A well designed disease control programme will increase both the health and profitability of the herd by controlling the effects of BVDV

Bovine virus diarrhoea virus – strategic decisions for diagnosis and control

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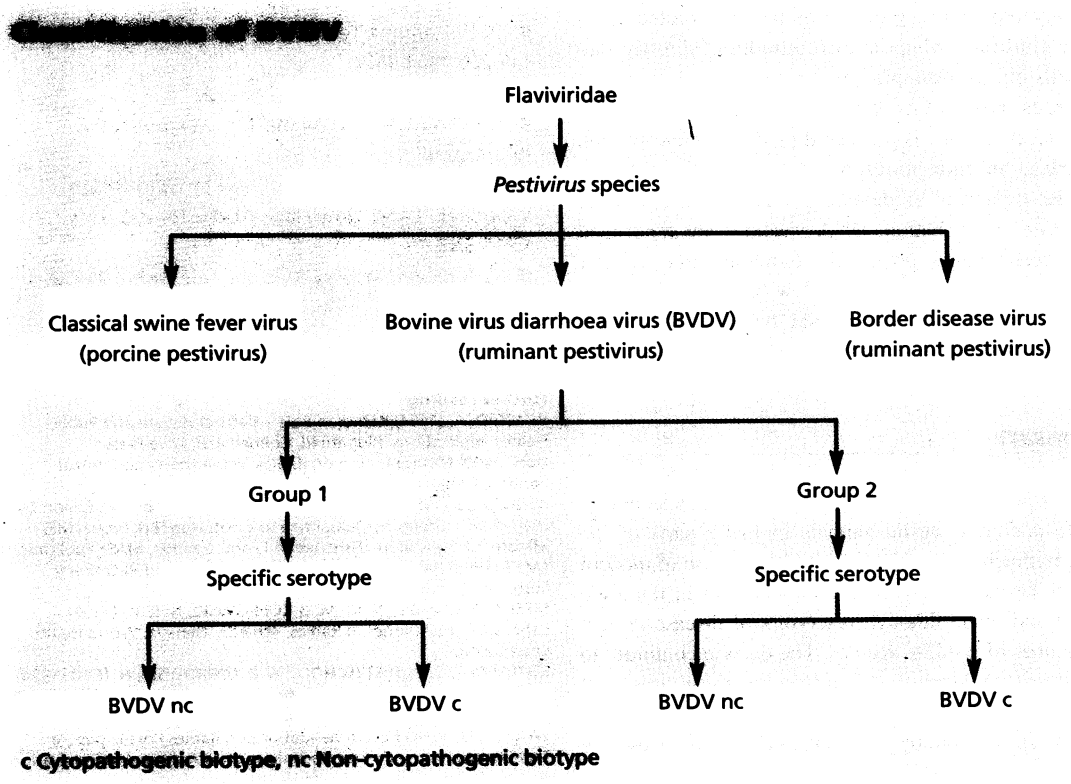
IN the 15 years since the last *In Practice* article on bovine virus diarrhoea virus (BVDV) (Brownlie 1985), there has been an explosion in the understanding of the molecular mechanisms of viral replication and mutation, especially those related to biotypic variation. Hand in hand has come a greater understanding of the importance of BVDV as a primary pathogen of cattle, particularly as a cause of reproductive loss. A BVDV vaccine is now available in the UK, giving better prospects for protection against infection. However, for the veterinary clinician, the strategic decisions regarding diagnosis, control and vaccination continue to pose difficult dilemmas and it is on these issues that this article focuses.

WHAT IS BVDV?

CLASSIFICATION

Bovine virus diarrhoea virus (BVDV) is a member of the *Pestivirus* genus within the family Flaviviridae (see box below). In the same genus are classical swine fever virus and border disease virus. Recently, the International Committee on Taxonomy of Viruses has proposed that a fourth distinct species containing the BVDV group 2 isolates (BVDV-2) be recognised. There



c Cytopathogenic biotype, nc Non-cytopathogenic biotype

are differences in the geographical distribution of the different BVDV species. BVDV-1 viruses, of which there are at least five serologically distinct subspecies (1a to 1e), have a worldwide distribution; the majority of BVDV isolates found in the UK belong to the 1a subgroup. BVDV-2 viruses are, as yet, largely restricted to the USA and Canada.

Striking differences exist between the disease syndromes following infection with BVDV. Severe outbreaks have been associated with the BVDV-2 species but, more recently, the importance of BVDV-1 isolates in severe outbreaks has also been recognised.

GENOMIC ORGANISATION

BVDV is a small enveloped virus with a genome consisting of a single positive RNA strand of around 12·5 kb. The genome encodes a variety of structural and non-structural proteins (see box, right).

Structural proteins

The structural proteins ultimately assemble to form the virion, in which the major envelope glycoprotein (E2) is anchored in a host-derived lipid bilayer surrounding a capsid containing the newly synthesised viral RNA. E2 is the major target for neutralising antibodies, which confer protection following infection or vaccination. The highly variable nature of epitope-rich regions within the E2 sequence dictate that the E2 protein is the most important source of antigenic variability between different BVDV strains. A second glycoprotein, E0, differs from E2 in that it has no membrane anchor and is most likely to form a non-covalent association with E2 at the virion surface. E0 can be found free in the serum of persistently infected (PI) animals, giving this protein potential as a diagnostic antigen. Antibodies to E0 may also be neutralising.

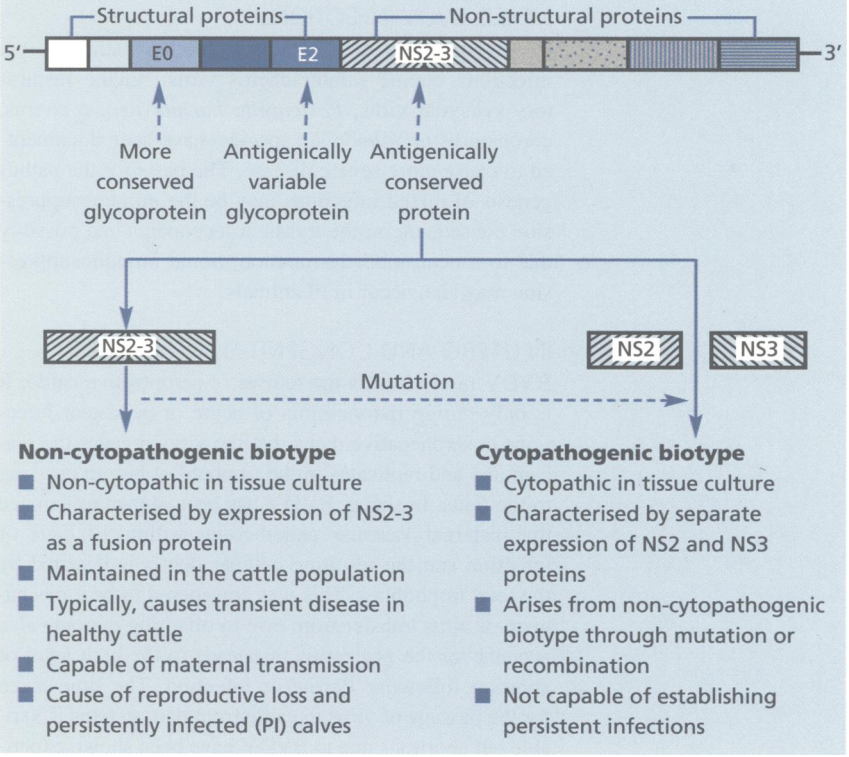
Non-structural proteins

Of the non-structural proteins, the most studied is the NS3 protein, associated with the lytic activity of cytopathic viruses. This protein is both highly conserved and immunogenic, and forms the basis of several commercially available antibody and virus detection assays. Antibodies against NS3/NS2-3 are non-neutralising, but may play an important role in cell-mediated immunity. Non-structural proteins may also be important for major histocompatibility complex restricted cytotoxic T cell killing.

THE BIOTYPES

BVDV may exist as two distinct biotypes: non-cytopathogenic (BVDV nc) and cytopathogenic (BVDV c). The 'nc' biotype causes no cytopathology in cell culture, whereas the 'c' biotype does. It is the non-cytopathogenic biotype that persists in the cattle population (mainly within PI calves) and thereafter gives rise to the cytopathogenic biotype. This occurs through a variety of mutation events, the inevitable consequence of which is the cleavage of the NS2-3 protein and the subsequent separate expression of NS3. These mutations may occur spontaneously through insertion of host protein sequences, duplication of viral genes, or even as point mutations within key areas of the viral genome. The cytopathogenic biotype can also arise through recombination with other BVDV strains (eg, attenuated live vaccine strains).

BVDV: genomic organisation and origin of biotypes



WHAT DISEASES ARE CAUSED BY BVDV?

ACUTE BVDV INFECTIONS

Acute BVDV infection in non-pregnant cattle is generally inapparent to the stockman. It occurs commonly, with an estimated 95 per cent of milking herds within the UK having seroconverted to BVDV. With the acute infection, there is inevitably a pyrexia, a leucopenia from about days 3 to 7 post-infection and a limited recovery of virus from both blood and nasal secretions during the first three to 10 days.

It is clear that BVDV can, under certain circumstances, cause severe clinical disease. The original description was of a transmissible disease characterised by a profuse diarrhoea in adult cattle (Olafson and others 1946); episodes of agalactia and diarrhoea are not uncommonly recorded and, more recently, severe and fatal adult disease has been described in the UK following acute infection (David and others 1993, Hibberd and others 1993).

The importance of acute infections in the transmission and maintenance of BVDV within a herd or population should not be underestimated (Houe 1995). They are responsible for 93 per cent of all in utero infections that result in the birth of PI calves (Grotelueschen and others 1998).

SEVERE HAEMORRHAGIC DISEASE

In the late 1980s, an acute and fatal syndrome of veal calves was reported in New York State. It was characterised by a profound thrombocytopenia and haemorrhagic disease. The cause was shown to be a new variant of BVDV and, on the basis of genomic sequence, it was possible to distinguish these isolates; they were subsequently classified as BVDV group 2 (see box, page 176). BVDV-2 viruses have spread across the USA and into

Canada, causing widespread and severe disease. As yet, there is limited evidence of spread beyond North America.

MIXED BVDV INFECTIONS

Mixed infections of BVDV and another pathogen (eg, infectious bovine rhinotracheitis virus, bovine respiratory syncytial virus, *Pasteurella haemolytica*, rotavirus, coronavirus or *Salmonella* species) have been documented to cause more severe disease. The basis for the pathogenesis of mixed infections may be the immunosuppression consequent on the transient leucopenia and possibly due to a neutrophil dysfunction. Some immunosuppression may also occur in PI animals.

IN UTERO AND CONGENITAL INFECTIONS

BVDV rarely infects the fetuses of seropositive cattle. It is only during the viraemia of acute or persistent infections in seronegative dams that the virus invades the placentome and replicates in the trophoblast before crossing to the fetus. In sheep, BVDV has been shown to damage the maternal vascular endothelium within 10 days of infection and the resulting cellular debris is ingested by the fetal trophoblast. This was considered to be a mechanism of virus transfer from ewe to offspring but may also account for the placentitis that leads to the high level of abortion following *Pestivirus* infection. The time taken for the passage of virus in cattle from dam to fetus is variable but abortions due to BVDV have been shown experimentally to occur within 10 to 18 days of intramuscular infection. In the authors' own experience, abortions can take place several months after fetal infection.

Early embryonic death, infertility and 'repeat breeder' cows are frequent sequelae to *Pestivirus* infection during pregnancy. In a study of a herd infected with BVDV, conception rates were found to be reduced from 78·6 per cent in the immune cows to 22·2 per cent in infected cattle (Virakul and others 1988). In a further study, BVDV infection at the time of conception reduced pregnancy rates at 77 days from 79 per cent in the control animals to 33 per cent in the virus-challenged group (McGowan and others 1993).

Most, if not all, fetuses born to PI dams likewise become persistently infected. This near 100 per cent vertical transmission from dam to fetus is an important concept for veterinary practitioners to keep in mind when investigating disease outbreaks. Thus, the question to be asked of all PI animals is the viral status of their dams. However, the proportion of PI calves that are born to PI dams is reportedly only 7 per cent (Groteluesch and others 1998), inferring that the remaining 93 per cent arise as a result of acute infection of the seronegative dam in early pregnancy.

The outcome of fetal infection is dependent on two main variables: the age of the fetus at the time of infection and the biotype of the infecting virus.

- Infection during the FIRST TRIMESTER (0 to 110 days) of fetal life can result in abortions, congenital damage or the birth of PI calves;
- During the SECOND TRIMESTER (111 to 180/200 days), there can be congenital damage and fetal loss;
- During the THIRD TRIMESTER, the fetus is immunocompetent and able to mount an active immune response.

The biotype responsible for in utero infections is noncytopathogenic. Experimental infections during the first trimester have shown that up to 30 per cent of fetuses are aborted even though the majority of the surviving fetuses go to full term and are born persistently infected. In contrast, no animal has yet been demonstrated persistently infected with the cytopathogenic biotype. Experimental in utero infection with the cytopathogenic biotype does not result in abortions or PI calves, hence it is doubtful whether this biotype can even establish in the early fetus.

BVDV causes significant intrauterine growth retardation in many of the fetal tissues, particularly the central nervous system (CNS), skeletal system and thymus. Hypomyelination in the CNS, associated with cerebellar hypoplasia, has also been observed. A further consistent finding is viral localisation in the vascular endothelium and, in association with the resulting vasculitis, there can be inflammation, oedema, hypoxia and cellular degeneration. Ocular lesions, primarily cataracts, have been observed in both field and experimental BVDV infections.

Abortions and stillborn calves are frequent sequelae to BVDV infection during pregnancy

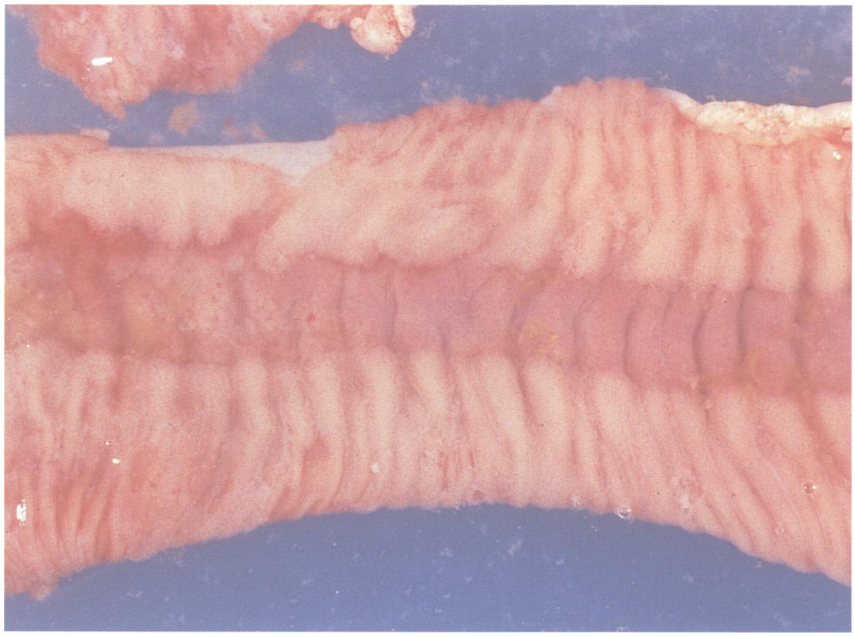
Weak calf with respiratory disease and ocular lesions (mainly cataracts) following in utero BVDV infection

MUCOSAL DISEASE

Mucosal disease was first reported in 1953 and described as a fatal condition of cattle, characterised by severe erosive lesions in the oral and intestinal mucosa (Ramsey and Chivers 1953). Over the next 30 years, a series of observations was made about the association between BVDV and mucosal disease. These observations were finally refined into a hypothesis (see box, below right) and proven experimentally. The hypothesis states that an initial transplacental infection of the early fetus with the non-cytopathogenic virus results in the birth of a calf which has a lifelong persistent viraemia. These calves (and *only* these calves) may later develop mucosal disease as a result of superinfection with a 'homologous' cytopathogenic BVDV. In the field, mucosal disease usually affects animals of six to 18 months of age, although it has been reported in calves of only a few weeks old and in adult cattle aged five to 10 years.

As there are a number of bovine vesicular-like diseases, the following definition of mucosal disease is suggested:

Mucosal disease is a fatal condition, mainly of young cattle aged six to 18 months, with characteristic erosive pathology in the oral/intestinal mucosa from which the cytopathogenic biotype of BVDV can be isolated. The clinical disease is typically rapid in onset, although chronic debilitating forms can occur.



Intestinal lesions in a case of mucosal disease

Antibody detection

Demonstration of BVDV antibody provides an insight into the level of exposure to BVDV within the herd. Diagnosis at a group or herd level is an important part of the assessment stage of a disease control programme. Blood can be taken from representatives of a group of animals and tested for the presence of

HOW IS BVDV INFECTION DIAGNOSED?

BVDV and BVDV antibodies can readily be detected in both blood and milk samples. These tests are reliable and can be carried out on individual animals or groups of animals (see box on page 185).

WHAT TESTS CAN BE DONE AND WHEN?

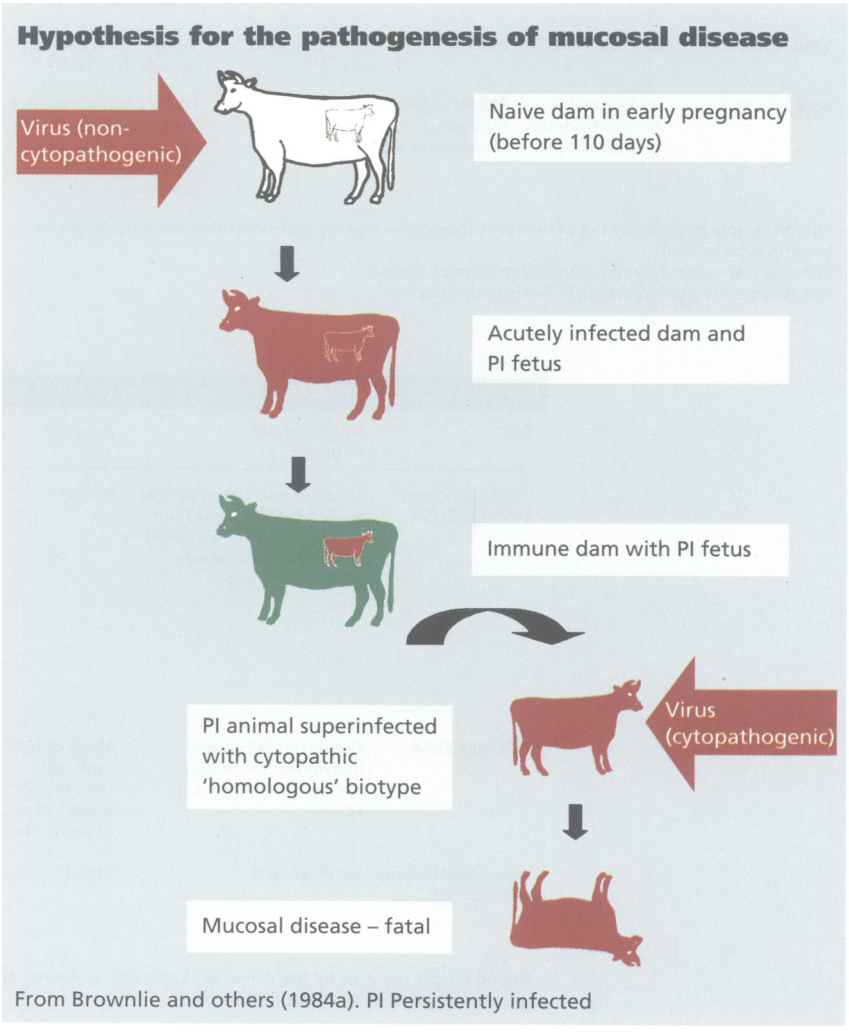
The diagnosis of BVDV infection hinges on the identification of virus (using virus isolation, antigen ELISA, polymerase chain reaction [PCR] or immunoperoxidase staining techniques) or evidence of exposure to virus (by antibody ELISA).

Antibody tests, in providing an indication of exposure, are useful in assessing the status of a group of animals or a whole herd prior to, or as a part of, a disease control programme. Tests for BVDV identify those animals that are persistently infected. It is these tests that should be used on a whole herd basis for virus eradication programmes.

Virus detection

The critical reservoir of BVDV is the PI animal. The only certain way of identifying a PI animal is by the demonstration of persisting virus. As the viraemia following acute infection usually lasts no longer than 10 to 14 days, any animal that has a positive viraemia on first sampling and also at a second sampling performed a minimum of three weeks later, can be considered persistently viraemic. These animals usually have a low level or total absence of specific BVDV antibodies in both samples.

Virus can be demonstrated by isolation of infectious virus or by viral antigen detection (see top table overleaf).



From Brownlie and others (1984a). PI Persistently infected

BVDV, germline cells and the bull

BVDV has a tropism for the germline cells of both sexes. The virus can infect ovarian tissues and has been demonstrated in oocytes within ovarian follicles (as illustrated on the right). Similarly, border disease virus antigen has been found in the germinal cells of the sheep's ovary. The longevity of viral infection in the ovary is unclear but viral antigen has been demonstrated in the ovaries of cattle at least 60 days after intramuscular inoculation. The risks that germline cell infection will lead to vertical transmission of virus are, as yet, unproven but the implications are obvious.

The bull can play an important, if sometimes overlooked, role in the transmission of BVDV. All PI bulls produce semen that is infected with BVDV and, therefore, it is inexcusable for any health check of the bull not to include a blood test to examine for persistent BVDV infection. Furthermore, acute infection of the seronegative bull is not without risk. BVDV infects testicular tissues and virus can be recovered from semen for a limited period (Paton and others 1989). The semen is often of poor quality and has the potential to spread infection to seronegative heifers.

Recently, a further potential consequence has been demonstrated following an acute infection in a young bull (Voges and others 1999). The bull appeared to become infected during adolescence (possibly at six to nine months of age), at which time the virus crossed the blood/testes barrier to the testis. Although the bull produced antibodies to the virus, they were unable to cross the testes barrier; thus, the virus was able to establish a persistent infection in the seminiferous tubules. In this case, virus was continually shed in the semen over a prolonged period of time (between seven and 22 months of age). Normal blood screening techniques would have indicated that this bull was immune and therefore not shedding BVDV in its semen. Although a further case has been described (C. J. M. Bruschke, 1999, personal communication), the incidence of viral persistence in the testes of seronegative bulls is presently unknown.

DIAGNOSTIC TESTS AVAILABLE FOR DETECTION OF BVDV OR BVDV ANTIGEN

Test	*Single animal or group*	*Requires*	*Measures*	*Interpretation*
Immunoperoxidase staining	Single animal	Blood* or tissue sample	Viral antigen	Test provides a positive or negative result
Antigen ELISA	Single animal	Blood*	Viral antigen	Test provides a positive or negative result
Virus isolation	Single animal	Blood*	Live virus	Test provides a positive or negative result
Bulk milk PCR	Pooled milk sample from up to 100 animals	300 ml of fresh bulk milk (no preservative added)†	Viral RNA	Positive result indicates presence of a least one PI animal in milking group at the time of sampling

*Blood sample required by the Veterinary Laboratories Agency and most other laboratories is one heparin tube (green)
†Discuss with laboratory regarding submission of sample
PCR Polymerase chain reaction, PI Persistently infected

antibodies to determine whether the group as a whole is likely to have been exposed to the virus.

A series of tests is available and these have different end-points (eg, optical densities or dilution titres of serum [eg, 1/64]) (see table below).

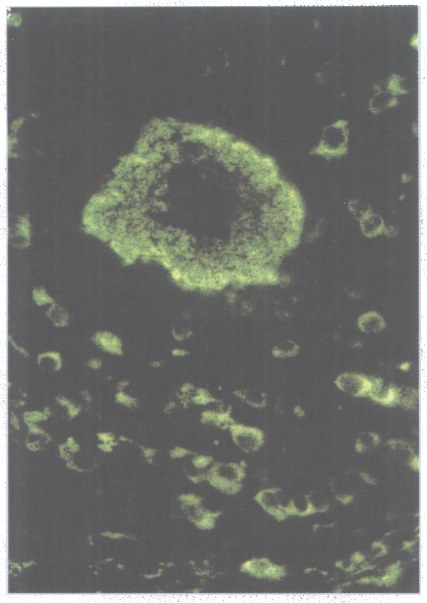
Bulk milk antibody testing

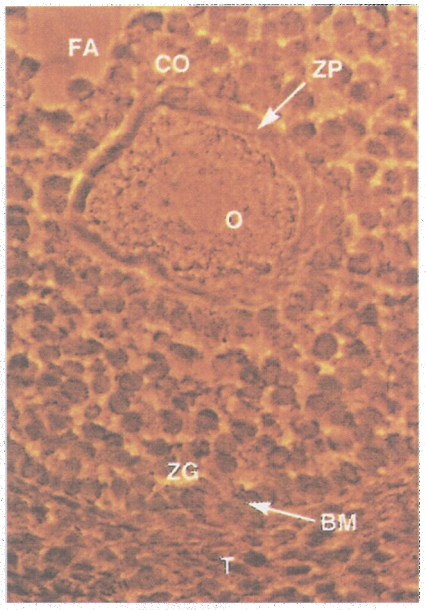
Milk samples can also be examined for the presence of antibodies. While such tests on bulk milk provide only an 'average' figure for the herd, they do offer a straightforward and simple method of obtaining an insight into the level of exposure to BVDV within the milking herd (see table, page 183). Pooled milk samples can also be tested for the presence of viral antigen (PCR test) to determine the presence of a PI animal within the milking group; this test is unlikely to give a positive result to acute viraemia.

DIAGNOSTIC TESTS AVAILABLE FOR DETECTION OF BVDV ANTIBODY

Test	*Single animal or group*	*Requires*	*Measures*	*Interpretation*
Individual blood antibody ELISA	Single animal blood sample. Pooled blood samples can be submitted for a qualitative assessment of exposure within the group	Blood*	IgG antibody	Result expressed as an OD ratio. The values may vary between laboratories but, in general, the following guidelines apply: OD <0·2 = seronegative OD >0·2 = seropositive Higher OD results (eg, >0·7) are associated with recent infection although, once raised, antibody titres may persist for some time. Seroconversion is confirmed by an increase in OD between paired samples of at least 0·2 units
Bulk milk ELISA	Group test (although individual milk samples can be tested using the ELISA)	15 ml of bulk tank milk with specific preservative in sample bottle	IgG antibody	See table, page 183
Serum neutralising antibody test	Single animal	Blood*	Serum neutralising antibodies	Test is not routinely employed, but is available. Measures neutralising antibodies as distinct from antibodies which may not play a role in immune protection

*Blood sample required by the Veterinary Laboratories Agency and most other laboratories is one clotted blood tube (red)
IgG Immunoglobulin G, OD Optical density





(left) Demonstration of a BVDV-infected oocyte within the ovary of a PI cow by immunofluorescent microscopy. (right) Phase contrast microscopy of the same ovarian section, showing an infected oocyte (O) and scattered infected follicle cells within the cumulus oophorus (CO) and zona granulosa (ZG). The zona pellucida (ZP), follicle basement membrane (BM), theca (T) and follicular antrum (FA) are clearly defined. Reproduced, with permission, from Brownlie and others (1997)

In addition to submitting a sample of milk from the bulk tank for antibody analysis, milk samples from freshly calved heifers can be taken to obtain further information on disease dynamics. A full explanation of this cohort milk testing is available elsewhere (Pritchard 1998). Testing of blood samples from a group of six homebred heifers, aged between eight and 18 months, provides further information about the spread of the virus and the likely presence of a PI animal (Houe 1995).

What are the exceptions for diagnosis?

There are a number of clinical situations that provide a challenge for the process of diagnosis. These, together with some suggested courses of action, are highlighted in a box overleaf.

Legal considerations of diagnosis

BVDV is a significant pathogen that can affect both male and female cattle. Screening for BVDV should, therefore, be a part of all veterinary 'examinations for fitness' in both male and female animals. Failure to carry this out may have legal implications (Brownlie and others 1984b).

The situation regarding the sale of PI animals is less clear. To knowingly sell, or advise the sale of, PI animals, in the full knowledge that they are the major reservoir of BVDV, is professionally unsound. Interestingly, in Denmark, bovine virus diarrhoea (BVD) is a notifiable disease and it is illegal to allow, knowingly, a PI animal onto open pastures. However, in the UK it remains that any purchaser who buys an animal in good faith must accept that caveat emptor ('let the buyer beware').

DIAGNOSTIC TESTS AVAILABLE FOR DETECTION OF BVDV ANTIBODY IN MILK

*Antibody level (OD)**	*Herd score*	*Likely percentage of seropositive milking cows*	*Herd status*	*Further action to be considered*
<0·10	0	<5%	Naive	Test a sample of young stock for antibodies to confirm no evidence of exposure to virus (such as from a young PI animal). Comprehensively review herd biosecurity (see Duncan 1994). Consider vaccination where there is a risk of introduction of the virus
0·10-0·35	1	5-25%	Low level of exposure	Test a pooled sample of milk from first-lactation heifers for antibodies. Also blood sample six homebred heifers (eight to 18 months old) and test for antibodies. Where there is no evidence of exposure, review herd security, repeat bulk tank test every three months and consider vaccination if there is a risk of introduction of the virus. The presence of antibodies in these younger animals is evidence of active/recent infection; a significant number of the herd will be at risk
0·35-0·70	2	25-65%	Moderate level of exposure	
>0·70	3	>65%	High levels of antibodies suggest active or recent infection. These herds can contain large numbers of animals not exposed to virus, as individual cows carrying a PI calf will produce very high levels of antibodies	Action should be taken to control the ongoing losses associated with circulating virus. The extent of the infection can be confirmed using the antibody detection tests discussed in the text. The presence of a PI cow can be determined by PCR test on a bulk milk sample. Control measures, including eradication and/or vaccination policies, should be advised

Antibodies reflect either past exposure in older/bought-in animals *or* early evidence of acute herd infection. These herds may be in a transition phase and so represent a 'grey area'

*Individual laboratories may have validated their test against slightly different optical density (OD) ratios

Diagnostic challenges

A definitive diagnosis of a PI animal may be hindered in the following situations:

Acute infection
A blood sample taken at the peak of acute viraemia may occasionally be positive by ELISA antigen and immunoperoxidase tests.
■ SOLUTION: Paired blood samples are taken three to four weeks apart. Both samples must be virus positive to confirm persistent infection. Acutely infected animals will have seroconverted by the time of the second sample

Colostrum
Colostrum intake can mask the detection of persistent viraemia in the blood for three to four months.
■ SOLUTION: Blood sample calves either precolostrally or after four months of age

PI calves in utero
Calves infected in utero can remain persistently infected throughout pregnancy and at birth reintroduce virus into the herd.
■ SOLUTION: Do not buy in-calf cattle, or ensure excellent herd security for any newly introduced in-calf dam into the milking herd. Dams with PI fetuses often have very high antibody levels and so a serum antibody test may give a good indication of the forthcoming birth of a PI calf

Antibody-positive PI animals
Some PI animals can make antibodies to BVDV. Usually the antibodies are to 'heterologous' BVDV strains (there is always a maintenance of viraemia) or to 'homologous' BVDV variants (there can appear to be a transitory loss of viraemia).
■ SOLUTION: Perform repeat blood sampling on cattle causing concern. White blood cells recovered from the sample require extensive washing to remove antibody before re-examining for virus

Bulls
It has now been shown that antibody-negative (PI) bulls secrete virus in semen and, exceptionally, some antibody-positive bulls can secrete virus in semen (see text).
■ SOLUTION: Examine semen for BVDV

Emergence of genetically divergent BVDV strains
Any new genetically divergent strains of BVDV may not be detected by all of the presently available tests.
■ SOLUTION: Maintain surveillance for BVDV-associated disease. Ensure laboratory availability of 'catch-all' cell culture and molecular methods for detection

TOWARDS A DISEASE CONTROL PROGRAMME

An on-farm disease control programme can be broken down into four main elements:
■ Assessment: 'Where are we now?'
■ Objective and Strategy: 'Where do we want to be?'
■ Tactics and Action: 'How are we going to get there?'
■ Review: 'How are we getting on?'

There should be a written record of the details of the programme, and this should be viewed as a dynamic and working document. It is a source of information for all parties and should be reviewed on a regular basis.

ASSESSMENT: 'WHERE ARE WE NOW?'

There are several prerequisites for a successful disease control programme. It is crucial that all parties involved understand the disease and the risk factors. This requires a level of commitment both to educate and to implement control strategies.

Risk factors: clinical history of the herd (over past two years)

■ Clinical history of the farm
■ Open vs closed herd
– contact with other cattle (eg, across neighbours' fences)
– contact through markets or shows
– shared or hired bull
– timing and BVDV status of bought-in cattle
■ Herd records (over 18 to 24 months)
– fertility, herd health, milk production
■ Postmortem examination results
■ Bulk milk test results for BVDV
■ Blood test results for BVDV

An assessment of the herd should be carried out to establish the current disease status and the relative risks of reinfection. The factors that need to be taken into consideration in order to establish the current disease status of the herd are listed in the box above. Meanwhile, the various different routes by which virus could potentially reinfect a herd should be reviewed (see box below).

OBJECTIVE AND STRATEGY: 'WHERE DO WE WANT TO BE?'

The control programme should be clearly defined and realistic. A well designed programme will increase both the health and profitability of the herd by controlling the effects of BVDV. In certain herds, the objective will be to minimise the economic losses associated with exposure to the virus; in other situations, the objective may be to eliminate the virus from the herd.

The decision about which route to take must take account of farm biosecurity (could it be maintained as a closed unit?) and the management (are replacement cattle bought in and are shared/hired bulls used?). Where there is any doubt about the feasibility of maintaining a virus-free unit, then vaccination should be considered.

TACTICS AND ACTION: 'HOW ARE WE GOING TO GET THERE?'

A number of different policies can be considered:
■ The 'do nothing' policy;
■ Use of a PI animal as a 'vaccinator';
■ Eradication;
■ Vaccination;
■ Eradication and vaccination.

Risk factors: sources of virus

■ PI animal
■ Heifer or cow carrying a PI fetus
■ Acutely infected animal (eg, incoming animal or one returning from a show)
■ Cattle-to-cattle contact
■ Other ruminants (eg, sheep, deer)
■ Infected material (eg, vaccines, semen)
■ Biting flies*

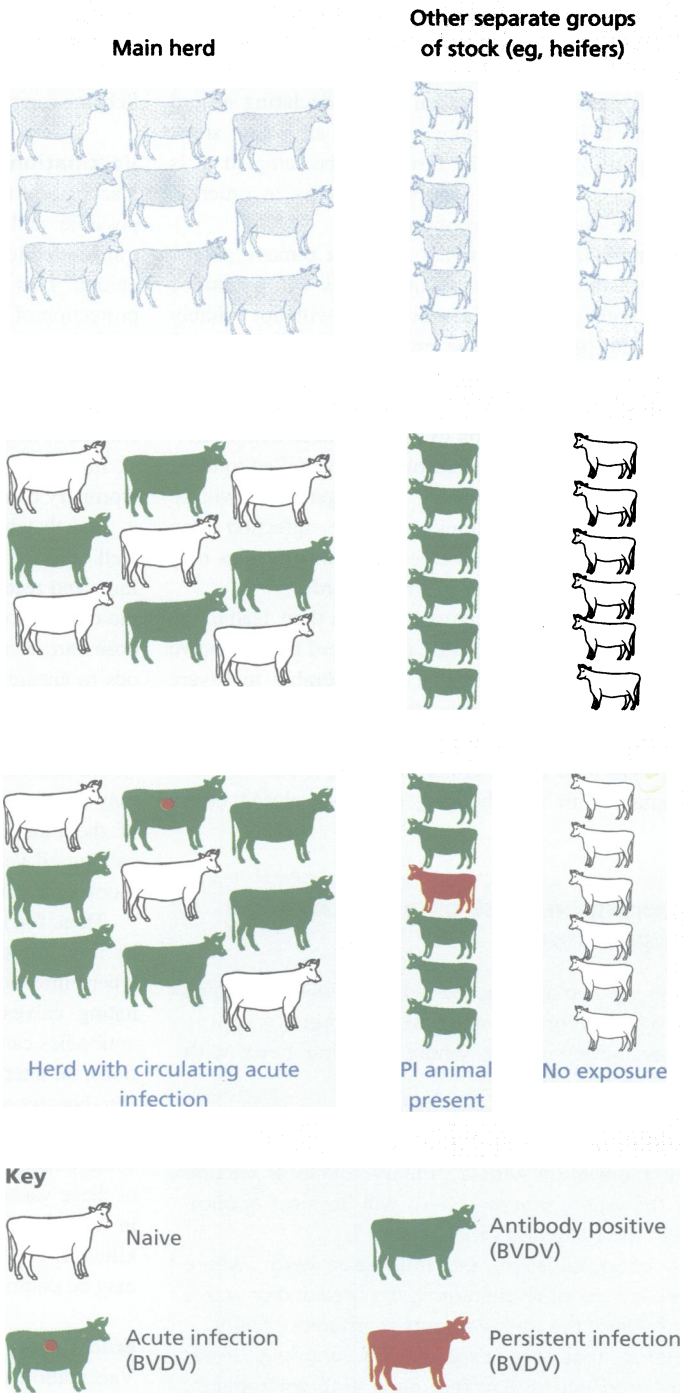
*Experimental evidence only

Herd assessment of BVDV infection

The investigation commences with the undifferentiated herd. Separate groups of animals should also be considered, such as heifer groups, animals that will be bought into the main herd, and so on

Bulk milk samples and/or individual blood samples tested for antibody provide an indication of the level of exposure within the herd. The antibody status of six animals from a group that have been reared together provides clear evidence of the level of exposure for the whole group

The greater the level of antibody or number of seropositive individuals, the greater the likelihood that virus is present on the farm, either in the form of a PI animal or as circulating acute infection



The 'do nothing' policy

The 'do nothing' option should not be considered a control policy. Where exposure to BVDV is left to chance, the likelihood of acquiring good protective immunity is random, whereas the losses that can occur as a result of infection can be significant. Furthermore, natural immunity will wane and lack of subsequent virus challenge could compromise immune protection. For example, virus has been shown to have re-entered a herd that, three years previously, had undergone a testing and eradication programme. Animals that had tested antibody positive three years earlier were subsequently found to be antibody negative. Seroconversion, associated with ill health, was recorded in a number of these animals (D. Leonard, 1998, personal communication).

Use of a PI animal as a 'vaccinator'

In the past, PI animals have been maintained as natural 'vaccinators' within herds as a means of increasing levels of natural immunity in the absence of an effective BVDV vaccine. There have been a number of problems associated with this method of control; not least, naive animals must sustain a period of acute infection before any protective immunity can develop. Acute BVDV infection can compromise cattle health, particularly when the virus gains access to breeding cattle. In some cases, complete seroconversion within the group has not been achieved following PI 'vaccination'. Furthermore, the PI animal can, at any time, develop mucosal disease with fatal consequences. With the availability of efficacious vaccines, this option should not be used.

Eradication

The routine availability of laboratory tests to determine BVDV status allows the identification and elimination of PI animals. However, as there are exceptions to the definitive determination of PI status (see box on page 184), care must be taken before declaring a herd virus-free. It is vital to remember that all young stock subsequently born onto the farm must be sampled. It is prudent to continue this sampling process in order to monitor the ongoing status of the herd.

The removal of PI animals may not remove all the virus from the farm. The available tests will determine animals with persistent infections but will not reliably detect acute infections. The problem of slow spread of virus by acute infection within the herd, in the absence of a PI animal, has been identified. This would explain those cases where seroconversion to virus has been demonstrated but subsequent whole herd bleeds have failed to identify a PI animal. It is probable that larger herds will be more capable of sustaining an acute infection than smaller herds. For this reason, eradication strategies may achieve more rapid success in smaller herds.

The eradication of PI animals will, in time, lead to the presence of seronegative cattle in the herd that are naive to disease and to a herd that is vulnerable to severe losses should BVDV re-enter the herd. This means that eradication schemes (in the absence of follow-up vaccination) will tend to suit either biosecure herds that have no contact with neighbouring cattle, or closed herds; in addition, there must be complete commitment, understanding and enthusiasm for eradication on the part of the herd owner and veterinary surgeon.

Eradication schemes for BVDV are available as part of Cattle Health 2000 and the Premium Cattle Health Scheme run by the Scottish Agricultural College.

Commencement of a vaccination programme

There are two approaches to the commencement of a vaccination programme within the herd:

- **Vaccination of the whole breeding herd, with boosters thereafter;**
- **Vaccination of heifers (bulling and first-calved animals), with boosters thereafter.**

Immunisation with a primary course of vaccine for the whole breeding herd will be most applicable in the following situations:

- **Antibody-negative, and thus naive herds, where there is a risk of virus entering the herd and/or where the value of the stock warrants an insurance policy;**
- **Herds that are experiencing ongoing losses associated with BVDV (eg, early embryonic death, poor conception rates, abortion, enteric disease, immunosuppression);**
- **Herds of high genetic worth and those herds undergoing embryo transfer work.**

The alternative route forward is a progressive approach, starting with the heifers and building up each year towards a fully vaccinated herd. Heifers are normally the animals on the farm into which the greatest level of genetic investment has been made. Increasingly, heifers may be reared away from the main herd and, as such, may have a different disease status. In the first year, bulling and first-calved heifers can be vaccinated with a primary course. The following year, these animals are given a booster dose and the next group of bulling heifers receives a primary course. With time, this results in a fully vaccinated and protected herd.

Vaccination

Vaccination to control and prevent BVDV is now both possible and cost effective. BVDV can be vertically transmitted to the next generation via the creation of a PI animal. This means that long-term control hinges on the protection of the breeding herd and the prevention of the birth of new PI animals. The availability of vaccines, which have proven protection against transplacental BVDV infection, represents a major development in the control of this pathogen in cattle.

In the UK, only killed BVDV vaccines (which require a primary course of two injections) have been licensed. It is vital that breeding cattle receive their primary course well before first service. Heifers can be batched as yearlings and receive the primary course in good time before the commencement of service. Thereafter, single booster doses are recommended before subsequent service periods to ensure maximum immunity is present at times of greatest potential risk (ie, the service period and early to mid-pregnancy). However, where losses are ongoing or where known naive animals are at risk of infection, there may be a requirement to vaccinate animals at other stages of the reproductive cycle. Similarly, in herds that are calving all year round it may be more straightforward to block vaccinate the herd.

Thus, for long term control, the breeding herd should be immunised and boosted on a regular basis. In herds where infection is active, there may be a role for vaccinating calves to reduce acute infection. As colostral antibodies can protect against the viraemia of acute infections, an alternative approach to protecting young calves is to booster colostral antibodies by vaccinating the dam.

Live BVDV vaccines are commercially available in some countries. The recommendations attached to some of these vaccines stipulate that they should only be used in animals that have initially been vaccinated with a killed BVDV vaccine. Their use in pregnant animals may be contraindicated.

Eradication and vaccination

Vaccination and eradication are both routes to controlling the losses associated with BVDV. However, they should not be considered to be opposing strategies. Eradication alone leads to a herd which, while free from BVDV, is vulnerable to the reintroduction of virus. Vaccination programmes provide protection to the herd, but vaccination will not alter the status of PI animals that are already in the herd prior to the start of the vaccination programme, nor any PI animals bought into the herd. These PI animals will die in time and their cohorts will be immunised. However, if these PI animals are female and reach breeding age, their progeny will be persistently infected.

The eradication of PI animals, following confirmatory blood testing, can be carried out in combination with vaccination of the breeding herd. This is the 'Rolls Royce' method of BVDV control that will lead to the most rapid and complete resolution of all BVDV-related problems within the herd.

FUTURE CONSIDERATIONS

HEALTH SCHEMES AND NATIONAL ERADICATION

Over the past 20 years the whole farming industry has undergone considerable change. It is already clear that there will be significant commercial advantages for the stockowner from membership of farm assurance and health schemes. BVDV is a cause of appreciable economic loss and it is through health schemes and control programmes that knowledge regarding the disease can be translated into improved herd health and profitability. Several European countries have embarked upon BVDV eradication campaigns and the prospect exists that lack of disease control could be used as a barrier to trade. The veterinary profession should be actively involved in herd health schemes, as it is the veterinary surgeon who will be able to provide the expert help and advice that the stockowner requires to implement the most appropriate control policy. It is entirely possible that, in the future, eradication of BVDV in selected areas (presently restricted to the Shetland Islands) or on a national scale will make great demands on cattle healthcare programmes and resources.

BVDV 'MARKER' VACCINES

The monitoring of future eradication schemes will have to utilise assays for BVDV antibody – most likely, the antibody status in bulk milk samples. The concurrent use of vaccines could compromise this monitoring and so, to maintain the protection offered by vaccines during this period, it will be necessary to develop vaccines of 'marker' status. 'Marker' vaccines permit distinction between vaccinal and natural immunity; their construction demands a degree of molecular wizardry and immunological insight!

NEW VIRAL VARIANTS AND CONTROL

The emergence of BVDV strains of greater virulence (eg, those isolates causing severe haemorrhagic disease) underlines the need to maintain surveillance, both within the national herd and on the importation of animals and biological materials. At present, isolates in the UK, and possibly elsewhere, apart from North America, appear to be group 1 viruses. While virulence and antigenicity may not necessarily correlate, the emergence of new antigenic variants may have implications for the design and validation of future vaccines. It is important that veterinary practitioners are provided with full documentation of vaccine usage and vaccine efficacy. Fortunately, there appears, at present, to be considerable cross-protection between BVDV isolates, particularly against isolates in the same viral group (eg, group 1). Present evidence shows that, with the correct selection and use of existing vaccines and eradication programmes, there are excellent prospects for the control of BVDV.

SUMMARY

BVD is, undeniably, one of the most important viral diseases of cattle. The paradox for diagnosis is that clinical signs range from the inapparent to either severe haemorrhagic disease or fatal mucosal disease, while the immunosuppressive effect of acute BVDV infections can enhance clinical disease from other pathogens. In recent years, there has been a growing awareness of the major role of BVDV in reproductive loss, causing early embryonic loss, abortions and the birth of persistently viraemic calves.

In the pathogenesis of mucosal disease, the two biotypes of the virus, non-cytopathogenic and cytopathogenic, act sequentially. The initial transplacental infection of the early fetus with the non-cytopathogenic virus can result in the subsequent birth of calves persistently viraemic for life with this biotype. These calves may later develop mucosal disease as a result of superinfection with the cytopathogenic virus. For a number of years, the origin of this cytopathogenic virus was suggested to be by mutation from the persisting non-cytopathogenic virus. Now that the genomic organisation of several pairs of viral biotypes is known, the mutational origin has been confirmed. The published data on a variety of these mutational rearrangements in different isolates has highlighted the importance of two viral proteins, E2 and NS2-3.

The laboratory tests for both BVDV and viral antibody are excellent. Detection of the PI animal is a central part of all eradication strategies; however, many herds may benefit from an eradication and vaccination programme. The interpretation of antibody titres, as a basis for vaccination in these programmes, may be more complex. This article has described how strategic decisions for BVDV control can be made.

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