INFECTIOUS BOVINE RHINOTRACHEITIS AND BOVINE VIRAL DIARRHOEA: REPERCUSSIONS FOR ANIMAL HEALTH AND INTERNATIONAL TRADE

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Summary: Infectious bovine rhinotracheitis (IBR)/infectious pustular vulvovaginitis (IPV) is caused by an alphaherpesvirus, bovine herpesvirus 1 (BHV1), also known as IBR virus. Bovine viral diarrhoea (BVD) is caused by a pestivirus, bovine viral diarrhoea virus (BVDV), which is now known to be composed of two genotypes, BVDV1 and BVDV2. Both BHV1 and BVDV produce respiratory and reproductive disorders in cattle. BVDV also produces gastrointestinal disorders, and the genotype BVDV2 can produce haemorrhagic disease and acute fatal disease ('acute BVD') in cattle. Both BHV1 and BVDV produce persistent infections, and the viruses remain present in carrier animals. As latency is a normal sequel to BHV1 infection, the virus is shed only intermittently, whereas BVDV is shed continuously by persistently infected animals. The outcome of persistent infection in cattle with BHV1 and BVDV also differs. Control of both disease agents may involve prevention of infection/disease by vaccination, or eradication of the virus from individual or national herds. Marker vaccines for BHV1 are seen as important tools for eventual eradication in a country with high seroprevalence of the disease; their use allows distinction between infected animals and vaccinates. Several European countries have eradicated BHV1 and several others have recently embarked on control programmes aimed at eradicating BVDV from their national herds. Diagnostic tests should be appropriately sensitive and specific to meet each country's objectives in the control of these diseases. For BVDV, diagnostic methods should be reassessed to ensure that the methods used are capable of detecting infections with BVDV2. Vaccination practices should ensure adequate protection for the herd against both acute disease and reproductive losses caused by BVDV2. Given the increasing importance of BVDV infection and the interest shown by several countries in its eradication, the establishment of OIE reference laboratories for BVDV should be considered.

1. INTRODUCTION

Bovine herpesvirus 1 (BHV1) and bovine viral diarrhoea virus (BVDV) are two of the most important viruses of cattle, causing significant disease. Both viruses induce a state of persistence in carrier animals which is life-long, although the state of persistence is quite different between BHV1 and BVDV infections. Diagnostic laboratories world-wide test for evidence of these infections. Health certification of cattle for trade normally includes requirements by the importing country that testing for infections with both BHV1 and BVDV has been carried out.

Diagnostic methods for BHV1 and BVDV involving the polymerase chain reaction (PCR) and monoclonal antibodies are becoming more common. PCR appears to be especially valuable for detection of BHV1 in bovine semen, whereas multiplex PCR and type-specific monoclonal antibodies are useful for genotyping BVDV.

Control of BHV1 and BVDV infections involves vaccination or eradication. Control/eradication schemes may involve special vaccines called marker vaccines to identify vaccinates from wild-type virus infections. For BHV1 eradication programmes and for proper BVDV control, biosecurity is critical. For BVDV, identification of persistently infected (PI) animals and their removal from the herd is important whether the control programme involves vaccination or its aim is eradication. Biosecurity involves keeping acutely infected or PI animals away from the herd. The challenge for countries seeking to eradicate BVDV will be to keep virulent BVDV from entering naïve, unvaccinated herds where these viruses can cause severe losses through acute disease.

The Veterinary Services of Argentina, Boliva, Brazil, Canada, Chile, Columbia, Costa Rica, Cuba, Mexico, and
Paraguay provided comments in response to a questionnaire on aspects of the diagnosis and control of BHV1 and BVDV. Their comments are discussed below in the section entitled: 'Responses to a Questionnaire on Aspects of Diagnosis and Control of BHV1 and BVDV'.
2. VIRUS CLASSIFICATION

BHV1 is a member of the Alphaherpesvirinae (55). It is a large (150-200 nm), enveloped virus. The BHV1 genome consists of double-stranded DNA that is approximately 140 kilobase (kb) pairs in length (64). The genome is thought to encode about 70 proteins. Three major glycoproteins, gB, gC, and gD induce neutralising antibody responses (64).

Initial characterisation of BHV1 isolates found them to be indistinguishable serologically. However, restriction enzyme analysis allowed BHV1 isolates to be classified into three subtypes, BHV1.1, BHV1.2 (comprising BHV1.2a and BHV1.2b), and BHV1.3 (comprising BHV1.3a and BHV1.3b) (76). These three subtypes were designated 'infectious bovine rhinotracheitis (IBR)-like' isolates, 'infectious pustular vulvovaginitis (IPV)-like' isolates, and encephalitic isolates, respectively. However, a strict correlation between clinical origin of the isolate (i.e. respiratory or genital) and the subtypes BHV1.1 and BHV1.2 is not found. Bovine encephalitis herpesvirus, formerly subtype BHV1.3, is now known to be a different herpesvirus from BHV1. It has been reclassified as bovine herpesvirus-5 (55).

BVDV is a member of the pestiviruses, a group of antigenically related, small (40-60 nm), enveloped RNA viruses belonging to the family Flaviviridae (41, 75). The genome is approximately 12 kb in length and encodes four structural proteins: the nucleocapsid protein C and three glycoproteins, Ems (gp48) E1 (gp25), and E2 (gp53) (29). The E2 glycoprotein is the major neutralising protein (28). Of the nonstructural proteins, only the NS3/NS2-3 (p80/p125) protein is highly immunogenic.

The pestiviruses include border disease virus (BDV) of sheep and hog cholera virus of swine, also known as classical swine fever virus (CSFV). With the recent subdivision of BVDV into two genotypes, BVDV 1 and BVDV2, four pestivirus genotypes are recognised (CSFV, BDV, BVDV1 and BVDV2) (8, 46, 52, 74). Two pestiviruses obtained from wild ruminants (a deer and a giraffe) were recently proposed to be additional genotypes (9, 74). Whereas in cattle only BVDV1 and BVDV2 appear to be readily infectious (BDV has not been isolated from North American or European cattle in several reports [45, 54, 62]), sheep can be infected with BDV, BVDV1, and BVDV2, while swine can be infected with all four recognised pestivirus genotypes.

3. DISEASE AND PERSISTENT INFECTIONS

BHV1 causes respiratory and reproductive disease, and multisystemic disease in young calves (39). Respiratory tract infections produce fever, a serous to mucopurulent nasal discharge, necrotic lesions in the nose, conjunctivitis, inappetance, and a reduction in milk yield. Fetal abortions may also occur after respiratory infections (59). BHV1 may be an initiator virus of the bovine respiratory disease complex known as Shipping Fever (64, 77). In this disease complex, a severe pneumonia occurs when the viral infection is accompanied by a secondary bacterial infection. BHV1 also causes infectious pustular vulvovaginitis and balanoposthitis. Bulls may shed the virus in their semen during both clinical and subclinical infections (3, 69, 70).

After acute infection with BHV1 and seroconversion, the virus localises and persists in the trigeminal or sacral ganglia (1, 2, 44). The infection maintains a latent or 'silent' state when no virus is produced. Virus shedding reoccurs during periodic reactivation of viral replication (60). Viral reactivation is generally thought to be stress-induced, but can also be induced by the injection of corticosteroids (43).

Although latency is not fully understood, past research has shown that in the latent state a viral latency-related RNA is produced in neurons, and this RNA is thought to somehow regulate latency. Recent developments in the study of latency include the discovery and identification (for BHV1) of a 41 kilodalton (kd) protein as a gene product of the latency-related RNA (31). The protein appears to bind to a cellular protein in neurons called cyclin A, a protein involved in cell-cycle progression (57). Inappropriate expression of cyclin A causes cell death and therefore it has been hypothesised that the 41 kd protein may inhibit cell-cycle progression and enhance survival of the infected neurons.

BVDV causes gastrointestinal, respiratory, and reproductive disease including infertility, abortion, and congenital defects (6, 49). Subclinical infections are also common. Acutely and PI bulls shed virus in their semen (33, 50). In addition to the above, viruses of the BVDV2 genotype can cause thrombocytopenia, haemorrhagic disease, and acute fatal disease or 'acute BVD'. Recently, in Great Britain, virulent BVDV1 has also been implicated in causing severe disease in cattle (18).

BVDV of either genotype may exist as one of two biotypes, noncytopathic and cytopathic, as determined by their
behaviour in cell cultures (30, 36, 52). Noncytopathic BVDV does not produce apparent cytopathic effect, whereas cytopathic virus kills the infected cells. Both biotypes can be pathogenic in the animal (25).

Noncytopathic BVDV is the most prevalent of the two biotypes, accounting for over 90% of BVDV isolates. When a fetus is infected with noncytopathic BVDV in the first trimester of gestation, a persistent infection can be established that is life-long. The PI animal may be born stunted or may appear to be normal. It may reach breeding age and produce PI offspring (49).

The PI animal is immunotolerant to the virus with which it is persistently infected and does not produce antibodies to it (38). The animal constantly sheds the virus and maintains it in the environment. PI animals invariably die from mucosal disease, a disease characterised by gastrointestinal erosions and severe diarrhoea. This occurs when the PI animal is superinfected with a cytopathic BVDV that is antigenically similar to the persisting virus (12, 17, 19). Superinfection can occur by mutation of the noncytopathic to the cytopathic form or from external infection. Thus, both viral biotypes can be isolated from PI animals that have succumbed to mucosal disease. Modified live vaccines containing a cytopathic biotype of BVDV may, on occasion, precipitate the disease in PI animals (15, 53).

In the past several years, much work has been done on the molecular characterisation of the noncytopathic and cytopathic 'virus pairs' obtained from cases of mucosal disease (25, 40). Cytopathic BVDV is distinguished from noncytopathic BVDV in that cytopathic BVDV produces in cells one extra protein named NS3 (p80), which is involved in cytopathic effect. The NS3 protein is related to and can be derived from the NS2-3 (p125) protein. In cells infected with noncytopathic BVDV, only the uncleaved NS2-3 protein is observed.

Genetic sequencing of viral pairs obtained from cases of mucosal disease has shown that, in comparison with the noncytopathic virus of the viral pair, gene arrangements or recombination events are often observed in the cytopathic virus (25, 40). These changes allow expression of NS3 by the cytopathic virus. This has led to the conclusion that mutational events in the persisting noncytopathic virus allow expression of NS3 and produce the cytopathic biotype.

In most cases of mucosal disease, the cytopathic virus probably arises from mutational events that occur spontaneously during replication of the noncytopathic virus in the animal. Vaccination can sometimes provide the cytopathic BVDV and precipitate mucosal disease. However, it appears that antigenic similarity with the noncytopathic virus is required to precipitate mucosal disease; otherwise, neutralising antibodies are produced to the superinfecting cytopathic virus. Vaccination can also lead to mutational events in the persisting virus, precipitating mucosal disease. In a recent report, an animal that was persistently infected with noncytopathic BVDV2 was vaccinated with a modified-live vaccine containing the NADL1 strain, a cytopathic BVDV1 strain (53). The animal died of mucosal disease. When the viral pairs were sequenced, it was discovered that a recombination event between the noncytopathic virus and the vaccine virus produced a cytopathic BVDV2 with a small insertion of sequences from the vaccine strain, NADL.

In recent years, BVDV2 has emerged to cause severe disease in cattle. Thrombocytopenia with haemorrhage associated with BVDV infection was first reported in 1987 within a summary of case reports of illness in dairy herds in the northeastern United States of America (47). It was not until 1994, however, that the causative agent was recognised as a separate genotype from classical (type 1) BVDV.

Virulent BVDV2 can cause severe thrombocytopenia with or without haemorrhages. Bleeding at injection sites and, occasionally, bleeding into the eyes producing 'blind' animals can result (7). Experimental infection of calves with BVDV2 has produced severe thrombocytopenia (fewer than 5000 platelets/µl in some animals), haemorrhages, and death, although most of the animals recovered (14, 20).

In the BVDV2 outbreaks in Ontario, Canada, during the peak years of 1993 and 1994, haemorrhagic syndrome was not prominent. Instead, an acute disease was observed, which resembled mucosal disease with gastrointestinal syndrome and diarrhoea (65). The initial sign in herds was often one of respiratory disease. Abortions were commonly seen and occurred at all stages of gestation. In 10 examined herds with acute BVD infection, the mean crude mortality rates were 10% and 54% for adult animals and immature animals (<2 years of age), respectively. The outbreaks progressed slowly through herds with a mean duration of 13 weeks. In 1993, Quebec lost an estimated 25% of itsveal calves to infections attributed to BVDV2 (46).

Acute BVD attributed to BVDV2 may be difficult to distinguish clinically from mucosal disease. However, the two can be distinguished by laboratory isolation of both cytopathic and noncytopathic virus from individual animals with

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mucosal disease, whereas only noncytopathic virus is isolated from acute BVD caused by BVDV2. Usually only a few cases of mucosal disease are observed in herds because the disease occurs only in PI animals. However, if many PI animals exist in a herd, larger outbreaks of mucosal disease can occur.

4. DIAGNOSIS

Virus (serum) neutralisation (VN) tests and indirect or blocking (competitive) enzyme-linked immunosorbent assays (ELISAs) are commonly employed for the detection of BHV1 antibodies in bovine serum. VN tests with 1-hour or 24-hour incubations of test serum with 100 TCID50 (50% tissue culture infective dose) of BHV1 (before the addition of susceptible cells) are often used. The latter test has a higher sensitivity than the former (10, 24). All seropositive cattle except for calves that have ingested colostrum containing BHV1 antibodies are considered to be carriers of BHV1. A rise in antibody titre indicates an acute infection or reactivation of virus from a latent infection.

In a recent European trial involving 17 laboratories in 15 countries, serological tests for detection of antibodies to BHV1 were evaluated against 12 duplicate samples including three European Union (EU) reference standards (negative, weak-positive, and positive) and four post-infection (day 7, 9, 11, and 13) samples (35). The EU weak-positive reference standard has been agreed upon to as the detection limit for artificial insemination (AI) purposes by the European AI Veterinarians Group (48). One-hour, 2-hour, and 24-hour VN tests and commercial and home-made ELISAs (indirect and blocking) were used in testing. Home-made blocking ELISAs and 24-hour VN tests were found to be the most reliable. These could, in general, score the three EU standards correctly and detected antibodies at 11 days post-infection. Commercial ELISAs were, in general, less reliable and often did not score the EU reference weak-positive sample correctly. Although all (three) 1-hour VN tests detected antibodies at nine days post-infection in this study, 1-hour and 2-hour VN tests were also not reliable in scoring the EU reference weak-positive correctly. The standardisation of serological tests to detect low antibody titres in BHV1-infected cattle and the use of EU standard reference sera in standardisation were proposed (35). In another study, an indirect ELISA was found to be more sensitive than a blocking ELISA for the detection of BHV1 antibodies early after infection, whereas for detection of declining and residual maternal antibodies, the blocking ELISA was the most sensitive test (H.J. Cho, personal communication).

Detection of BHV1 is often accomplished by virus isolation in cell culture. A viral cytopathic effect generally occurs within three days. Identity of the virus is then confirmed by a VN test using BHV1 antiserum or a neutralising BHV1 monoclonal antibody or, alternatively, by direct demonstration of BHV1 antigen by immunofluorescent or immunoperoxidase antibody staining techniques. Recent methods for detection of the virus include PCR. This method appears to be very suitable for detection of the virus in semen (37, 67, 68). BHV1 was detected in the semen of infected bulls earlier, more often, and for a longer duration by PCR than by virus isolation.

For BVDV, PI animals are often BVDV antibody negative because of specific immunotolerance. For detection of BVDV antibodies in cattle, the VN test is often used. 'Acute' and 'convalescent' samples can be tested and a rising titre indicates an acute infection. VN tests for BVDV antibodies can be completed in as little as three days with a highly cytopathic test virus such as the Singer strain (23). ELISAs can also be used for detection of antibodies to BVDV. In Scandinavian countries, the ELISA is used for determination of herd status for BVDV control and is used in monitoring the level of BVDV antibodies in bulk-milk (11).

Noncytopathic BVDV is a common contaminant of cell lines propagated in the presence of fetal bovine serum (FBS) (13). This is because FBS is often pooled sera obtained from slaughter houses and may be contaminated with the serum from PI fetuses. Thus testing serum and periodic screening of cells for BVDV contamination are essential quality control practices for BVDV diagnostics. Some cell culture systems use horse serum rather than fetal bovine serum to mitigate against BVDV contamination (23).

A major thrust in testing for trade is ensuring that cattle shipped are not PI animals. Detection of virus in test material, such as serum/blood and blood leukocytes, can be accomplished by several means including ‘micro-isolation’ in 96-well cell culture plates using immunoperoxidase staining methods (immunoperoxidase monolayer assay [IPMA]), immunofluorescent antibody (IFA) staining, antigen capture ELISA, and PCR (22, 26, 51, 56).

When screening herds for identification and removal of PI animals, if cattle are positive for BVDV it is necessary to differentiate between an acute infection and a persistent one. Two positive tests for BVDV on serum or blood samples obtained at least three weeks apart is indicative of a persistent infection. Colostral antibodies may interfere with detection of BVDV by ELISA and virus isolation methods (16, 58). Although colostral antibodies appear to decline
rapidly in PI animals and may often not be detectable at 8 weeks of age (42), it is recommended that young animals be retested at a minimum age of three months (16, 56, 58).

Methods used should be optimised to detect both BVDV1 and BVDV2. This may involve using broadly cross-reactive antiserum or monoclonal antibodies or using pooled reagents produced to both BVDV1 and BVDV 2, in the case of IPMA, IFA, and capture ELISAs, and primers to regions conserved in BVDV1 and BVDV 2 in the case of PCR.

For genotyping BVDV, type-specific monoclonal antibodies can be used in IPMA or IFA (27, D. Deregt & P.A. van Rijn, unpublished observations). Alternatively, genotyping can be accomplished by multiplex PCR. Multiplex PCR assays have been developed that use type-specific primers based on Emers or NS5b (polymerase) gene sequences (62, S.A. Gilbert & D. Deregt, unpublished observations). The multiplex PCR produces bands of different size for each genotype. Typing of BVDV isolates may be useful for herd health management and for determining the efficacy of BVDV vaccines used by the producer to control BVDV1 and BVDV 2 infections.

5. CONTROL AND ERADICATION

Vaccination is commonly used for control of BHV1 and BVDV. For BVDV, removal of PI animals from herds and avoidance of the reintroduction of PI animals into the herd (biosecurity) are also recognised as important control measures. A number of European countries have initiated programmes for the eradication of BHV1, and more recently for the eventual eradication of BVDV (11). Denmark and Switzerland were the first countries to have been recognised as having eradicated BHV1 from their national herds (71).

Conventional vaccines for BHV1 and BVDV are modified-live (attenuated) virus vaccines and killed virus vaccines. These can be formulated as single agent vaccines or combination vaccines against both BHV1 and BVDV as well as other disease agents. Modified-live vaccines are intended to replicate to a certain extent in the host, which increases the likelihood of protective immunity. Killed virus vaccines generally require a booster to ensure protective responses. The latter vaccines are often recommended for pregnant animals.

Recent developments in the area of control/eradication include the development of BHV1 marker vaccines and their proposed use in control/eradication programmes and the announcement of national control/eradication programmes for BVDV.

For BHV1, vaccination with conventional modified and killed vaccines may be protective against disease, but these do not allow the distinction to be made between animals that have been vaccinated and those that have been infected by wild-type virus. A new generation of vaccines are now being designed to enable this distinction to be made, so named 'marker vaccines'.

Marker vaccines do not present all of the antigens that are presented by wild-type BHV1 and thus the serological responses of vaccinates can be distinguished from animals that have been BHV1-infected (72). Examples are protein subunit vaccines based on a single glycoprotein (such as gD) or vaccines in which the virus has been engineered to carry a deletion of a nonessential gene (such as gE) (61, 64). DNA immunisation with noninfectious plasmid containing a single BHV1 gene is another example (5, 21, 64).

For marker vaccines to be useful in distinguishing vaccinated animals from those animals that are infected, a companion diagnostic test is required. Animals vaccinated with a gD subunit vaccine could be distinguished from those naturally infected by testing with an ELISA developed to measure responses to gB (34). Animals showing gB positive serology are considered to be infected with BHV1, whereas vaccinates will test gB negative. In turn, for gE deletion vaccines, an assay is necessary for testing responses to gE. Animals showing positive responses to gE are considered to be infected with wild-type BHV1. Recently, an ELISA for detection of antibodies to gE was developed and considered to be suitable for differentiating between infected cattle and those vaccinated with a gE deletion vaccine (73).

Marker vaccines are proposed for use in eradication programmes for which the first step is intensive vaccination against BHV1 (72). The use of marker vaccines is proposed for countries that have an interest in eradication of the BHV1 but have a high seroprevalence to the virus. The intention is to reduce the transmission of BHV1 and to allow identification of those animals that are infected. At the point where the seroprevalence to wild-type BHV1 becomes low, a test and reactor removal programme can begin. The final step is cessation of vaccination.
For control of BVDV by vaccination, two other elements are important: removal of PI animals and biosecurity. Removal of PI animals is important because these animals continuously shed large amounts of virus into the environment and constantly challenge the immunity of the herd. PI cattle can be identified by herd screening with various diagnostic tests as described above. The removal of PI cattle from the herd should be accompanied by establishing appropriate biosecurity measures. Biosecurity involves testing replacement cattle for BVDV infection to avoid bringing PI cattle into the herd. It also involves avoiding infection of pregnant cattle. Care must also be exercised to avoid acquiring infections at trade shows and during pasturing of cattle from adjacent herds.

Previous vaccination strategies were primarily aimed at vaccinating breeding animals to prevent infection of the fetus. With the emergence of virulent BVDV, it may be considered prudent to vaccinate all cattle in the herd. Reports of vaccine failures and reproductive disease in vaccinated cattle suggest that vaccines should incorporate antigens from both type 1 and type 2 BVDV (52, 66).

Control of BVDV on a national level has been implemented in Sweden, Norway, Finland, and Denmark (11). These control programmes are conducted without vaccination. The programmes in Sweden and Denmark were recently described (4, 32). In Sweden, the national programme to control the spread of BVDV began in 1993 and is a voluntary programme financed entirely by producers (4). In Denmark, a BVDV eradication programme was initiated by the dairy industry in 1994, and this was followed by a government order to support the programme in 1996 (32). Both the Swedish and Danish programmes involve classification of herds as to their BVDV status, removal of PI animals from infected herds, monitoring herd status and prevention of infection in BVDV-free herds. Bulk milk testing for antibodies against BVDV constitutes an important component of each programme and is used to classify and monitor herds as to their BVD status. In Denmark, bulk milk testing is accomplished using a blocking ELISA and in Sweden using an indirect ELISA (4, 32).

6. TESTS AND TRADE

As discussed above, there are two trends in the control of BHV1 and BVDV: control by vaccination and control by eradication. For BHV1, vaccination with marker vaccines has also been proposed as a tool for eventual eradication. Countries that have opted for either strategy to control BHV1 and BVDV may have differing views on testing requirements for trade purposes. In regards to testing, the OIE Manual of Standards for Diagnostic Tests and Vaccines (3rd edition) describes prescribed tests for both BHV1 and BVDV for trade purposes. In addition, for World Trade Organization signatory countries, the Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement) set rules for formulating and adopting health measures that affect trade (63). Under this agreement, countries have the right to establish health measures to protect animal health. However, they should ensure that these measures do not unjustifiably discriminate between members where conditions are similar. Importing countries that follow the OIE standards, guidelines or recommendations will be presumed to have met their obligations under the SPS agreement. However, more stringent requirements may be applied by the importing country if these requirements are scientifically justifiable and required to maintain the country’s appropriate level of sanitary protection (63).

7. RESPONSES TO A QUESTIONNAIRE ON ASPECTS OF DIAGNOSIS AND CONTROL OF IBR/IPV AND BVD

Most of the countries in the Americas responding to the questionnaire considered IBR/IPV and BVD to be of medium to high importance to the cattle industry in their country. Seven of ten countries stated that they vaccinated to control both IBR/IPV and BVD, whereas three stated that they did not vaccinate for either disease. Four countries said they had restrictions on the type of vaccines that can be used; specifically live vaccines could not be used for IBR/IPV and BVD. None of the countries used marker vaccines and none had eradication programmes in place. Two countries said that they plan to initiate eradication programmes for IBR/IPV and BVD in the near future (in the next one to three years). Four of the ten countries game-ranched deer (one also game-ranched elk) for domestic consumption or for trade. The majority of countries thought that it was somewhat important or important that more research be carried out on IBR/IPV and BVD in deer and/or elk. Seven of ten countries had a preference for which test (the VN test or ELISA) was used for detection of BHV1 antibodies for importation; four preferred the VN test and three preferred the ELISA. A majority, nine out of ten countries, stated that they thought that BVD should be in the International Animal Health Code and that there should be OIE reference laboratories for BVD.
REFERENCES


