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CONSENSUS STATEMENT

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Bovine viral diarrhea virus: An updated American College of Veterinary Internal Medicine consensus statement with focus on virus biology, hosts, immunosuppression, and vaccination

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Abstract

Control of bovine viral diarrhea virus (BVDV) in cattle populations across most of the world has remained elusive in spite of advances in knowledge about this viral pathogen. A central feature of virus perseverance in cattle herds is the unique mechanism of persistent infection. Managing BVDV infection in herds involves controlling persistently infected carrier animals using a multidimensional approach of vaccination, biosecurity, and identification of BVDV reservoirs. A decade has passed since the original American College of Veterinary Internal Medicine consensus statement on BVDV. While much has remained the same with respect to clinical signs of disease, pathogenesis of infection including persistent infection, and diagnosis, scientific articles published since 2010 have led to a greater understanding of difficulties associated with control of BVDV. This consensus statement update on BVDV presents greater focus on topics currently relevant to the biology and control of this viral pathogen of cattle, including changes in virus subpopulations, infection in heterologous hosts, immunosuppression, and vaccination.

KEYWORDS

bovine viral diarrhea, immunosuppression, vaccination, viral persistence

Abbreviations: ACE, antigen-capture ELISA; AI, artificial insemination; BDV, border disease virus; BHV-1, bovine herpesvirus 1; BRDC, bovine respiratory disease complex; BRSV, bovine respiratory syncytial virus; BVDV, bovine viral diarrhea virus; CL, corpus luteum; CP, cytopathic; IFOMA, in the face of maternal antibodies; KV, killed virus; MLV, modified-live virus; NCP, noncytopathic; PCR, polymerase chain reaction; PI, persistently infected; RT-PCR, reverse transcription-polymerase chain reaction; UTR, untranslated region; WBC, white blood cell.

1 | INTRODUCTION

Bovine viral diarrhea virus (BVDV) has remained an important viral cause of disease in cattle throughout the world. The initial descriptions of disease caused by BVDV involved the gastrointestinal system[1,2]; however, the virus is capable of causing disease in multiple organ systems including the respiratory and reproductive systems.[3] Bovine viral diarrhea virus employs an exclusive strategy among all cattle viruses for its maintenance within cattle populations, which is the generation of offspring that are immunotolerant to and persistently infected (PI) with BVDV.[4] An in utero BVDV infection before fetal development of immunocompetence is the mechanism by which BVDV PI offspring arise. Except under rare circumstances, PI animals shed high titers of infectious BVDV from nasal and ocular secretions, urine, semen, colostrum/milk, and feces. Because of this continuous and large source of virus, all BVDV control strategies and principles have centered on the elimination of PI animals. In North America, a three-dimensional approach to BVDV control involves use of diagnostics to identify and remove PI, use of effective vaccination to prevent the in utero development of PI, and the implementation of biosecurity/biocontainment principles.

Bovine viral diarrhea viruses are enveloped, single-stranded RNA viruses of the genus *Pestivirus* within the Family *Flaviviridae*.[5] Originally, viral isolates were designated as BVDV on the basis of host origin, so any pestivirus isolated from cattle was referred to as BVDV. Historically, the genus *Pestivirus* included only 4 classical species (BVDV1, BVDV2, classical swine fever virus, and border disease virus [BDV]); however, newly discovered virus species have prompted the reorganization of this genus.[6,7] Eleven species of pestiviruses, designated *Pestivirus* A-K, are currently recognized,[6] although the number of recognized species might increase by discovery using metagenomics. Under this new classification scheme, *Pestivirus* A-D correspond to the classic 4 species BVDV1, BVDV2, classical swine fever virus, and BDV, 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.[6] Logic for this new species classification arose from information obtained by genetic sequencing, which will enable the addition of new members. This reorganization of the genus *Pestivirus* only relates to the nomenclature of species, and the naming of the virus isolates/strains does not require a change from the classic BVDV designation.[7] The consensus panel recognizes the confusion a reclassification of virus species creates, but also accepts the importance of sequence-based virus taxonomy, as new pestiviruses will undoubtedly be discovered using metagenomics.

In 2010, the first American College of Veterinary Internal Medicine (ACVIM) consensus statement on control of BVDV was published,[3] and the principles of BVDV control outlined in the first consensus statement still apply. While information on clinical signs of disease, epidemiology, pathogenesis, transmission, diagnosis, and economics remains correct,[4,8,9] additional information arose that impacts our understanding of BVDV control. The objective of this consensus statement is to provide information on 4 specific topics identified by the panel on important issues related to BVDV. The first topic involves virus biology, and the importance of changing patterns of BVDV subtypes circulating in cattle. An increased prevalence of the BVDV1b subtype in North America has created concern with respect to BVDV control, but the BVDV1b subtype can be an example of changing virus subtypes and pestivirus species in other parts of the world. Since the original BVDV consensus statement, there has been increased recognition that BVDV is not host restricted, and the importance of heterologous hosts infected with BVDV is the second topic. Immunosuppression and the role of BVDV in concurrent disease processes is the third topic. Finally, vaccine efficacy and safety is the basis for the fourth topic. The panel also acknowledges that some topics apply mainly to the current situation in North America. As an example, modified-live virus (MLV) vaccines are not available in all countries, so the topic of vaccine efficacy of MLV versus vaccines containing inactivated fractions of BVDV might not apply everywhere.

2 | VIRUS BIOLOGY: WHAT FACTORS HAVE PROMPTED CHANGES IN THE DISTRIBUTION OF BVDV SUBTYPES?

Phylogenetic analysis indicates that BVDV has been circulating in cattle populations for hundreds of years.[10,11] Recent advances in diagnostic methods, sequencing, and phylogenetic analyses have identified 21 *Pestivirus* A subtypes (BVDV1a-u) and 4 *Pestivirus* B subtypes (BVDV2a-2d).[12] Although at this point considered a virus foreign to North America, there are 4 *Pestivirus* H subtypes (HoBi a-d).[13] The HoBi pestiviruses are of great concern, as these cattle-infecting pestiviruses are not routinely detected by current diagnostic tests used for BVDV detection. In addition, immunity created by currently available vaccines might not fully prevent viremia and generation of PI offspring. The objective of this section is to assess the strength of evidence explaining the mechanisms and consequences of infection with BVDV subtypes.

While multiple regions of the pestivirus genome have been targeted for characterization and differentiation of isolates, the 5′ untranslated region (UTR) has the highest level of conservation and was initially targeted for differentiation of BVDV isolates, and this part of the genome is still considered a reliable region for rough differentiation of subspecies.[14] However, the 5′UTR region is not the best option to do a full and detailed phylogenetic analysis.[15-18] For example, the use of Npro- and E2-based analyses indicates that the BVDV2 strains circulating in North America can now be reliably identified as substrains 2a, 2b, and 2c.[16,18]

Recommendation #1: While sequencing or differential polymerase chain reaction (PCR) can be used for defining species or subgenotypes, examination of multiple BVDV genomic regions is necessary to make conclusions on phylogenetic relationships among BVDV strains.

2.1 | What is importance of BVDV subtypes?

Initial reports describing methods for differentiating BVDV isolates into the 2 main species were published in 1994[19] and methods

for differentiating *Pestivirus* A into subtypes were published in 1998.[14] The ability to differentiate BVDV isolates into species and subtypes prompted prevalence estimations of BVDV species and subtypes in diagnostic submissions, fetal bovine serum, PI cattle, and field samples. Initial surveys published in the late 1990s and early 2000s reported BVDV1b to be the most prevalent subtype in samples. The most recent report in the literature concurs with previous reports, where 82% of the isolates obtained from 119 PI cattle originating in 5 different states within the United States were BVDV1b.[18] However, retrospective evaluation over a 20-year period (1988-2008) suggests that BVDV1a was the most prevalent subtype in 1988, while BVDV1b predominated in 1998 and 2008. While BVDV1a was accounting for 51% in 1988, this subtype underwent dramatic reductions in prevalence: 31% in 1998 and 18% in 2008.[20]

The presence of emerging or novel BVDV isolates as well as the prevalence of pestivirus species and subtypes is clinically and biologically important, as there are antigenic differences among the pestivirus species and also among BVDV subtypes.[21,22] Providing protection against BVDV is challenging because of the antigenic diversity among BVDV strains and ability of BVDV to infect the fetus, therefore complicating vaccine design and composition to prevent infection in the developing fetus. Collectively, data from prevalence studies and antigenic comparisons suggest that the prevalence of BVDV1b is increasing over time and this increase could be in part from the lack of antigenic similarity between BVDV1a and BVDV2a antigens in currently licensed US vaccines.[20] While this concept is plausible, fetal protection studies using currently licensed US vaccines have demonstrated protection against BVDV1b challenge or exposure.[23-25] However, when naïve control dams are exposed to the same number of BVDV1a, BVDV1b, and BVDV2a PI cattle, BVDV1a[23] or BVDV2a[26] could be detected most often in the resulting PI calves and fetuses, indicating that in the absence of BVDV 1a- or 2a-specific immunity, there might not be a selection pressure for BVDV1b to predominate. Naïve control animals provide a population of susceptible cattle that lack any specific immunity against BVDV and demonstrate which of the viruses used to expose the dams would predominate in the case of an unprotective immune response. Data to support BVDV strain differences have also been reproduced in vitro, demonstrating the BVDV2a isolate that predominated from the in vivo study[26] also predominated in cell culture when cells were inoculated with the same amount of virus from the 3 most predominant BVDV1a, 1b, and 2a isolates causing PI offspring.[27] Collectively, these results highlight that the outcome of BVDV exposure can be dependent on a variety of factors with one of those factors being the efficiency of transmission of the virus. Reasons for increased prevalence of BVDV1b isolates in the field might then be due to the increased probability of exposure to a BVDV1b PI because of prevalence or greater tendency of BVDV1b PI to remain in the population longer, coupled with greater antigenic differences between BVDV1b and the BVDV1a and 2a strains in current vaccines.

Given the prevalence of BVDV1b detection in BVDV-positive samples, and the antigenic diversity among BVDV subtypes,[20] potential inclusion of BVDV1b strains in vaccines is being considered. While it is reasonable to anticipate the inclusion of BVDV1b in vaccines would confer increased protection, this does not exclude the possible emergence of new BVDV subtypes,[16,28] neither does it assure the reduction in BVDV1b PI prevalence. Initially, BVDV vaccines only contained BVDV1a antigen. After the emergence of the high virulent BVDV2 strains and the antigenic mismatch between BVDV1a and 2, BVDV2 antigens were included in vaccines.[21,29] Reports of high virulent BVDV outbreaks declined since the use of BVDV1a/2 combination vaccines, but data from prevalence surveys do not suggest a decrease in prevalence of BVDV2.[20] Furthermore, newly emerging BVDV2b and c subtypes have been identified in recent years.[16] At present, there are no scientific data to explain the increased prevalence of the BVDV1b subtypes in cattle populations. The consensus panel concludes that there is low quality evidence that BVDV1b subtypes are the result of vaccination of cattle with vaccines containing the BVDV1a and 2a subtypes. The panel recognizes that this lack of understanding of selection pressure on BVDV subtypes is a major knowledge gap that has tremendous potential to impact BVDV control.

Recommendation #2: Examination of the role of vaccination or immunity pressure on BVDV subtype prevalence is recommended to fill the gap in knowledge on Pestivirus species or BVDV subtype emergence and dominance.

2.2 | How do new BVDV variants emerge?

As a single-stranded RNA virus, BVDV is heterogeneous, and genetic and antigenic changes are expected within serotypes. Since the RNA polymerase of BVDV lacks proofreading, mutations and substitutions can be expected, and these changes are in the range of 1.26×10^{-3} nucleotide substitutions/site/year in the envelope glycoproteins genes, E1-E2.[15] This substitution rate has important implications, specifically when the efficacy of vaccines is dependent on the ability of the antibodies and T-cell responses generated by the vaccines to prevent infection. Mismatches between vaccine strains and field strains can compromise the efficacy of these vaccines. Unfortunately, the amount of antigenic variation in the viruses currently in circulation is unknown, which makes the development of broadly protective vaccines difficult.[16] Evaluation of the E2 proteins from circulating BVDV1a strains indicated that 10% (47 out of 444) of the amino acids differed when compared to viruses similar to the currently used vaccine strains.[10] The relevance of these amino acid differences in neutralizing ability of vaccine induced antibodies remains to be determined.

Cattle pestiviruses remain in the population by establishing PI animals during pregnancy. As such, persistent pestiviral infections are a unique model for studying the evolutionary potential of single stranded RNA viruses, as no other virus can induce a persistent infection in the absence of an adaptive immune response. The unique way in which pestiviruses persist in the population, its diversity, and the short generation time of BVDV[30] allows the best-fit variants to rapidly adapt to a new environment, multiply quickly, and become dominant. These different environments can be found in individual infected animals, enabling selection of tissue specific variants.[31] Less fit virus

mutants can still remain present in low frequencies, enabling quick adaptation to changing circumstances.[32] The residues in the viral genome that can vary were thought to reside in the envelope proteins, mainly E2 as this is the immunodominant protein.[33,34] Within analyzed genes, highly variable positions and very conserved positions exist, generally 2 domains (I and II) of E2 contain the majority of the variation, with notable differences between 1a and 1b strains.[35] Several sites in genes coding for nonstructural proteins were also found to be variable, and whether this variation is partially responsible for differences in virulence of BVDV strains remains a topic for future study.

Generation of PI animals has impact on the variation of BVDV. The mutation rate of BVDV in infected pregnant animals appears to be higher than in nonpregnant animals.[36] Specific virus variants are selected during infection of the pregnant dam, likely as a result of the immunotolerance of pregnancy. While it might seem plausible that an anatomic bottleneck, consisting of placental tissues between cow and fetus, selects these virus variants,[31,36] the virus variants might also arise as a result of chance or because of a specific replicative advantage. There are strong indications that the establishment of a PI animal contributes not only to virus persistence and spread in the population, but also greatly diversifies the virus, to a greater level than that observed during acute infections.[36] The outcomes of this diversification process are currently unknown. Considering the region of positive selection in the genome of BVDV, it seems unlikely that the avoidance of antibodies is the driver of diversification.[37] Other options are that genetic diversification enables host-tropism changes which could play a role in the avoidance of either the CD8 T-cell responses or the innate immune system.[37]

3 | INFECTIONS IN HETEROLOGOUS HOSTS: WHAT IS THE IMPORTANCE OF BVDV INFECTIONS IN HETEROLOGOUS HOSTS AND TO BVDV CONTROL?

Infections with BVDV in heterologous hosts such as swine and deer were reported soon after the first description of BVDV in cattle 1946.[38,39] Since that time, strong experimental and seroepidemologic evidence demonstrates that BVDV infections are possible in at least 7 of the 10 families in the mammalian order *Artiodactyla*. Additionally, BVDV infections occur in non-artiodactyl hosts including the European rabbit (*Oryctolagus cuniculus*), European hare (*Lepus europaeus*), and, after experimental infection, laboratory mice, but the epidemiological importance of these infections is unclear.[40-42]

The clinical and epidemiological features of BVDV infections in several heterologous hosts have been reviewed,[3,43-46] indicating that characteristics of BVDV infections in other species are largely similar to those in cattle. Postnatal infection of nonpregnant hosts often results in nondetectable to mild disease marked by pyrexia and hematologic abnormalities, despite detectable viremia and seroconversion. In contrast, the most notable outcome of BVDV infection in pregnant heterologous hosts is transplacental infection and reproductive disease, and pregnancy losses up to 100%.[47-50] Strong experimental and field evidence supports that, as in cattle, BVDV readily causes transplacental infection in some heterologous hosts with resulting fetal death, congenital defects, or birth of nonviable offspring. Importantly, congenital BVDV infection of heterologous host in early gestation can also result in birth of viable, PI offspring that are infected for life. An additional phenomenon, termed chronic infection, has been described in some congenitally infected alpacas and swine. Like PI animals, chronically infected crias and piglets are born viremic and seronegative to the infecting BVDV, but clear the infection upon seroconversion after several weeks to months of life[51,52] by a currently unknown mechanism. While the published literature clearly demonstrates that BVDV exposure and infection of noncattle hosts is common and can negatively affect health of infected animals, the objective of this section is to assess scientific evidence on whether BVDV infections have an impact on health in heterologous hosts, whether BVDV infected hosts other than cattle can shed and transmit the virus, what is the source of BVDV for infection in heterologous hosts, and can current BVDV diagnostics detect infection in heterologous hosts.

3.1 | Do heterologous BVDV infections have a negative impact on herd or population health?

While many seroepidemiological studies demonstrate widespread exposure of heterologous hosts to BVDV and several case reports of BVDV-associated disease exist, fewer studies have evaluated the population-wide or regional impact of BVDV in heterologous hosts. There are case reports of BVDV-associated disease in sheep,[47,53,54] goats,[55,56] swine,[57-59] camelids,[51,60,61] and various captive and free-ranging artiodactyls.[62-66] Comprehensive investigations into the role of BVDV as cause of disease in heterologous hosts at a regional or population level are less common. An outbreak of "border-disease like" disease with abortions and birth defects in sheep flocks in northwestern and central Spain in 2015 was determined to have been caused by BVDV2.[67] In an Iranian study, investigating the presence of BVDV in aborted ruminant fetuses from 4 provinces by antigen-capture ELISA (ACE) and reverse transcription-polymerase chain reaction (RT-PCR), BVDV was detected in approximately 15% and 17% (ACE and RT-PCR) of ovine, caprine, bubaline, and cameline samples, which was similar to bovine fetuses of which 17.9% and 20.5% were positive.[68] Another study detected the presence of pestiviral antigen in 47.4% and 100% in 19 aborted lambs and 2 kids in western Turkey, which was similar in aborted calves (51.7%); however, this study did not discern the species of infecting pestiviruses.[69] In a study from southwestern China, 38/217 (17.5%) of sick goats with clinical signs including diarrhea, respiratory tract infection, and mucositis were positive for BVDV antigen and RNA,[70] corroborating the previously identified common exposure of Chinese goats to BVDV1b.[71] Similarly, BVDV was found to be highly prevalent in Chinese swine and was detected in 137/511 pigs from 11 provinces exhibiting clinical signs of fever, diarrhea, abortion, or piglet mortality.[72] After the first description of a PI

alpaca in 2005,[61] BVDV was recognized as an emerging pathogen of New World camelids in North America and the United Kingdom that causes ill-thrift, abortions, and birth of PI crias and prompted concerted control measures by the alpaca industry.[73-75] A recent study evaluating the association of BVDV exposure of farmed red deer in New Zealand with the occurrence of abortion detected an overall seroprevalence rate of 12.5%.[76] In that study, BVDV seroprevalence was not associated with the occurrence of abortions and was similar in herds that had experienced abortions to those without abortions.[76]

The extent of harm caused by BVDV infection varies among animal populations, and is likely because of factors related to time of exposure, differences among the infecting viruses, and host immune status, as has been observed with BDV, a closely related pestivirus of sheep and goats. Outbreaks of BDV infections have decimated some Pyrenean chamois (*Rupicapra pyrenaica pyrenaica*) populations in Spain, France, and Andorra and continue to drive population dynamics.[77-79] In contrast, in other populations of Pyrenean chamois and populations of Alpine chamois (*R rupicapra rupicapra*) that are also exposed to BDV, clinical disease and population decline were negligible or not detected, possibly because of differences among infecting viruses, viral ecology, or immune-status at the time of infection.[77,79-81] The lack of regular surveillance, difficulties in sampling free-ranging species, and lack of validated tests for BVDV detection in heterologous hosts pose challenges in comprehensively assessing the impact of BVDV on heterologous hosts.[82] Based on the limited available information, moderately strong evidence supports the conclusion that BVDV infection can negatively impact populations of heterologous hosts.

3.2 | Do heterologous hosts shed BVDV efficiently and cause transmission to susceptible animals?

Several studies have evaluated viral shedding from acutely infected or PI heterologous hosts. After experimental acute infection, BVDV was detected in nasal, or oral, or rectal, or any combination, swab samples from alpacas,[83] elk,[84] mule deer,[85] sheep,[86] swine,[87] and white-tailed deer.[88,89] In experimentally infected swine, viral loads in blood and nasal swabs were low[90] or undetectable.[91] Similarly, in 6 acutely infected alpacas after contact with PI alpacas, oral and nasal swabs remained negative for BVDV by virus isolation and PCR.[92] Although viral loads of BVDV can be variable in heterologous hosts, there is transmission of BVDV from acutely infected animals to susceptible cattle or conspecifics by direct or indirect routes.[84,87,88]

In PI heterologous hosts including alpacas, goats, white-tailed deer, and swine, BVDV can be detected in nasal swabs for the entire life of the animal.[52,55,92-94] Limited information exists about the viral load in PI heterologous host; however, viral titers of 10^4 to 10^6 $CCID_{50}$/mL occur in nasal swabs or blood of PI goats,[55,93] a PI pig,[52] and a PI white-tailed deer,[94] which is similar to viral loads in PI cattle. Another possible mode of viral shedding appears to be semen of PI heterologous hosts.[52,95] Studies evaluating BVDV transmission from PI heterologous hosts are sparse; however, transmissions rates of up to 100% to in-contact conspecifics have been reported under experimental conditions.[55,92,96] In a recent study exposing susceptible sheep and cattle to a neonatal PI lamb, only 1/9 sheep and 0/10 cattle became infected, and the low rate of transmission was likely caused by high titers of maternal antibodies during the study period.[97] With exception of studies demonstrating transmission of BVDV from PI lesser Malayan mousedeer by direct and indirect transmission,[98,99] there is a scarcity of publications demonstrating spill-back infections from heterologous hosts to cattle. However, based on the available information, there is strong evidence that BVDV is shed by acutely infected and PI heterologous hosts, providing potential for transmission to other animals.

3.3 | What is the source for BVDV in heterologous host populations and is the virus maintained?

While the source for BVDV exposures of heterologous host populations often cannot established with absolute certainty, exposure to infected cattle is the most plausible source of infection. Exposure to PI cattle can readily cause BVDV infection of heterologous hosts,[96,100] and several studies have identified greater BVDV infection rates in heterologous hosts that have contact to cattle implying their causal role.[101-111] In contrast, infection with BVDV in heterologous host populations not related to cattle contact or density occurs, suggesting independent circulation of the virus in some heterologous host populations.[112-115] Furthermore, high seroprevalence rates as identified in some host populations (eg, mule deer)[116-118] could indicate circulation and maintenance of BVDV. A third epidemiologic scenario in which cattle and heterologous host infections both contribute to maintenance of BVDV in a geographic region has been identified in cattle and red deer in south-central Spain, and cattle and small ruminants in southern Italy.[119,120] Based on the moderately strong available evidence, heterologous species could be incidental spillover hosts, maintain BVDV independent of cattle contact, or contribute to BVDV maintenance together with other artiodactyl hosts. The latter scenario would largely depend on opportunities for direct or indirect interspecific contact, which are more frequent under certain management strategies such as presence of multiple species on the premises, communal alpine farming, shared use of public lands, or provision of anthropogenic food sources during winter.[103,110,121,122]

Recommendation #3: Investigations into the role of heterologous hosts as a source of incidental spillover to cattle are needed. In individual herds, states, or countries applying BVDV control and eradication programs, information on the importance of heterologous hosts as reservoirs of BVDV is lacking.

3.4 | Can currently available diagnostic tests developed for cattle be accurately used in heterologous species?

Many epidemiological studies have determined the presence of BVDV antigen or antibodies in samples from heterologous hosts using commercially available antigen-capture or antibody ELISA assays developed for use in cattle. Unfortunately, there is a scarcity of formal

validation studies for bovine BVDV assays for use in other species. A study utilizing sera from naïve and BVDV inoculated sheep suggested alteration of manufacturer-recommended threshold values for 2 bovine ELISA assays for optimal performance in sheep,[123] and it is plausible that similar changes are necessary for evaluation of samples from other species. In cattle, detection of BVDV antigen in ear-notch samples by ACE represents an economical and accurate method of identifying PI animals.[124] While this detection method has also been used for the screening of heterologous hosts for BVDV in various studies and has 100% agreement with a single-tube-time RT-PCR in 764 samples from negative red deer,[125] formal evaluation has not been performed for heterologous hosts. In some studies, unexpectedly high numbers of ACE-positive samples were detected: for example, 41.4% in Algerian camels with an overall seroprevalence rate of 9.0%; 6/84 (7%) in mule deer; and 22/440 (5%) in white-tailed deer.[122,126,127] While these results suggest a high proportion of PI animals in the sampled populations, this conclusion is unlikely because the PI prevalence rate in cattle is generally below 1%. Confirmatory testing using a paired sample and another testing modality, such as VI or RT-PCR, should be considered when screening heterologous hosts for PI animals by ACE. The consensus panel concludes that there is low quality evidence that BVDV diagnostic testing methods available for testing cattle samples are appropriate for testing of BVDV infection in heterologous hosts.

Recommendation #4: Further research is critical to validate BVDV tests in heterologous species to ensure accurate use.

4 | BVDV-INDUCED IMMUNOSUPPRESSION: WHAT IS IMPACT OF IMMUNOSUPPRESSION ON CATTLE HEALTH AND WELL-BEING?

Immunosuppression associated with BVDV infections has become doctrine; and, evidence for this includes changes in number or degree of function of immune cells in BVDV-infected cattle, and occurrence of disease and pathology of increased severity when BVDV-infected cattle are coinfected with other pathogens. This immunosuppression has been identified in cattle after naturally occurring BVDV infection, either transient or persistent, and also in experimentally infected cattle. The objective of this section is to assess the strength of evidence that BVDV is immunosuppressive, that BVDV biotype, genotype, or strain influences immunosuppression, and whether BVDV contributes to the bovine respiratory disease complex (BRDC). Evidence was assessed from English-language published reports describing naturally occurring disease in which cattle were confirmed to be infected with BVDV by identification of the virus (virus isolation, immunofluorescence or immunohistochemistry, or PCR) or by seroconversion. Evidence was also assessed from experimental challenge studies; data are included only from research in which immune responses of BVDV-infected cattle were compared to concurrently sampled age- and breed-matched controls, and for which outcomes were compared by statistical analysis. Evidence has not been included from research in which the response of immune cells isolated from healthy cattle and exposed to BVDV in vitro was the only outcome assessed.

4.1 | What is evidence for defects in immune cell function during BVDV infection?

An early description of BVDV-induced immunosuppression demonstrated that blood lymphocytes from 5 calves with naturally acquired "chronic" (presumably persistent) BVDV infection had lethargic responses to mitogen stimulation, as compared healthy cattle.[128] Neutrophils from PI cattle have decreased ability of phagocytosis of *Staphylococcus aureus*, decreased cytochrome C reduction, reduced function of the antimicrobial myeloperoxidase-H_2O_2-halide system, and decreased antibody-independent cell-mediated cytotoxicity, compared to neutrophils from noninfected cattle.[129] In the same study, lymphocytes from PI cattle have decreased blastogenesis in response to stimulation with mitogens. PI cattle vaccinated against *Mannheimia haemolytica* have lower antibody titers at 28 days postvaccination than healthy control vaccinates.[130] Similarly, calves exposed to BVDV PI cattle before experimental *M haemolytica* challenge produce lower antibody titers to the *M haemolytica* leukotoxin, compared to calves only challenged with *M haemolytica*.[131] The quality of evidence that PI cattle have defects in immune function as compared to age- and breed-matched non-PI cattle is strong.

Numerous investigators[131-135] have demonstrated significant decreases in the peripheral blood concentration of leukocytes, neutrophils, lymphocytes, and platelets in cattle experimentally challenged with BVDV, as compared to baseline or as compared to control cattle sampled on the same day. Multiple investigators have found the degree of viremia after experimental challenge to be related to the severity of resulting disease, with viruses reaching higher viral titers in blood being associated with more severe disease.[135,136] It is not clear whether this relationship is because of replication characteristics of the virus leading to higher titers or the ability of the virus to induce a greater degree of immunosuppression, allowing it to replicate more efficiently, or a combination of both. The quality of evidence that BVDV infection leads to decreases in blood concentration of neutrophils, lymphocytes or platelets, or both lymphocytes and platelets, is high. The quality of evidence that BVDV infection leads to specific defects of immune function is moderate.

4.2 | What is evidence for differential effects of BVDV biotypes/genotypes/strains on immune function?

Two biotypes of BVDV exist, noncytopathic (NCP) and cytopathic (CP). Most vaccines contain CP BVDV strains, while NCP BVDV strains are more common in nature. In a small number (n = 3-4 per group) of calves challenged with either a CP or NCP version of a homologous pair of BVDV isolates (BVDV strain Pe515), calves exposed twice at a 91-day interval with the NCP virus generate higher

serum neutralizing antibody titers than calves exposed to the CP virus, whereas calves challenged twice with the CP virus produce higher lymphocyte blastogenesis responses than calves challenged with the NCP virus.[137] These results suggest that NCP BVDV induces better humoral immunity, while CP BVDV induces better cell-mediated immunity; however, the small setup of the study warrants confirmation of this conclusion. Another study compared the response of calves to challenge with either NCP or CP BVDV from a matched pair of isolates obtained from a calf with mucosal disease,[138] but only 2 calves were evaluated in each group at each necropsy time point, so it is not possible to assess whether the resulting disease was significantly different. The quality of evidence that BVDV biotype influences the nature and degree of immunosuppression after BVDV infection is weak.

Research in the late 1990s indicated that in vitro infection of bovine cells by NCP BVDV suppressed their interferon production, while infection by CP BVDV activated interferon pathways. These findings led to speculation that NCP BVDV-mediated interferon suppression enabled the establishment of persistent infection with NCP but not CP BVDV.[139] However, an important recent discovery is that PI fetuses can respond to in utero NCP BVDV infection with expression of mRNA for interferon alpha (IFN-α), IFN-β, and IFN-γ, as well for interferon stimulated genes known to play a role in clearance of other viral infections.[140,141] Fetuses infected by intranasal exposure of their dams to NCP BVDV2 strain 96B2222 at 75 days of gestation had higher concentrations of IFN-γ in their serum but not amniotic fluid, as compared to fetuses from cows not exposed to BVDV2, when they were collected by Cesarean section at 97 days of gestation.[141] This was in contrast to their BVDV2-infected dams, in which greater concentrations of serum IFN-γ were measured on day 89, but which had returned to concentrations not different than uninfected cows by day 97. As the liver is a site of immune activation in fetal life, expression of MHC I and MHC II by cells isolated from liver tissue of fetuses collected by Cesarean section 14 days postinfection was assessed.[142] The percent of cells expressing MHC I and MHC II was significantly higher in PI fetuses than noninfected control fetuses.[142] Taken together, these findings indicate that, in contrast to long held dogma, fetal calves can mount an immune response when they are exposed to NCP BVDV in the gestational window when PI infection can occur. However, the reason that these immune responses do not lead to clearance of infection is not yet clear. It could be that the responses measured in these studies ultimately lead to immunologic tolerance. While the research quality is high, the fact that the findings have to date been made in cattle infected with only 1 NCP BVDV strain limits the degree to which they should be generalized. The quality of evidence that fetal immune system recognizes and responds to NCP BVDV infection during the gestational window resulting in persistent infection, in spite of failing to resolve infection, is moderate.

The concept that BVDV2 is more virulent than BVDV1 was established when outbreaks of unusually severe disease were described in North America in the early 1990s.[143,144] These outbreaks were characterized by respiratory disease, diarrhea, abortion, profound thrombocytopenia with multisystem hemorrhage, and sudden death in calves and mature cattle infected with NCP BVDV2 strains. Notably, affected cattle sometimes displayed lesions suggesting mucosal disease, but these cattle were not simultaneously infected by a NCP and CP BVDV strain as required for mucosal disease.[143] Isolates from at least some of these outbreaks were confirmed by genetic and antigenic analysis to be NCP BVDV2.[19,145] Subsequently, experimental challenge studies with some BVDV2 isolates confirmed that they could induce severe disease similar to that seen in the naturally occurring outbreaks.[146,147] The identification of BVDV2 in cattle with severe disease and hemorrhagic syndrome in different regions by different investigators has strengthened the confidence of the scientific community that BVDV2 isolates can be unusually virulent, as compared to BVDV1 isolates. In an experimental challenge study comparing the responses of calves to challenge with BVDV2 890, BVDV2 7937, or BVDV1 TGAN,[135] calves challenged with BVDV2 890 had higher titers of virus in the blood than calves in the other 2 challenged groups, and also control calves that were not challenged. Calves challenged with BVDV2 890 also had diarrhea and fever on more days than control calves or calves in the other challenge groups. Platelet counts dropped to <200 000 cells/μL in some calves challenged with BVDV2 but in none of the control calves or calves challenged with BVDV1. Alterations in platelet function were identified in calves challenged with the BVDV2 strains but not the BVDV1 strain.[148]

A limitation of the available evidence regarding the relative virulence of BVDV2 versus BVDV1 is that substantial genetic variation has been described within these genotypes, leading to designation of numerous subgenotypes. However, the relative virulence of only a handful of BVDV1 and BVDV2 isolates has been compared in side-by-side challenge studies. Thus, while the available evidence that some BVDV2 isolates can cause disease of increased severity relative to some BVDV1 isolates is strong, not all BVDV2 isolates have been compared to all BVDV1 isolates, and not all BVDV2 isolates have been associated with severe disease. Moreover, because BVDV is always evolving, it is possible that BVDV1 isolates could be found that are more virulent than at least some BVDV2 isolates. The quality of evidence that some BVDV2 isolates cause more severe disease than some BVDV1 isolates is high, but this should not be extrapolated to indicate that all BVDV2 isolates cause severe disease, or that all BVDV2 isolates are more virulent than all BVDV1 isolates. The evidence that differences in virulence are directly the result of immunosuppression is limited and thus weak.

Most research comparing effects of strain have focused on BVDV2. In young (2- to 3-week-old) Holstein calves, NCP BVDV2 890 caused more severe disease than NCP BVDV TGAN,[136] although no effort was made to compare responses using statistical analysis, limiting the strength of this evidence. In a study comparing clinical signs of disease in seronegative beef calves challenged with 1 of 5 different BVDV2 isolates from natural outbreaks,[133] the 2 isolates (17583 and 23025) obtained from mature cows that died of peracute BVDV infection caused more severe disease than 3 other BVDV2 isolates obtained from fetuses aborted from cows with transient nonfatal infection. Calves challenged with 17583 or 23025 developed diarrhea, coughing and nasal discharge, and had higher rectal temperatures on day 6 after challenge, and significantly lower blood lymphocyte counts on several days

after challenge; these signs were not seen in calves infected with the 3 strains from aborted fetuses. This study provided high quality evidence that, under conditions of experimental challenge, BVDV2 strains can differ in virulence. The quality of evidence that some strains (isolates) of BVDV2 are more virulent than other strains of BVDV2 is strong. The evidence that differential virulence is directly related to immunosuppression is limited and thus weak.

4.3 | What is evidence for a role for BVDV in the BRDC?

The evidence for a role for BVDV in BRDC includes: (1) associations with BVDV infection (either by virus identification or seroconversion) with naturally occurring respiratory disease; (2) increases in BRD morbidity and death in cattle or groups exposed to PI cattle, versus individuals or groups not exposed; (3) gross or microscopic respiratory pathology in cattle experimentally challenged with BVDV; and (4) respiratory disease of increased severity in cattle challenged with BVDV at or near the time cattle are challenged with other agents, as compared to control cattle challenged with the other agent alone. A reduction of BRDC morbidity or death as a consequence of BVDV vaccination could demonstrate its role, but available research has so far not indicated that BVDV vaccination specifically was responsible for decreasing risk of naturally occurring BRDC.

Seroconversion to BVDV during an observation period has been associated with treatment administration for BRDC in commingled and transported cattle.[149,150] In 2 consecutive years, BVDV was more likely to be isolated from calves that were treated for respiratory disease than calves in the same group that were not treated.[149] In addition, calves treated for respiratory disease were also more likely to seroconvert to BVDV than pen mates who were not treated for respiratory disease. Being seropositive to BVDV at feedlot arrival has been associated with decreased risk of treatment for BRDC, indirectly indicating a role for BVDV in BRDC.[151] Similarly, in a trial evaluating BRDC risk in 24 groups of calves entering a retained ownership program,[149] the association between BVDV1 antibody titer at arrival and protection against BRDC approached significance (P = .07), and low BVDV1 or BVDV2 titer at arrival was associated with several performance outcomes. Three well-designed studies have evaluated BRDC morbidity and risk of death in trials evaluating individual or groups of cattle naturally exposed to PI cattle. In 2 reports, PI exposure increased morbidity or risk of death,[152,153] and in the third it did not.[154] The quality of evidence that BVDV infection or exposure can be associated with increased risk of BRDC is high, but this should not be interpreted to indicate that BVDV infection or exposure always increases risk of BRDC.

Experimental challenge of cattle with BVDV can lead to mild pneumonia,[155] and occasionally herd outbreaks of BVDV are first identified by signs of respiratory disease, such as fever, tachypnea, and loud bronchovesicular sounds.[156] The ability of BVDV to cause respiratory disease appears to depend in part on the strain of infecting virus.[157,158] Experimental coinfection with BVDV increases the severity of disease because of infection with *M haemolytica*,[131,155] bovine herpesvirus 1 (BHV-1),[159] or bovine respiratory syncytial virus (BRSV).[160] Lack of reported blinding by individuals assessing cattle for signs of disease weakened the quality of this evidence, although inclusion of objective outcomes such as rectal temperature supported conclusions. The quality of evidence that experimental BVDV infection can induce respiratory pathology, and that BVDV coinfection increases severity of respiratory disease caused by other infections, is moderate.

Few clinical trials have evaluated the impact of BVDV vaccination on BRDC with a design that provides the possibility of strong confidence that BVDV vaccination specifically was responsible for decreasing BRDC risk. In many published trials, a nonvaccinated control group was omitted; in others, vaccination with multivalent vaccines made it difficult or impossible to separate the effect of the BVDV components from the effect of other antigens. One study assessed the impact of BVDV1 vaccination before or at feedlot arrival in groups of cattle purposely exposed to PI cattle for various durations of time before or after feedlot arrival.[161] The evidence that BVDV vaccination decreases naturally occurring BRDC in field settings is limited and of low quality.

Recommendation #5: Effects of BVDV on immune function are well established, but research involving interactions of virus type, host immunity, and environmental factors are needed to ultimately determine impact of BVDV infections in cattle populations.

5 | VACCINATION AGAINST BVDV: WHAT FACTORS IMPACT VACCINE EFFICACY AND SAFETY?

Improving herd immunity through vaccination is an essential step to reduce morbidity and mortality associated with BVDV infection in cattle. The results of multiple scientific reports suggest that the use of MLV or killed virus (KV) vaccines prevents the presentation of diverse clinical manifestations of BVDV infection in cattle; however, individual studies report inconsistent results with respect to efficacy and safety of BVDV vaccination when used in different cattle populations. The objective of this section was to provide an assessment of the quality of evidence on whether MLV and KV vaccines provide similar clinical protection against the different clinical manifestations of BVDV infection, whether maternally derived BVDV antibodies from colostrum affects efficacy of BVDV vaccination programs in young calves, and whether MLV vaccines are safe to use in cattle at any stage of production?

5.1 | Do MLV and KV vaccines provide similar protection against the different clinical manifestations of BVDV infection in cattle?

Commercially available BVDV vaccines contribute to the prevention and control of acute BVDV infection in pregnant and nonpregnant cattle. Acute BVDV infection in young, nonpregnant cattle can result

in subclinical or clinical disease associated with affection of the hematopoietic, lymphoid, respiratory, digestive, and reproductive systems. In contrast, acute BVDV infection in adult, pregnant cattle can result in reproductive failure and more importantly in the generation of PI offspring.[3,162]

The primary goals of BVDV vaccination of young nonpregnant cattle are prevention of morbidity (viremia, pyrexia, nasal discharge, diarrhea, leukopenia, and thrombocytopenia) and death because of acute BVDV infection.[3] Seventeen studies evaluated the effect of vaccination with MLV (n = 12) or 2 doses of KV (n = 5) BVDV vaccines on clinical protection after experimental infection with BVDV.[161,163-178] The age at vaccination varied from 3 days of age to 16 months of age. The time between vaccination and challenge/exposure varied from 3 to 230 days. These studies reported between 80% and 100% reduction of mortality and between 72% and 90% reduction of morbidity in vaccinated calves. The higher percentages of protection corresponded to MLV vaccination. The ability to induce a high antibody response as well as the degree of homology among vaccine and challenge BVDV strains was associated with better clinical protection in cattle vaccinated with KV vaccines.[22,163,179] A meta-analysis demonstrates that calves vaccinated with an MLV vaccine had reduced risk of morbidity and death after experimental infection with BVDV. In contrast, calves vaccinated with a KV vaccine had a reduced risk of death but did not have reduced morbidity risk after BVDV challenge.[180] The evaluation of MLV versus KV vaccination in calves indicated that MLV-vaccinated calves had lower morbidity rates compared with KV-vaccinated, and unvaccinated control calves after experimental BVDV infection.[179] Some of the studies lacked adequate randomization, blinding to treatment allocation, and incomplete accounting of outcome events, or only incomplete accounting of outcome events, affecting their evaluation.

The primary goals of BVDV vaccination of pregnant cattle are the prevention of early embryonic death, abortion, and generation of PI/seropositive calves after acute BVDV infection during gestation.[162] Twenty-two studies evaluated the effect of vaccination of heifers or cows, or both, prebreeding with an MLV (n = 18) or KV (n = 4) vaccine on clinical protection after experimental BVDV infection during gestation.[23-26,181-197] The time between vaccination and experimental challenge/exposure varied from 70 to 490 days. These studies reported between 22% and 100% protection against fetal infection, between 82% and 100% protection against abortion, and between 8% and 100% prevention of generation of PI or BVDV-seropositive calves. The higher percentages of protection corresponded to MLV vaccination. The inability of KV vaccines to induce long-lasting humoral protection could explain the higher rates of fetal infection observed in some studies.[26,196] An opportunity might exist for KV vaccines to be utilized as an immunization booster. Vaccination of heifers with MLV vaccine at weaning and before breeding followed by KV vaccination 6 months later (at pregnancy examination) resulted in higher fetal protection rates as compared to heifers that were administered MLV vaccination at the same times before breeding and then again at pregnancy examination[23] Similarity among vaccine and challenge BVDV strains could also influence clinical protection provided by vaccination.[182,188] A meta-analysis demonstrates that multivalent BVDV vaccines provide better coverage to heterologous strains compared with monovalent vaccines.[198] Additionally, the risk of fetal infection and abortion is lower in cattle vaccinated with MLV vaccines versus cattle vaccinated with KV vaccines.[198] Based on these findings, the consensus panel concludes that there is high quality evidence that clinical protection offered by MLV BVDV versus KV BVDV vaccines to pregnant cattle is not similar. Modified live virus vaccines provide better clinical protection against fetal infection, abortion, and generation of PI calves.

5.2 | Do maternally derived BVDV antibodies from colostrum affect the efficacy of BVDV vaccination in young calves?

The presence of maternally derived BVDV antibodies from colostrum interferes with induction of antibody responses to vaccination in young calves[199]; however, MLV vaccination of calves in the face of maternal antibodies (IFOMA) primes cell mediated responses in absence of seroconversion.[200-202] Controversy exist about the efficacy of vaccination IFOMA on clinical protection of calves after natural or experimental infection with BVDV after maternal antibodies decay. Eight randomized clinical trials evaluated the effect of vaccination IFOMA with an MLV vaccine on clinical protection after experimental infection with BVDV.[202-209] The age of calves at vaccination varied from 3 to 93 days. The time between vaccination and experimental infection varied from 21 to 270 days. There is 33.3% to 100% reduction of death, and between 0% and 100% reduction of clinical disease in vaccinated calves. Six studies reported between 77% and 100% reduction of viremia and 2 studies reported between 77% and 87% reduction of nasal shedding in vaccinated calves. The age and serum titer of BVDV antibodies at vaccination, and the similarity between vaccine and challenge virus influenced clinical protection provided by vaccination IFOMA. Calves under 14 days of age at the time of vaccination and at a time with a high titer of maternal BVDV antibodies can develop severe clinical disease, develop viremia, or die after experimental challenge with a heterologous BVDV strain.[206,207] In contrast, calves vaccinated after 28 days of age with moderate to low maternal antibodies at vaccination, develop antibody responses that protect against viremia and virus shedding after experimental BVDV infection.[203,204,208] Based on these findings we conclude that there is moderate quality evidence that vaccination of calves IFOMA with a MLV vaccine does not affect the efficacy of BVDV vaccination.

5.3 | Are MLV vaccines safe to use in cattle at any stage of production?

The use of MLV vaccines has raised concerns because of their potential of causing undesirable reactions in young calves and breeding females.[29] Potential adverse effects associated with MLV vaccination include transmission of vaccine virus to susceptible cattle, immunosuppression, reduced pregnancy rates, abortion, and generation of PI offspring.[21]

Transmission of BVDV from calves vaccinated with an MLV vaccine to susceptible pregnant and nonpregnant cattle has been a concern because transmission of vaccine strains of BHV-1 and abortion were demonstrated in pregnant cattle that came in contact with calves recently vaccinated with a MLV BHV-1 vaccine.[210] Two randomized clinical trials evaluated the effect of vaccination of seronegative cattle with a parenteral MLV vaccine on the transmission BVDV and BHV-1.[130,211] Both studies commingled vaccinated and unvaccinated, susceptible, pregnant and nonpregnant cattle in a small pen with single feed bunk and water sources. The duration of commingling varied between 42 and 103 days after vaccination. Vaccinated cattle seroconverted to BVDV and tested positive to the virus in white blood cell (WBC) and nasal secretions between days 7 and 10 after vaccination. The WBC and nasal secretions from unvaccinated control cattle in contact with vaccinates remained negative by virus isolation and RT-PCR for BVDV1, BVDV2, and BHV. Additionally, unvaccinated control cattle did not seroconvert to BVDV1, BVDV2, or BHV-1. Based on these findings, we conclude that there is high quality evidence that transmission of BVDV vaccine strains from cattle vaccinated with an MLV vaccine to susceptible cattle is unlikely.

Vaccination of heifers and cows with MLV vaccines containing BVDV and BHV-1 around the onset of standing estrus could have deleterious effects on corpus luteum (CL) function and can result in transient subfertility after breeding.[212,213] The majority of the concerns on these effects have been associated to the BHV-1 fraction of multivalent MLV vaccines.[214] Although BVDV vaccine antigens are present in the ovaries of cattle up to 30 days after vaccination with an MLV vaccine, its effect on reproductive efficiency is unknown.[215] Six randomized clinical trials evaluated the effect of MLV-, inactivated-, or no-vaccination (control group) of heifers and cows during the prebreeding period on overall pregnancy rates after breeding.[210,216-220] One of the studies evaluated initial prebreeding vaccination of BVDV and BHV-1 naïve heifers while the others evaluated prebreeding revaccination of previously vaccinated animals. The number of days between vaccination and start of estrous synchronization protocol varied from 0 to 21 days. The number of days between vaccination and breeding varied from 8 to 45 days. Compared with animals vaccinated with an inactivated BVDV and BHV-1 vaccine or with nonvaccinates, the overall pregnancy rate in animals vaccinated with an MLV BVDV and BHV-1 vaccine before breeding was reduced between 0% and 42%; however, these differences were not significant in all studies. Vaccination of BVDV and BHV-1 naïve heifers 8 days before breeding was detrimental for pregnancy rates in 1 study.[218] Another study reported a 3.6% reduction in pregnancy rates at day 56 after artificial insemination (AI) but not in subsequent days in cows vaccinated 30 days before AI with a MLV vaccine versus nonvaccinated cows.[221] Based upon this data, the timing of vaccination is important, and the closer time proximity to vaccination with developing and midluteal phases of the estrous cycle, the greater is the negative effect on pregnancy rate.[218-220] In contrast, the presence of immunity to BVDV and BHV-1 acquired from previous vaccinations prevents the negative effects on CL function and fertility associated with prebreeding vaccination with an MLV vaccine.[216,219,220] Limitations such as small sample sizes, absence of unvaccinated control groups, and lack of randomization and accounting for potential confounding factors affected the evaluation of some of these studies. Based on these findings, we conclude that there is moderate quality evidence that MLV BVDV vaccines administered 30 days or more before breeding have no detrimental effects on pregnancy rates after breeding.

The majority of commercially available MLV vaccines labeled for pregnant cattle often contain BHV-1. The label of these vaccines states previous vaccination with the same vaccine according to label directions at least 12 months prior is strictly necessary before their use. These recommendations are critical for safety, as vaccination of BVDV and BHV-1 naïve pregnant cattle with a MLV vaccine poses a high risk of pregnancy loss after vaccination.[222,223] Recently, increased concerns regarding pregnancy loss associated with BHV-1 after vaccination with MLV vaccines have been raised even after adhering to vaccine label directions.[210,214] A previous study and a field investigation reported reproductive losses attributed to BHV-1 after vaccination of pregnant cattle with MLV vaccines within label recommendations.[214,217] Two randomized clinical trials evaluated the effect of revaccination of pregnant cattle with an MLV BVDV and BHV-1 vaccine or an inactivated BVDV and temperature-sensitive MLV BHV-1 vaccine between 63 and 200 days of gestation.[23,217] One of the trials evaluated clinical protection provided by annual revaccination against rigorous challenge with PI cattle and intravenous BHV-1 injection. Revaccination during pregnancy was not associated with abortions in our study.[23] Generation of PI calves after vaccination of pregnant cows with a MLV vaccine is unlikely as the majority of MLV vaccines contain CP strains; however, contamination of MLV vaccines with NCP strains becomes a hazard when those vaccines are administered to naïve cattle. Acute disease, abortion, and generation of PI offspring can result from vaccination with contaminated vaccines.[224] Based on these findings, we conclude that there is high quality evidence that the risk of abortion or reproductive failure is low after revaccination of pregnant cattle with an MLV BVDV vaccine during pregnancy when compliant with vaccine label recommendations.

Recommendation #6: Optimizing efficacy yet maintaining safety of vaccination against BVDV is important, and additional research studies are needed to evaluate strategic use of KV, MLV, and new-generation vaccines in priming and boost protocols.

6 | SUMMARY AND FUTURE DIRECTIONS

While considerable advancements have been made regarding our understanding of BVDV, its associated diseases, and the methods for control, BVDV remains an important cause of disease in cattle populations in many parts of the world. The consensus panel agrees many tools are available for controlling BVDV, including safe and efficacious vaccines, sensitive and specific diagnostic assays, and the knowledge of BVDV transmission routes, whereby biosecurity principles can be applied. In Europe where control and eradication programs have been established at national levels, the prevalence of PI cattle has decreased or the virus has been eliminated from the cattle populations. But the consensus panel also admits that there are still important knowledge gaps related to

BVDV that could impact control and eradication. The threat of BVDV and pestivirus diversification could impact the ability of diagnostics to detect and vaccines to protect. This should be an area of future study to define what drives subtype emergence and dominance. As stated in the first BVDV consensus statement, BVDV has undergone surges and lulls in importance since its discovery in 1946, and pestivirus diversification could serve as the next surge in importance. The potential for nonbovine reservoir hosts to serve as a source of novel pestiviruses and as a spill-back source to cattle populations is another area of concern and should garner attention for future study. Finally, the consensus panel agrees that continued investments in BVDV awareness and education are important for adoption of BVDV control by cattle producers.

CONFLICT OF INTEREST DECLARATION

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OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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