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BVD: More answers. . . and questions

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Bovine Viral Diarrhea Virus is a general term that describes an array of viruses within the *Pestivirus* genus and *Flavivirus* family. Currently, two* primary and distinct species (genotypes) of BVDV are described in cattle, including BVDV1 and BVDV2. Within each species there are various subgenotypes including 12 in BVDV1 and two within BVDV2.

(: Three new species of BVDV have been identified including HoBi, pronghorn, and Bungowannah. Only HoBi has been associated with clinical signs [reproductive and PI] in cattle from South America and Southeast Asia. HoBi is proposed to be renamed BVDV3).*

Within each species two distinct biotypes are observed, including non-cytopathic (NCP) and cytopathic (CP). Furthermore, two states of infection (persistent and acute) and five clinical forms (acute, severe acute, hemorrhagic, acute-respiratory tract, and acute-immunosuppression) are also described. Finally, persistent infection (PI) with a noncytopathic BVDV followed by acute infection with a similar cytopathic BVDV strain results in mucosal disease.

The practical importance of genotypes and subgenotypes is several fold. First, it is uncertain if cross protection occurs across subgenotypes. Second, it is unclear whether diagnostic tests have comparable sensitivities across subgenotypes. Finally, the predominant genotype isolate in the U.S. is BVDV1b, however, many commercial vaccines and diagnostic tests are based on BVDV1a and BVDV2a.

Acute or transient BVDV infection can result in enteric, respiratory, or reproductive tract diseases of variable severity. Clinical variation from subclinical to fatal is believed to be dependant on viral strain, immune status of the host, reproductive status of the host, and secondary pathogens.

While the majority of acute BVDV infections is not clinically significant, infection of pregnant cattle can result in abortion, stillbirth, birth defects, or persistent infection (dam infected less than 125 days of gestation). Persistently infected (PI) calves may be born weak and fail to thrive, or may appear healthy. No matter their clinical appearance, PI calves can potentially shed large amounts of virus, and current control efforts in the U.S. are focused on the detection and removal of these animals.

The hemorrhagic syndrome due to *thrombocytopenia* is clinically characterized by bloody diarrhea, nosebleed, external or internal hemorrhages, and bleeding from injection sights. It is primarily associated with infection with NCP BVDV2. BVDV also occurs in a variety of domestic and wild ruminants including New World Camelids and several species of deer.

Testing strategies

Several testing strategies are available for BVDV, each having distinct advantages and disadvantages. The type of test chosen also depends on what samples are easiest to obtain. The following is a list of testing strategies with selected comments.

Viral Isolation (VI): (serum, blood or tissue)
Labor intense. Can be used in groups. Maternal antibodies may interfere.

Immunohistochemistry (IHC): Detection of Antigen in tissues (ear notch)
Can formalin fix tissues. Used to identify PIs. not always available

Reverse Transcriptase PCR (RT-PCR): (blood, milk, ear notch)
For individuals and herds, can not differentiate persistently infected from transiently infected.

Ag Capture ELISA (Ag cELISA): (serum, ear notch) Fast. Less expensive. Good sensitivity/specificity. Takes place of IHC.

Serology: Used in unvaccinated herds to determine BVDV free status.

Combinations: Example – PCR on pooled whole blood + IHC of PCR positives.

Economic Impact

Several approaches have been proposed to determine the cost of BVDV infection in cattle populations. Most of the published data are in regard to estimates in dairy cattle, with little information available concerning cow-calf, feedlot, and stocker operations. As well, a large proportion of estimates are based on data collected from countries other than the U.S.

Enumerating production costs is difficult due to the large number of variables in many analyses. A brief list of cost factors might include reduced milk production, high somatic cell counts, reduced conception rates, immunosuppression, increased susceptibility and severity of disease, treatment costs, animal mortality, feed efficiency, etc. A model that does not include every possible variable will likely underestimate the true cost of BVDV. Lastly, variation in virulence of different BVDV strains clearly exists. Some published reports have provided cost estimates in herds with mild clinical signs, versus others having more severe clinical signs due to infection with highly virulent strains.

All said, the complexity of determining the economic impact of BVDV should not prevent practitioners from consulting with producers to determine the best means of addressing BVDV. In general, the economic impacts can be categorized into production

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BVDV . . .

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losses, costs associated with treatments and testing, and costs associated with implementing biosecurity efforts. Producers can be given a general outline regarding the potential effects of BVDV based on their type of operation.

Dairy: Detrimental effects in dairy cattle include reduced milk production, reduced fertility, poor growth of replacement heifers, increased secondary disease, early culling, and increased mortality. Ongoing BVDV infections has also been shown to increased the risk of clinical mastitis, retained placenta and increased calving intervals. Several studies have indicated specific monetary losses, however these were clearly dependant on the particular operation, situation and event.

Cow/calf: BVDV has been associated with reduced fertility, abortion and poor growth rates. In addition, the purported immunosuppressive effects of BVDV result in increased secondary diseases. Studies have shown that calves born during BVDV outbreaks suffered increased mortality. Others have demonstrated increased incidence of respiratory viruses and bacteria found in calves previously exposed to BVDV.

Feedlot: Studies have demonstrated an increased risk for respiratory tract diseases in cattle exposed to PIs in either the same or adjacent pens. Other studies have shown that cattle in pens with PIs had decreased gains, more cost of gain, and an overall loss in profit after feeding.

Persistence of infectivity in transient infections (TI)

Evidence suggests that within herds with acute or transient infections (TI) BVDV can persist for months to years despite aggressive testing, removal of PI animals, and stringent biosecurity measures. In addition, prolonged viral presence in the testicles of bulls following acute infection suggest the possibility of a chronic form of BVDV persistence that resembles that of hepatitis C virus.

Studies suggest that BVDV-infected, recovered, and immune animals have the potential to remain infectious for significantly longer than previously demonstrated. The importance of TI animals in maintaining BVDV infections within herds needs to be considered.

Control: vaccination, testing, biosecurity, etc.

The practical importance of the antigenic differences between strains relates to the failure of BVDV1 strain vaccines to protect against BVDV2 strains. In addition, the practical importance of subgenotypes is still unclear as it is uncertain whether cross protections from vaccination is conferred between subgenotypes, or if diagnostic tests will have comparable sensitivities between different subgenotypes. In the U.S. BVDV1a, BVDV1b and BVDV2a are currently the prevalent subgenotypes.

Prevalence rates over the past 10 years suggest there has been a shift in relative predominance indicating most field isolates are now BVDV1b. Importantly, most commercially available vaccines and diagnostic tests are based on BVDV1a and BVDV2a strains. In 2007, a BVDV variant was identified that escaped detection by available IHC and Ag Capture ELISA tests. Clearly, a need exists for BVDV tests that can differentiate between all BVDV species and subgenotypes. This will be important to determine which BVDV strains exist within the US and how they might be changing. Only then will we have a better handle on how such variation contributes to diagnostic and vaccine failures.

BVDV infections in wildlife and non-bovine domestic species

BVDV replicates in a variety of wild ruminant species including many cervids such as white tail deer, mule deer, elk, fallow deer, red deer, roe deer, eland, and mouse deer. In white-tail deer, clinical signs are similar to that seen in cattle and persistent infections result from natural infections. Experimental infection of pregnant does during the first third of gestation results in PI fawns. However, little is known regarding the prevalence or survival of PI cervids. Transmission between PI cervids and cattle has been reported but information is limited regarding transmission between TI cervids and cattle. The significance of this information lies in consideration of management strategies of cattle exposed to wild cervids and how this will be considered as a control point in US BVDV control programs.

Available BVDV tests

test	sample	detects	cost
serology	blood	exposure or vaccination	$4 ($6 out of state)
Virus isolation	blood	infection	$45
PCR	blood	infection	$55
Ag-ELISA	blood or ear notch	infection (PI)	$5
Ag-IHC	ear notch	infection (PI)	$13

Until the last several years, BVDV infection in New World camelids was believed to be of limited importance. Early studies demonstrated serologic evidence of exposure yet no clinical disease was reported. Recent studies have shown the existence of PI alpacas which both suffer clinical disease and can also transmit virus to other camelids. Questions remain whether or not a strain of BVDV has emerged in camelids or if it is the same as that most prevalent in cattle. Overall, knowledge is lacking regarding the prevalence of BVDV in camelid populations, the need for implementing control programs, whether current diagnostic tests possess the sensitivity and specificity to accurately diagnose BVDV in camelids, and the need for and efficacy of current vaccines for use in camelids.

Finally, research is needed to determine the potential for transmission of BVDV between cattle and other ruminants, both domestic and wild. Information gained will determine the need for control programs in non-bovine species.

Efficacy of current BVDV vaccines

Opinions vary in determining what exactly vaccine efficacy for BVDV is. Currently, two separate label claims are used for licensing BVDV vaccines. The first label claim indicates that a vaccine will aid in the prevention or reduction of clinical disease. Efficacy models typically involve experimental challenge followed by evaluation of "measureable effects" associated with reduced animal health.

Clinical signs may include pyrexia, diarrhea, or nasal discharge. Factors associated with immunosuppression may include leucopenia. Hemorrhage due to thrombocytopenia may be used as well. Unfortunately, in real-life situations BVDV infections are frequently associated with pneumonia or abortions. Because no models exist for reproducing such outcomes under experimental conditions, it is difficult to determine how effective vaccination may be in reducing these real-world occurrences.

The second label claim involves a vaccine's ability to aid in the prevention of fetal infections, including those which result in the development of PI calves. Licensing requirements for this claim are based on a single intranasal inoculation challenge with a BVDV field strain. However, it is likely that under most field conditions animals are exposed to virus over an extended period of time (via exposure to PIs). One can argue the need for studies which compare the existing 1-time exposure model versus continual PI exposure.

Lastly, little information is available regarding the nature of the immune response needed to protect against BVDV infection, specifically that required to prevent either acute disease or fetal infection. The most frequently studied immune response has involved an antibody (B-cell) response. However it is known that cellular (T-cell) immune responses are protective against BVDV. Obviously, research is needed to determine what protective levels of immunity are needed, what types of immunity are best, and how to manipulate the immune response with vaccines to provide long lasting, broad protection against the possible genotypes and subgenotypes of BVDV.

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