a cytopathic biotype of BVDV will result in abortion. However, fetal infection prior to the development of immune competence with a noncytopathic biotype of BVDV will result either in abortion, or in a certain percentage of infections, the survival of a calf that is immunotolerant to and PI with that noncytopathic strain of BVDV.[20,22] Age at immune competence in the face of BVDV exposure is variable and has been reported to range

from 90 to 125 days.[20,22,23] If PI fetuses survive to term, they are continually infected, but immunotolerant to the homologous BVDv.[23,24]

Role of cattle PI for BVDv as viral reservoir

Cattle PI with BVDv are the primary reservoir for the virus, 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 much higher levels of virus for a much longer period of time. In experimentally-challenged, transiently infected cattle, the median minimum number of days until BVDv shedding was detected was 2 days.[25] The median peak of BVDv shedding occurred at 7 days post challenge with shedding ending at a median of 12 days post challenge.[25] In contrast, PI animals usually have a very high and persistent viremia[26], 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.[27-29] Horizontal transmission of BVDv to seronegative cattle has been shown to occur after only one hour of direct contact with a single PI animal.[30]

Transiently infected cattle are considered to be far less efficient at transmitting BVDv to susceptible animals than PI cattle.[31,32] 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.[33,34]

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, [35,36] an important percentage survive to weaning and studies have reported 0.2% to 0.4% of cattle entering U.S. feedlots to be PI with BVDv.[4,37-39]

Direct Health Risk of BVDv PI Feedlot Cattle

In a study that evaluated lung pathology and infectious agents associated with deaths in a single feedyard over a one-year period of time, 0.70% of cattle in the study died of BRDC and 5.3% of cattle that died due to BRDC were estimated to be BVDv PI. [40] Assuming that the percentage of BVDv PI cattle arriving at the feedlot was similar to that reported in other studies (i.e. 0.2%-0.4%), BVDv PI cattle are much more likely to die due to BRDC than non-PI cattle. The negative effect on mortality risk of feedlot cattle being BVDv PI was also reported in a study where 25.6% of cattle PI for BVDv at feedlot arrival died compared to 2.4% of non-PI cattle.[41] An earlier study also showed that BVDv PI cattle were more common in populations of dead cattle (2.5%) and chronically-ill cattle (2.6%) than in cattle arriving at a feedyard (0.3%).[4]

USDA estimates 23.8 million cattle were placed on feed in the U.S. in 2011 and 2.0% of cattle (476,000 head) placed on feed died or were sent to market prior to reaching desired slaughter weight [42]. Estimates from published research indicate that 0.2%-0.4% (47,600-95,200) of cattle arriving at U.S. feedlots are PI for BVDv [4,37-39] and 25.6% of PI cattle (12,000 – 24,400) died prior to slaughter [41]. Meaning that eliminating BVDv PIs from the U.S. beef population would decrease feedlot losses by

about 12,000 to 24,400 animals per year (i.e. decrease losses from 2% of placements to 1.90 to 1.95% of placements) due to direct effects of losses of BVDv PI cattle.

Therefore, although direct losses due to BVDv PI cattle in the feedlot are measureable, addressing other contributions to feedlot losses probably take priority.

Health Risk of Feedlot Cattle In-Contact with BVDv PI Cattle

In addition to the direct losses of cattle PI with BVDv, feedlots may experience losses among non-PI cattle that are transiently infected with BVDv due to transmission of the virus from PI cattle. Transmission of BVDv from PI cattle to in-contact susceptible cattle occurs during marketing, trucking, and while in feeding pens and pastures. [43] The likelihood and extent of health and growth performance effects of non-PI feedlot cattle being exposed to BVDv PI cattle has been reported to vary greatly – including both positive and negative effects. BVDv viremia or seroconversion has been associated with respiratory disease outbreaks in feedlot situations. [2-4]. In a study by Loneragan et al., [4] the investigators reported that exposure to a PI animal appeared to have little effect when exposure was narrowly defined to include just those cattle within the pen of a PI animal. However, when exposure was defined more broadly to include pens adjacent to a pen containing a PI animal, exposure had a detectable adverse effect on risk of illness compared with not-exposed cattle. The risk of initial treatment for respiratory tract disease was 43% (95% CI 2-102%) greater in cattle exposed to a PI animal in the same or adjacent pen, compared with those not exposed to a PI animal. Overall, 15.9% of initial respiratory tract disease events were attributable to exposure to a PI animal.[4]

Similarly, Hessman et al [41] not only evaluated the risk of cattle in the same feedlot pen as cattle PI for BVDv throughout the feeding phase, but also cattle in pens adjacent to pens containing PI cattle throughout the feeding phase, as well as cattle that were in the same pen or next to pens with PI cattle that were identified and removed within 72 hours of feedlot arrival. The investigators found that pens of cattle that did not have any PI cattle at the time of feedlot arrival and adjacent pens also lacked PI cattle or PI cattle were removed within 72 hours had significantly higher weight gain than pens with PI cattle present at arrival, whether or not those PI cattle were removed within 72 hours. [41] The same study found that cattle in feedlot pens with PI cattle present either in the same pen throughout the feeding phase or present for 72 hours or less (PI cattle in the pen were removed within 72 hours) and exposed to PI cattle in adjacent pens throughout feeding, were more likely to be identified as ill than cattle in pens with no PI cattle at arrival and PI cattle in adjacent pens were removed within 72 hours. [41]

However, exposure to BVDv PI cattle or seroconversion to BVDv after feedlot entry is not always reported to have a negative association. In a study investigating the risk factors of commingling and presence of PI cattle in feedlot pens, disease prevalence (mean $\pm$ SD morbidity, $7.9 \pm 3.1\%$) was lowest in pens containing single-source cattle and a BVDv PI calf; and in pens with commingled cattle, the presence of a PI animal (mean morbidity $28.6 \pm 10.1\%$) was not associated with increased disease prevalence compared to pens without PI cattle (mean morbidity, $29.3 \pm 16.22\%$) [38] A study that used PCR analysis of blood samples collected at feedlot arrival to identify initial BVDv infection status and immunohistochemistry (IHC) of a skin biopsy to identify

BVDv PI status found that presence of PI cattle did not have a large negative impact on pen-level health and growth performance outcomes in feedlot cattle.[44]

A study that evaluated the effect of either short-term (i.e. 60 hours) or long-term (throughout feeding phase) exposure of BVDv-vaccinated feedlot heifers to PI cattle did not identify a negative effect of either exposure length on health, growth performance, or carcass characteristics compared to un-exposed controls.[45] Even in the study reported by Hessman et al., pens of cattle with the least exposure to PI cattle (i.e. no PI at arrival and no exposure to PI cattle at any time during feeding) did not have the lowest morbidity percentage, first relapse percentage, fatality percentage, treatment costs, or mean number of treatments per illness compared to pens with some exposure to PI cattle.[41] Based on currently-available studies, the direction and magnitude of response of feedlot cattle exposed to BVDv PI cattle cannot be predicted. A number of reviews have suggested that the range in response of feedlot cattle to BVDv exposure could be due to: variation in virulence or pathogenicity characteristics of specific BVDv to which cattle are exposed, immune status of the exposed cattle, extent of concurrent or serial exposure to other infectious, physiologic, or metabolic insults, or other unknown risk factors. [8,46-48]

Considerations of BVDv Species and Strains (Subtypes)

Studies have indicated that U.S. feedlot cattle are infected with diverse species of BVDv. Fulton et al., reported that using accessions to an Oklahoma diagnostic laboratory representing clinically ill or necropsied cattle during the year 2005, 45.8% of isolates were BVDv-1b, whereas 28.2% were BVDv-2a, and 26.0% were BVDv-2a.[49]

Similarly, a study of isolates from PI cattle in southwestern U.S. feedlots reported that 75.3% were BVDv-1b, 12.6% were BVDV-2a, and 12.1% were BVDv-1a.[50]

Some studies have shown differences in responses between strains in *in vitro* studies. Walz et al., found that in colostrum-deprived Holstein calves, altered platelet function was observed in calves infected with two type II BVDv isolates (BVDv 890 and BVDv 7937), but was not observed in calves infected with a type I BVDv (BVDv TGAN).[51] The same research group also reported that pathologic and immunohistochemical examinations revealed more pronounced lesions and more extensive distribution of viral antigen in colostrum-deprived calves inoculated with two type II BVDv (BVDv 890 and BVDv 7937) compared to calves inoculated with a type I BVDv (TGAN).[52]

Other studies have demonstrated differences at the animal- or pen-level between cattle that seroconvert to different species of BVDv. Booker et al [44] reported that cattle that were in pens that contained animals with type I BVDV infections had significantly more initial BRDC treatments, and overall mortalities, than cattle in pens that did not include PI cattle. In addition, individual cattle that seroconverted to BVDv type I infection were about four times more likely to die of all causes than to animals without BVDv type I infection. Moreover, at the pen level, seroconverting to BVDv type II appeared to convey a protective effect when compared with pens without BVDV type II infections.[44] Although there is some evidence for different outcomes based on exposure to different BVDv species, it is not clear that outcome severity can be directly related to species differences between BVDv-1 and BVDv-2.

BVDv Association with Diseases Other Than BRDC in Feedlot Cattle

Although very little published literature exists to document the extent and characteristics of non-BRDC, BVDv-associated disease in North American feedlots. Some case reports and anecdotal information suggest a potential sporadic association of BVDv with severe digestive tract disease.[53-55] Hessman et al., report a case of BVDv infection in non-PI feedlot cattle in two arrival cohorts in a single feedlot causing severe mucosal surface lesions in the oral cavity, larynx, and esophagus.[55] The cumulative morbidity and mortality losses were 76.2% and 30.8% respectively for one cohort and 49.0% and 5.6% respectively for the other cohort.[55] Other evidence of association between BVDv and digestive tract pathology is reported in experimental challenge of young, seronegative calves [56-58] which may not have direct relevance to cattle in typical feedlot settings.

Role of vaccination in the management of BVDv in feedlot settings

Vaccination against BVDv antigens at the time cattle arrive at a feedlot as well as earlier in the cattle production system is a common intervention to reduce the biologic and economic costs of BVDv in feedlot cattle.[42,59] Terrell et al., surveyed feedlot veterinarians providing cattle health and well-being recommendations for feedlot cattle in the United States and Canada and found that all surveyed veterinarians recommended that high-risk cattle be vaccinated with BVDv (types 1 and 2) vaccine, and 95.65% recommended that low-risk cattle be vaccinated with BVDv (types 1 and 2) vaccine. [59] However, very little clinical trial data exists illustrating the efficacy of

vaccination at feedlot arrival to prevent BVDv infection and clinical disease associated with BVDv.

Three days prior to exposure to cattle PI with BVDv-1b, Fulton et al., vaccinated cattle with a modified live viral (MLV) vaccine containing BVDv-1a and BVDv-2a and found that BVDv-1b was transmitted to both vaccinated cattle and unvaccinated controls. For cattle that were vaccinated at the ranch of origin and were seropositive for BVDv prior to PI exposure, BVDv-1b titers up to 64 did not prevent BVDv-1b from being isolated after exposure. In fact, BVDv-1b antibody titers up to 256 did not uniformly prevent 4-fold or greater rises in BVDv-1b antibody titers.[60] The authors concluded that even though the vaccinated calves responded with antibodies against BVDv, the onset of immunity preventing infection to a heterologous BVDv-1b strain requires more than three days.[60] Grooms et al., reported a series of trials that found in one trial that cattle vaccinated against BVDv within 24 hours of feedlot arrival had lower morbidity risk than unvaccinated cattle when the cattle were exposed to PI cattle; however in another study, they did not detect a difference in health and growth performance after exposure to PI cattle depending on whether cattle were or were not vaccinated against BVDv.[48]

Theurer et al. did a systematic review and meta-analysis of the effectiveness of commercially available vaccines against BVDv and other viral pathogens associated with BRDC.[61] They identified only two field studies that reported the effects of five trials that compared cattle vaccinated against BVDv, bovine herpes virus-1 (Infectious Bovine Rhinotracheitis), bovine respiratory syncytial virus, and parainfluenza-3 virus to unvaccinated controls on mortality and/or morbidity risk.[62,63] Randomized controlled

blinded field trials in commercial feedlots provide assurance of high internal study validity due to their ability to control for common sources of bias and confounding, and a high level of external validity for veterinarians advising feedlot managers as the host, environment, and pathogen triad are expected to be similar to typical feedlot production settings. Analysis of these five trials revealed a significantly lower morbidity risk for vaccinates compared with controls in two of the five trials, with no significant difference between groups in the remaining three trials.[61] The summary morbidity risk ratio for these five trials was 0.44 with a 95% CI of 0.26 to 0.74; this is interpreted as “Vaccination against the viruses included in the studied commercially available vaccines is estimated to decrease morbidity risk by about 44% with potential true reduction ranging from 26% to 74%, which is a significantly lower morbidity risk for vaccinated beef calves compared with that for non-vaccinated control calves.”[61] Therefore, if the group of cattle was going to have 30% morbidity without vaccination, they would be expected to have between 8% to 22% morbidity (with the most likely estimate of 17% if they were vaccinated. Mortality risk was reported for only four of the trials, and the summarized risk ratio for these four trials was 0.19, with a 95% CI of 0.06 to 0.67; indicating vaccination is expected to reduce mortality risk associated with viruses associated with BRDC by about 19% with a true magnitude of effect most likely being somewhere between a 6% to 67% reduced mortality risk for vaccinates, compared with controls.[61]

While randomized controlled blinded field trials provide a higher level of evidence compared to challenge studies, challenge studies do allow more in-depth evaluation of the pathophysiology of BRDC and the mechanisms of action of protective immunity.

However, demonstration of vaccine efficacy in a challenge study does not provide sufficient evidence for similar protection in a clinical setting; therefore, extrapolation of results from disease challenge studies to commercial field settings must be performed with caution. Reviewing challenge studies, Theurer et al. identified seven studies containing eleven trials that evaluated the effectiveness of an MLV BVDv vaccine against experimental infection with BVDv and signs attributable to BRDC in beef or dairy calves.[61] Analysis revealed a significantly lower morbidity risk for vaccinates, compared with controls, in six of the eleven trials, with no significant difference between groups in the remaining five trials. The summarized risk ratio for these 11 trials was 0.28, with a 95% CI of 0.17 to 0.45.[61] Two studies comprising four trials provided mortality data for MLV vaccinated and non-vaccinated calves following experimental BVDv challenge. The summarized risk ratio for these 4 trials was 0.26, with a 95% CI of 0.12 to 0.56, indicating a significantly lower mortality risk for vaccinates than for control calves.[61] Theurer et al. also identified two studies comprising two trials that evaluated the effectiveness of inactivated (killed) BVDv vaccine against infection with BVDv and signs attributable to BRDC in beef or dairy calves following experimental challenge with the virus. The summarized risk ratio for these 2 trials was 0.66, but was not significant because of a wide 95% CI of 0.35 to 1.26 morbidity risk between vaccinates and control calves.[61] One study comprising two trials evaluated mortality risk for calves that did or did not receive inactivated BVDv vaccine prior to BVDv challenge. The summarized risk ratio for these two trials was 0.12, with a 95% CI of 0.02 to 0.79, indicating a significantly lower mortality risk for vaccinates than for control calves.[61]

Theurer et al. conclude that although the available data support the use of vaccines directed against BVDv in feedlot cattle, published natural challenge field studies with blinded evaluation of clinically important outcomes are sparse.[61] In addition, extrapolation of positive challenge study evaluations of BVDv vaccine effectiveness in controlled settings to field settings is not wholly appropriate. More research needs to be published based on studies done in field settings with natural exposure to evaluate current available vaccine effectiveness as measured by clinically relevant outcomes with adequate blinding of evaluators to treatment groups and appropriate study design to truly determine the magnitude and direction of vaccine efficacy as Perino and Hunsaker previously described.[64]

Role of testing and removal of PI cattle in the management of BVDv in feedlot settings

The unique method by which BVDv establishes a PI state in the *in utero* fetus provides an opportunity to test for PI status at any time in an animal's life with the confidence that an accurate PI-status determination will remain the same throughout life. In other words, cattle that are truly-negative for BVDv PI status cannot become PI at a later time-point and cattle truly-positive for BVDv PI status cannot clear the infection and become PI-negative. Because of this constant PI-status and the understanding that a small percentage of cattle are PI with BVDv and constitute the primary reservoir for the virus, testing and removal of PI cattle at feedlot arrival or earlier can effectively remove nearly all the BVDv reservoir from the population if the test returns few false-negative results.

A number of diagnostic tests with good accuracy to identify BVDv PI status are available. Nickell et al. reviewed the published estimates for sensitivity and specificity of available BVDv PI tests and reported that:[65]

- Immunohistochemistry is expected to have a sensitivity of 99.6% (minimum 97.6% and maximum 100.0%) and a specificity of 99.6% (minimum 98.8% and maximum 100%)
- Antigen capture ELISA is expected to have a sensitivity of 100% (minimum 98% and maximum 100%) and a specificity of 99.3% (minimum 97.7% and maximum 100%)
- Real-time PCR is expected to have a sensitivity of 100% (minimum 99% and maximum 100%) and a specificity of 100% (minimum 99% and maximum 100%).

Because the sensitivity for each of the available tests is high ($\geq 97.6\%$) and the prevalence of BVDv PI cattle is low (0.2-0.4%) nearly all ($>99.5\%$) feedlot cattle if tested at arrival will have a negative test result, and the certainty that a test-negative animal is truly not PI is very high. Using the minimum likely sensitivity of 97.6% and the high end of the expected PI prevalence range of 0.4%, the Negative Predictive Value of BVDv PI tests in U.S. feedlot cattle populations is approximately 99.99%; therefore, at worst, one would expect one false-negative test result for every 11,000 tests performed.

In contrast, even though specificity is high for the available tests, because the prevalence of PI cattle at feedlot arrival is low (0.2-0.4%) and relatively few cattle will test positive for PI status ($<0.5\%$), the certainty that a test-positive animal is truly positive is problematic. Using the minimum likely specificity of 97.7% and the low end of the expected PI prevalence range of 0.2%, the Positive Predictive Value of BVDv PI

tests in U.S. feedlot cattle populations could be as poor as approximately 7.84%. Using a specificity of 99.9% and a PI prevalence of 0.4% results in a best-case Positive Predictive Value of 79.7%. In other words, at best, eight out of every ten positive animals are truly BVDv PI and at worst, less than one out of every ten positive animals is truly BVDv PI.

Because the costs associated with euthanizing cattle that have a false-positive BVDv PI test result are high, implementing PI testing in U.S. feedlot populations may require either a two-test strategy whereby cattle that test positive on an initial test for PI status are retested with a second PI test (with the results of the second test considered to be definitive) to better differentiate between true-positive and false-positive cattle; or to isolate all cattle that test positive on a single PI test (both true-positive and false-positive) away from the rest of the feedlot population to achieve removal of the BVDv reservoir.[37] A negative aspect of the strategy to test for BVDv PI status at feedlot arrival followed by removal of test-positive cattle is the time delay between initial sample collection and identification of PI animals for removal from the population. During this delay, PI cattle would be contacting pen mates and cattle in adjacent pens and potentially causing negative biologic and economic effects. Depending on how test-positive cattle are managed after the initial test, this delay could be increased with a two-step strategy versus a one-step testing strategy.

Before widespread adoption of any testing strategy can be recommended, more confidence in the estimated economic return for testing at feedlot arrival is needed, and the relative value of testing at feedlot arrival versus the value to the feedlot phase of production for testing at the ranch of origin or the point of sale (and hence, the price-

premium that could be paid) needs to be determined. The economic return of testing for BVDv PI cattle at feedlot arrival will depend on the prevalence of PI cattle, the confidence in results of the testing strategy, the true economic cost of the presence of PI cattle in feedlot operations, and the value of removal of PI cattle after test results are known.

The number of false-positive test results and the cost of testing populations that are not likely to contain PI cattle can be decreased by only testing populations of cattle at feedlot arrival that are considered to be high-risk for including PI animals rather than testing all arriving cattle lots. However, this strategy would require that populations that are truly low-risk and high-risk for including PI cattle can be accurately identified and the strategy would likely result in some PI cattle entering the feedlot in untested (presumed low-risk) populations.

Even though cattle that are identified as BVDv PI at feedlot arrival are much less likely to survive to slaughter weight than other cattle in the feedlot, the health and performance of cattle that actually have false-positive test results are not expected to compare negatively to other non-PI cattle and some true-positive PI cattle will reach a weight that can be economically harvested. Therefore, a strategy to capture value from cattle that test positive for PI status is an important consideration in the economic evaluation of testing. However, any strategy to capture some of the value of PI-test-positive cattle should try to avoid the sale of test-positive animals, or if PI-test-positive cattle are sold, full disclosure to and understanding by the buyer should be ensured. The Academy of Veterinary Consultants, the American Association of Bovine Practitioners, and the National Cattlemen's Beef Association have all developed

position statements that acknowledge that appropriate disposition of known PI cattle must take into account the adverse impact those cattle have on health, welfare and the economic return of the other cattle or cattle operations they may expose to BVDv.[66-68] The statements recognize that cattle PI with BVDv are defective and once confirmed, their PI status should thereafter be disclosed.

Summary

Bovine viral diarrhea virus is associated with BRDC and other diseases of feedlot cattle. Although occasionally a primary pathogen, BVDv's impact on cattle health is most importantly through the immunosuppressive effects of the virus and its synergism with other pathogens. Because BVDv is only one of many risk factors that interact with other pathogens and numerous metabolic, immunologic, and physiologic factors to contribute to disease syndromes of feedlot cattle, the simple presence or absence of the virus does not result in consistent health outcomes. Current interventions available to veterinarians providing services to feedlot operations to address BVDv involve: vaccination at feedlot arrival or earlier in beef cattle production, the use of testing for PI status and either euthanasia or segregation of test-positive animals to remove this important BVDv reservoir, and other animal husbandry and health interactions to limit concurrent or serial disease risk factors. All of these interventions have limitations and the optimum strategy for their uses to limit the health, production, and economic costs associated with BVDv have to be carefully considered for optimum cost-effectiveness.

References

- [1] Ridpath JF. Bovine viral diarrhea virus. In: Mahy BWJ, Regenmortel MHV, editors. Encyclopedia of virology. Oxford (UK): Elsevier; 2008. p. 374–380.
- [2] Fulton RW, Purdy CW, Confer AW, et al. Bovine viral diarrhea viral infections in feeder calves with respiratory disease: Interactions with *Pasteurella* spp., parainfluenza-2 virus, and bovine respiratory syncytial virus. *Can J Vet Res* 64:151-159, 2000.
- [3] Fulton RW, Ridpath JF, Saliki JT, et al. Bovine viral diarrhea virus (BVDV) 1b: predominant BVDV subtype in calves with respiratory disease. *Can J Vet Res* 66:181-190, 2002.
- [4] Loneragan GH, Thomson DU, Montgomery DL, et al. Prevalence, outcome, and health consequences associated with bovine viral diarrhea virus in feedlot cattle. *J Am Vet Med Assoc* 2005;226:595-601.
- [5] Potgeiter LND, McCracken MD, Hopkins FM, et al. Experimental production of respiratory tract disease with bovine viral diarrhea virus. *Am J Vet Res* 1984;45:1582-1585.
- [6] Potgeiter LND, McCracken MD, Hopkins FM, et al. Comparison of pneumopathogenicity of two strains of bovine viral diarrhea virus. *Am J Vet Res* 1985; 46:151-153.
- [7] Brakenbury LS, Carr BV, Charleston B. Aspects of the innate and adaptive immune responses to acute infections with BVDV. *Vet Micro* 2003;96:337-344.
- [8] Ridpath JF. The contribution of infections with bovine viral diarrhea viruses to bovine respiratory disease. *Vet Clin North Am Food Anim Pract* 2010;26:335-348.

- [9] Peterhans E, Jungi TW, Schweizer M. BVD virus and innate immunity. *Biologicals* 2003; 31:107–112.
- [10] Chase CC, Elmowalid G, Yousif AA. The immune response to bovine viral diarrhea virus: a constantly changing picture. *Vet Clin North Am Food Anim Pract* 2004;20(1):95–114.
- [11] Edwards, S., Wood, L., Hewitt-Taylor, et al. Evidence for an immunocompromising effect of bovine pestivirus on bovid herpesvirus 1 vaccination. *Vet. Res. Commun* 1986;10:297-302.
- [12] Wray, C., Roeder, P.L. Effect of bovine virus diarrhoea-mucosal disease virus infection on salmonella infection in calves. *Res Vet Sci* 1987;42:213-218.
- [13] Burciaga-Robles LO, Step DL, Krehbiel CR, et al. Effects of exposure to calves persistently infected with bovine viral diarrhea virus type 1b and subsequent infection with *Mannheimia haemolytica* on clinical signs and immune variables: Model for bovine respiratory disease via viral and bacterial interaction. *J Anim Sci* 2010;88:2166-2178.
- [14] Ridpath JF, Neill JD, Frey M, et al. Phylogenetic, antigenic and clinical characterization of type 2 BVDV from North America. *Vet Microbiol* 2000;77(1–2):145–155.
- [15] Ridpath JF, Neill JD, Peterhans E. Impact of variation in acute virulence of BVDV1 strains on design of better vaccine efficacy challenge models. *Vaccine* 2007;25(47):8058–8066.
- [16] Bolin SR, Ridpath JF. Differences in virulence between two noncytopathic bovine viral diarrhea viruses in calves. *Am J Vet Res* 1992;53(11):2157–2163.

- [17] Liebler-Tenorio EM, Ridpath JE, Neill JD. Distribution of viral antigen and development of lesions after experimental infection with highly virulent bovine viral diarrhea virus type 2 in calves. *Am J Vet Res* 2002;63(11):1575–1584.
- [18] Liebler-Tenorio EM, Ridpath JF, Neill JD. Distribution of viral antigen and development of lesions after experimental infection of calves with a BVDV 2 strain of low virulence. *J Vet Diagn Invest* 2003;15(3):221–232.
- [19] Done JT, Terlecki S, Richardson C, et al. Bovine virus diarrhea-mucosal disease virus: pathogenicity for the fetal calf following maternal infection. *Vet Rec* 1980;106:473-479.
- [20] McClurkin AW, Littledike ET, Cutlip RC, et al. Production of cattle immunotolerant to bovine viral diarrhea virus. *Can J Comp Med* 1984;48:156-161.
- [21] Orban S, Liess B, Hafez SM, et al. Studies on transplacental transmissibility of a Bovine Virus Diarrhoea (BVD) vaccine virus. I. Inoculation of pregnant cows 15 to 90 days before parturition (190th to 265th day of gestation). *Zbl Vet Med B* 1983;30:619-534.
- [22] Casaro APE, Kendrick JW, Kennedy PC. Response of the bovine fetus to bovine viral diarrhea-mucosal disease virus. *Am J Vet Res* 1971;32:1543-1562.
- [23] Roeder PL, Jeffrey M, Cranwell MP. Pestivirus fetopathogenicity in cattle: changing sequelae with fetal maturation. *Vet Rec* 1986;118:44-48.
- [24] Duffell SJ, Harkness JW. Bovine virus diarrhea – mucosal disease infection in cattle. *Vet Rec* 1985;117:240-245.

- [25] Grissett G, White BJ, Larson RL. Structured literature review of responses of cattle to viral and bacterial pathogens causing bovine respiratory disease complex. J Vet Int Med (In Press)
- [26] Nickell JS, White BJ, Larson RL, et al. Evidence of viral transmission and nasal excretion of virus without detectable serum viremia among beef calves exposed to a calf persistently infected with bovine viral diarrhoea virus. Inter J App Res Vet Med, 2010; 8:29-39.
- [27] Rae AG, Sinclair JA, Nettleton PF. Survival of bovine virus diarrhoea virus in blood from persistently infected cattle. Vet Rec 1987;120:504.
- [28] Bezek DM, Stofregen D, Posso M. Effect of cytopathic bovine viral diarrhoea virus (BVDV) superinfection on viral antigen association with platelets, viremia, and specific antibody levels in two heifers persistently infected with BVDV. J Vet Diagn Invest 1995;7:395-397.
- [29] Brock KV, Grooms DL, Ridpath, J, et al. Changes in levels of viremia in cattle persistently infected with bovine viral diarrhoea virus. J Vet Diagn Invest 1998;10:22-26.
- [30] Traven M, Alenius S, Fossum C, et al. Primary bovine viral diarrhoea virus infection in calves following direct contact with a persistently viraemic calf. J Vet Med B 1991;38:453-462.
- [31] Niskanen, R, Lindberg A, Larsson B, et al. Lack of virus transmission from bovine viral diarrhoea virus infected calves to susceptible peers. Acta vet scand 2000;41:93-99.

- [32] Niskanen R, Lindberg A, Traven M. Failure to spread bovine virus diarrhoea virus infection from primarily infected calves despite concurrent infection with bovine coronavirus. *The Vet J* 2002;163:251-259.
- [33] Meyling A., Houe H, Jensen AM. Epidemiology of bovine virus diarrhoea virus. *Rev. sci. tech. Off. Int Epiz.* 1990;9:75-93.
- [34] Moerman A, Straver PJ, de Jong MCM, et al. A long term epidemiological study of bovine viral diarrhoea infections in a large herd of dairy cattle. *Vet Rec* 1993;132:622-626.
- [35] Houe H. Survivorship of animals persistently infected with bovine virus diarrhoea virus (BVDV). *Prev Vet Med* 1993;15:275-283.
- [36] Graham DA, Clegg TA, O'Sullivan PO, et al. Survival time of calves with positive BVD virus results born during the voluntary phase of the Irish eradication programme. *Prev Vet Med* 2015; epublied Feb 2015 http://ac.els-cdn.com/S0167587715000653/1-s2.0-S0167587715000653-main.pdf?_tid=0ec94244-d33d-11e4-bdea-00000aabb0f27&acdnat=1427322172_edcd37ebb49caadd4897bd1da3631c04
- [37] Larson RL, Miller RB, Kleiboeker SB, et al. Economic costs associated with two testing strategies for screening feeder calves for persistent infection with bovine viral diarrhoea virus. *J Am Vet Med Assoc* 2005;226:249-254.
- [38] O'Connor A, Sorden SD, Apley MD. Association between the existence of calves persistently infected with bovine viral diarrhoea virus and commingling on pen morbidity in feedlot cattle. *Am J Vet Res* 2005;66:2130-2134.

- [39] Fulton RW, Hessman B, Johnson BJ, et al. Evaluation of diagnostic tests used for detection of bovine viral diarrhea virus and prevalence of subtypes 1a, 1b, and 2a in persistently infected cattle entering a feedlot. J Am Vet Med Assoc 2006;228:578-584.
- [40] Fulton RW, Blood KS, Panciera RJ, et al. Lung pathology and infectious agents in fatal feedlot pneumonias and relationship with mortality, disease onset, and treatments. J Vet Diagn Invest 2009;21:464-477.
- [41] Hessman BE, Fulton RW, Sjeklocha DB, et al. Evaluation of economic effects and the health and performance of the general cattle population after exposure to cattle persistently infected with bovine viral diarrhea virus in a starter feedlot. Am J Vet Res 2009;70:73-85.
- [42] USDA:APHIS:VS:NAHMS Feedlot 2011. Part III: Trends in Health and Management Practices on U.S. Feedlots, 1994-2011. July 2013.
http://www.aphis.usda.gov/animal_health/nahms/feedlot/downloads/feedlot2011/Feed11_dr_Part%20III.pdf
- [43] Grooms DL, Brock KV, Norby B. Performance of feedlot cattle exposed to animals persistently infected with bovine viral diarrhea virus. Proceedings of the 83rd Annual Meeting of the Conference of Research Workers in Animal Diseases, St. Louis, MO. November 11, 2002. Abstract #186.
- [44] Booker CW, Abutarbush SM, Morley PS, et al. The effect of bovine viral diarrhea virus infections on health and performance of feedlot cattle. Can Vet J 2008;49:253-260.
- [45] Elam NA, Thomson DU, Gleghorn JF. Effects of long- or short-term exposure to a calf identified as persistently infected with bovine viral diarrhea virus on feedlot

performance of freshly weaned, transport-stressed beef heifers. *J Anim Sci* 2008;86:1917-1924.

[46] Campbell JR. Effect of bovine viral diarrhea virus in the feedlot. *Vet Clin North Am Food Anim Pract* 2004;20:39-50.

[47] Ridpath JF, Fulton RW. Knowledge gaps impacting the development of bovine viral diarrhea virus control programs in the United States. *J Am Vet Med Assoc* 2009;235:1171-1179.

[48] Grooms DL, Brock KV, Bolin SR, et al. Effect of constant exposure to cattle persistently infected with bovine viral diarrhea virus on morbidity and mortality rates and performance of feedlot cattle. *J Am Vet Med Assoc* 2014;244:212-224.

[49] Fulton RW, Ridpath JF, Ore S, et al. Bovine viral diarrhea virus (BVDV) subgenotypes in diagnostic laboratory accessions: distribution of BVDV1a, 1b, and 2a subgenotypes. *Vet Microbiol* 2005;111:35-40.

[50] Ridpath JF, Fulton RW, Kirkland PD, et al. Prevalence and antigenic differences observed between bovine viral diarrhea virus subgenotypes isolated from cattle in Australia and feedlots in the southwestern United States. *J Vet Diagn Invest* 2010;22:184-191.

[51] Walz PH, Bell TG, Grooms DL et al., Platelet aggregation responses and virus isolation from platelets in calves experimentally infected with type I or type II bovine viral diarrhea virus. *Can J Vet Res* 2001;64:241-247.

- [52] Walz PH, Bell TG, Wells JL, et al., Relationship between degree of viremia and disease manifestations in calves with experimentally induced bovine viral diarrhea virus infection. *AJVR* 2001;62:1095-1103.
- [53] Janzen ED, Clark EG. The diagnosis of BVD outbreaks in Western Canada. In: *Proceedings of the international symposium on bovine viral diarrhea virus*. Cornell; 1996; p. 143–58.
- [54] Carman S, van Dreumel T, Ridpath J, et al. Severe acute bovine viral diarrhea in Ontario, 1993–1995. *J Vet Diagn Invest* 1998;10:27–35.
- [55] Hessman BE, Sjeklocha DB, Fulton RF, et al. Acute bovine viral diarrhea associated with extensive mucosal lesions, high morbidity, and mortality in a commercial feedlot. *J Vet Diagn Invest* 2012;24:397-404.
- [56] Marshall DJ, Moxley RA, Kelling CL. Distribution of virus and viral antigen in specific pathogen-free calves following inoculation with noncytopathic bovine viral diarrhea virus. *Vet Pathol* 1996;33:311–318.
- [57] Ellis JA, West KH, Cortese VS, et al. Lesions and distribution of viral antigen following an experimental infection of young seronegative calves with virulent bovine virus diarrhea virus-type II. *Can J Vet Res* 1998;62:161–169.
- [58] Stoffregen B, Bolin SR, Ridpath JF, et al. Morphologic lesions in Type 2 BVDV infections experimentally induced by strain BVDV2-1373 recovered from a field case. *Vet Microbiol* 2000;77:157–162.

- [59] Terrell SP, Thomson DU, Wileman BW, et al. A survey to describe current feeder cattle health and well-being program recommendations made by feedlot veterinary consultants in the United States and Canada. *Bov Pract* 2011;45(2):140-148.
- [60] Fulton RW, Briggs RE, Ridpath JF, et al. Transmission of bovine viral diarrhea virus 1b to susceptible and vaccinated calves by exposure to persistently infected calves. *Can J Vet Res* 2005;69:161-169.
- [61] Theurer M, Larson RL, White BJ. Systematic review and meta-analysis of the effectiveness of commercially available vaccines against bovine herpesvirus, bovine viral diarrhea virus, bovine respiratory syncytial virus, and parainfluenza type 3 virus for mitigation of bovine respiratory disease complex in cattle. *J Am Vet Med Assoc* 2015;246:126-142.
- [62] Stilwell G, Matos M, Carolino N, et al. Effect of a quadrivalent vaccine against respiratory virus on the incidence of respiratory disease in weaned beef calves. *Prev Vet Med* 2008;85:151–157.
- [63] Makoschey B, Bielsa JM, Oliviero L, et al. Field efficacy of combination vaccines against bovine respiratory pathogens in calves. *Acta Vet Hung* 2008;56:485–493.
- [64] Perino LJ, Hunsaker BD. A review of bovine respiratory disease vaccine field efficacy. *Bov Pract* 1997;31(1):59-66.
- [65] Nickell JS, White BJ, Larson RL, et al. A simulation model to quantify the value of implementing whole-herd Bovine Viral Diarrhea Virus testing strategies in beef cow-calf herds. *J Vet Diag Invest* 2011;23:194-205.

[66] Academy of Veterinary Consultant Position Statement on Disposal of BVDv PI cattle <http://www.avc-beef.org/Policy/positionstatements.asp>

[67] American Association of Bovine Practitioners Position Statement on Disposal of BVDv PI cattle <http://aabp.org/Members/Documents/PPM-SecE-3.24.2011.pdf#search=%22%20position%20statements%20%22>

[68] National Cattlemen's Beef Association 2014 Policy Book CH8.5 pp.46-47
[http://www.beefusa.org/CMDocs/BeefUSA/Issues/2014%20NCBA%20Policy%20Book.p
df](http://www.beefusa.org/CMDocs/BeefUSA/Issues/2014%20NCBA%20Policy%20Book.pdf)