Bovine viral diarrhoea: update on disease and its control

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in the first of a two-part article look at the syndromes caused by BVD virus before moving on to review diagnosis of this widely spread disease in UK herds

WE wouldn't say bovine viral diarrhoea (BVD) was similar to Marmite, that you either love it or hate it, but we would say you either believe it is important or you don't.

This article brings some recent evidence to update a previous review about the disease and its control (Brownlie et al, 2000).

It is clearly evident many people, even countries, believe BVD virus (BVDV) is a most important cause of ill health and lost productivity in their national herds. A number of European countries have national BVDV eradication programmes that have either succeeded (Scandinavian countries) or are on the way to total eradication (Austria, Switzerland, Germany and Luxembourg).

Closer to home, both Scotland and Ireland have national programmes to clear the virus from their herds; interestingly using different technologies, but both making good progress. England and Wales are considering what approach they would wish to take regarding national eradication.

So it is highly relevant we, as a profession, understand the disease, its diagnosis and its control. Several high profile educational initiatives for both veterinarians and farmers have been under way in the past few years, most notably those promoted by funding from the Rural Development Programme for England (RDPE). In England, the Animal Health and Welfare Board (AHWB) has identified BVD as a priority for a national control programme. There have been some major regional programmes – in the north-east/central UK with support from DairyCo and EBLEX (BVD Free), the north-west programme in association with NFU and SRUC (NW Dairy BVD) and the south-west in association with Duchy College (South West Healthy Livestock Initiative – SWHLI). All have undertaken major training programmes for veterinarians and for farmers about BVD, among other issues.

From the north-east/central programme (BVD Free), an industry-led BVD programme has had support from DairyCo, EBLEX and the NFU with RDPE funding (chaired by Bill Mellor of the NFU). There has also been a scientific and technical group that has provided teaching material and also reviewed testing regimes suitable for a national programme (chaired by Joe Brownlie). This will be published soon.

In this article, we will describe a number of syndromes caused by BVDV and then comment on diagnosis. An excellent and more detailed review has been published (Lanyon et al, 2014).

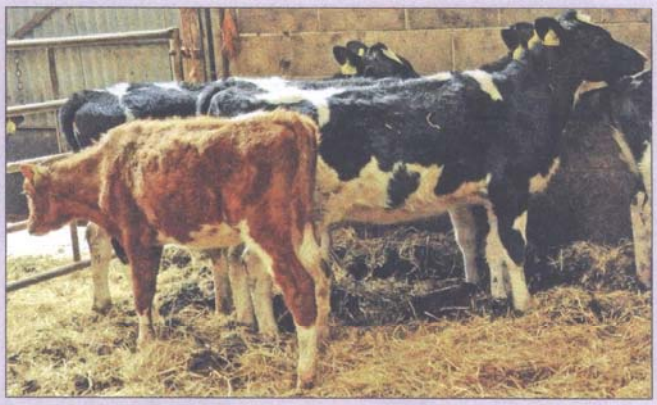

Figure 1. Persistently infected (PI) animals are often stunted; the PI calf (brown/white) is the same age as the other two calves.

ABSTRACT

Bovine viral diarrhoea (BVD) is a widespread infection of cattle throughout the world, although a number of European countries have undertaken national eradication programmes of the BVD virus (BVDV). The virus is classified in the pestivirus genus that also includes classical swine fever virus and border disease virus of sheep.

In recent years, novel viruses have emerged from this genus – some with devastating consequences for livestock health, that is, BVD type two viruses and the porcine Bungowannah virus in Australia. The complexity of BVD pathogenesis is focused on the persistently infected (PI) animal; this results from an early fetal infection where the fetus becomes tolerant to the virus and, as a result, remains PI into neonatal and adult life. These animals become the major reservoirs – the "super-shedders" of BVDV.

Understanding this allows veterinarians to design control strategies based on diagnosing and culling these PI animals. Acute infection with BVDV can also cause severe disease, both to young animals through its ability to cause immunosuppression, and to adult animals where it can cause reproduction losses.

Keywords: BVD, persistently infected (PI) animals, mucosal disease, Cumulus, reproductive diseases

The virus

BVDV is a member of the pestivirus genus in the Flaviviridae family. All are RNA viruses. It has traditionally contained three members – BVDV, classical swine fever virus (CSFV) and border disease virus of sheep (BDV).

In the past decade or more, there has been a greater awareness of other pestiviruses and this has led to a reappraisal of the family relationships (phylogenetic maps). A variant BVDV was identified as the cause of a catastrophic outbreak of acute fatal haemorrhagic disease in the US and Canada in the 1990s. This virus was later classified as BVDV group two, making the original viruses BVDV group one by default. It was first considered the group two viruses were the highly pathogenic ones and group one viruses were less so. Our more recent understanding is that virulence does not follow that division: virulent and less virulent viruses can be found in both groups. However, with the advance of molecular techniques to analyse the RNA genotype of a number of viral isolates from around the globe, a greater complexity of viruses has been revealed. This will all be discussed in a later article for *Veterinary Times* (*VT*44.34).

The virus exists in two biotypes: a non-cytopathogenic form (that can persist in cells without causing cell lysis) and a cytopathogenic form (which does lyse cells). Both biotypes are found in the different BVDV groups.

Acute infection

Most BVD infections are acute, although the acutely infected animal is not the major reservoir of the virus. This is the persistently infected (PI) animal. There has been a tendency for some diagnosticians to ignore or disregard the impact of acute infection. There are reasons not to do this.

- Highly virulent BVD viruses. Some viruses have mutated to become highly pathogenic and can cause severe disease, if not death, following acute infection. Prominent among the virulent ones, but not exclusively, are the BVD group two viruses.

In the outbreaks in the US and Canada in the 1990s, many thousands of calves died of an acute haemorrhagic disease caused by the group two viruses. In 2013 there was a fatal outbreak of haemorrhagic disease in Germany, with widespread losses of cattle on some 23 dairy cattle and veal farms. The clinical signs were abortions, milk drop and respiratory disease and, in some animals, a bloody diarrhoea. In dairy cattle, the mortality was up to 20 per cent, whereas in calf units, it could reach 80 per cent. The responsible virus has been typed as a BVDV Type 2c (Doll and Holsted, 2013).

Severe disease has also been recorded in UK cattle, but with BVDV type one viruses (Hibberd, Turkington and Brownlie, 1993).

- Reproductive losses. These can range from infertility, abortions and fetal abnormalities on to the extreme outcome of a persistent infection of a neonate following early fetal infection.
- Calf diseases. Most calves are born with no experience of infection with BVDV; they are thus "naïve" to the virus and have no immune protection. Unless they are on farms where there is no BVDV (on BVDV-eradicated farms), they are highly likely to become infected in their early years. The virus circulates readily, particularly when there is a PI animal present.

The virus is immunosuppressive and, for a few weeks after infection, will potentiate the establishment of other pathogens, thereby facilitating calf respiratory and enteric problems. In fact, in those countries and those regions where BVD has been cleared, there has been a notable improvement in calf health and welfare.

Persistent infection

The PI animal is the major reservoir of BVDV. Most farm control and eradication programmes require these PI animals are identified and culled, and that good biosecurity measures ensure no new PIs are brought on to the farm. Most national BVD eradication programmes depend on this approach.

Our understanding of the creation of PI animals has not changed over the past few decades. When a "BVD-naïve" dam is infected in early pregnancy, the virus can enter the maternal blood stream, cross the placenta and infect the fetus. The fetus, at this early stage, is not capable of recognising or removing the virus (it is immune-incompetent) and the virus becomes established in its tissues. Once it does become immune competent at about 100 to 120 days of gestation, the virus is accepted as a "self antigen" in the process of "central tolerance" to its own tissues. For this reason, PIs are always highly infected (a "super-shedder" of the virus), and yet do not make an antibody response to the circulating 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.

PI fetuses, if they don't abort, become PI neonates and some develop into adults and even into breeding stock.

So the question remains what happens to the offspring of PI mothers? 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 born to PI dams is reportedly only seven per cent (Grotelueschen et al, 1998), implying the remaining 93 per cent arise as a result of acute infection of the seronegative dam in early pregnancy. PI animals are often stunted **(Figure 1)** although many appear clinically normal.

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 following 30 years, a series of observations were made about the association between BVDV and mucosal disease. These were finally refined into a hypothesis and proven experimentally.

The hypothesis states an initial transplacental infection of the early fetus with the non-cytopathogenic virus results in the birth of a calf that has a life-long persistent viraemia.

These calves (and only these calves) may later develop mucosal disease as a result of superinfection with a "homologous" cytopathogenic BVDV **(Figure 2)**. 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 even 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 of young cattle that are persistently infected with a non-cytopathogenic BVD virus.

"It usually occurs between 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."

Reproductive consequences

The biotype responsible for persisting infections following in utero infections is always non-cytopathogenic. Experimental infections during the first trimester showed up to 30 per cent of fetuses are aborted, even though the majority of the surviving fetuses go to full term and are born PI. In contrast, no animal has yet been demonstrated as PI with the cytopathogenic biotype.

BVDV causes significant intrauterine growth retardation in many of the fetal issues, particularly the 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.

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 reduced from 78.6 per cent in the immune cows to 22.2 per cent in infected cattle (Virakul et al, 1988).

In a further study, a 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 et al, 1993).

Infection of the bull

We often underrate the importance of BVDV infection in the bull. The BCVA guidelines for "soundness" in the bull do not require any statement about its BVD status. However, a bull can be infected in three ways by the virus:

- Acute infection. During the viraemic stage of infection (usually in the two to three weeks post-infection), BVDV can be demonstrated in the semen, thereby providing a risk for onward transmission to "naïve" cattle. If semen was collected for AI, then there could be a greater and wider risk of viral transmission to all inseminated cattle.

A less appreciated risk is to the quality of semen following this viraemic two-to-three week period. There is a greater level of abnormal sperm from these bulls for at least three months after acute infection (90 per cent abnormal sperm at 40 days and still more than 50 per cent abnormal at 80 days post-infection; Paton et al, 1989). For this reason, a nine-week quarantine of bulls is recommended to ensure there is no virus shedding in the semen.

- Persistently infected. All PI bulls will continually produce infected semen. It reinforces the need for farmers (and their veterinarians) to be aware importing bulls on to farms carries this risk. All reputable bull studs are aware of this potential risk and test accordingly.
- The "Cumulus" bull. This was first recorded in New Zealand (Voges et al, 1999). Cumulus was a highly regarded young bull that had tested negative for BVDV by both antibody and antigen tests as a young calf. However, ⇨ page 12

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on entering the bull selection programme at about 11 months, he proved to be both antibody-positive and BVDV-positive in its semen (but not blood). Later tests established he had a localised, but persistent, infection in its testicular tubules.

From 11 months onwards, Cumulus produced infected semen for the following 11 months at which time (now 22 months old) he was culled.

So, over the following 15 years, we have seen a small number of other "Cumulus" bulls. It does appear a rare outcome of acute infection, but not unique.

For the veterinarian undertaking a thorough examination of a bull, it is expedient to consider a semen BVD test, particularly if the bull is serum-positive.

Diagnosis

The diagnosis of BVD-infected animals will be presented in a future and more detailed article. Basically, the diagnostic tests reflect the pathogenesis outlined above. An excellent website for more information on diagnostics can be found on the CHeCS website.

- BVDV. Detecting infected animals requires the demonstration of virus or viral RNA in samples taken from individual animals (blood, milk, semen or ear tags) or pooled samples from a number of animals (bulk milk [BM] or pooled blood samples). Virus can be detected by demonstrating viral protein (by either ELISA or immunofluorescence for viral antigen) or by viral RNA (using PCR).

The only caution is that it may be important to distinguish between those animals that are either acutely (transiently) or persistently infected. The accepted method is to retest at three to four weeks; by this time, acutely infected animals will have cleared the infection and mounted a specific immune response, whereas PI animals will remain virus positive.

- BVD antibody. Antibody indicates animals have been infected. The detection of antibody is most commonly undertaken by the use of ELISA on specific BVD plates. The real value of antibody testing is it gives a historical view of BVD infection among that animal or group of animals – this is most valuable in youngstock (usually over nine months) and gives a quick, reliable and economic assessment of the likelihood of the presence of a PI on the farm.

It should also be noted BVD antibodies can remain high for protracted periods of time (years more than weeks). This needs to be understood when interpreting the presence of antibody in adult animals and most particularly in BM samples. Thus, a single BM sample may be antibody-positive, but the source of infection, usually a PI animal, is no longer on the farm.

Summary

BVD is a widespread disease in our national herd. It has a complex pathogenesis, but, once understood, it prepares the veterinarian for the correct use of diagnostics to control and even eradicate the virus from cattle herds. Valuable websites for reference to BVD can be found at:

- www.rvc.ac.uk/bvd/Index.cfm or www.scotland.gov.uk/Topics/farmingrural/Agriculture/animal-welfare/Diseases/disease/bvd
- www.raftsolutions.co.uk
- www.dairyco.org.uk/technical-information/animal-health-welfare/biosecurity-and-diseases/diseases/bvd/#.U0PbXWCYZtR
- www.nfuonline.com/sectors/dairy/livestock
- www.checs.co.uk

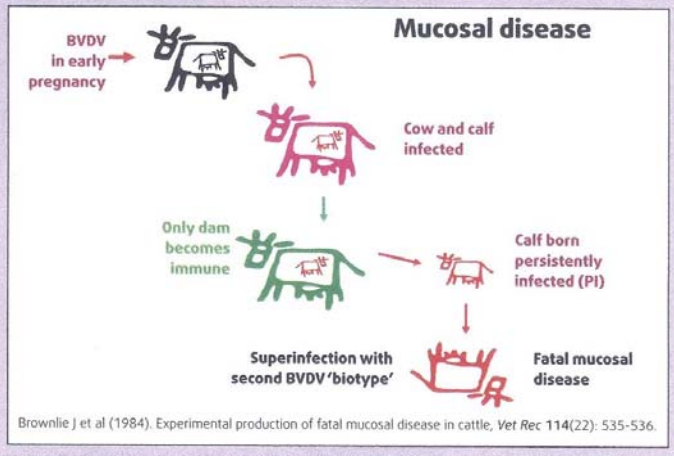

Figure 2. The establishment of the persistently infected (PI) calf, following an in utero infection of the fetus with a non-cytopathogenic biotype of BVDV, and the consequent development of mucosal disease, after a superinfection with the cytopathogenic biotype.

References and further reading

Brownlie J, Thompson I and Curwen A (2000). Bovine virus diarrhea virus – strategic decisions for diagnosis and control, *In Practice* **22**: 176-187.

Doll K and Holsted M (2013). BVD-virus type 2 – an outbreak in Germany, *Cattle Practice* **21**(3): 216.

Grotelueschen D M, Wittum T E, Brock K V, Kvasnicka W, Floyd J, Kelling C and Odde K G (1998). Persistent bovine diarrhea virus infection in US beef herds, *Proceedings of the XX World Buiatrics Congress Sydney, Australia* 2:1,007-1,010.

Hibberd R C, Turkington A and Brownlie J (1993). Fatal bovine viral diarrhoea virus infection of adult cattle, *Vet Rec* **132**(9): 227.

Lanyon S R, Hill F I, Reichel M P and Brownlie J (2014). Bovine viral diarrhoea: pathogenesis and diagnosis, *Vet J* **199**(2): 201-209.

McGowan M R, Kirkland P D, Richards S G and Littlejohns I R (1993). Increased reproductive losses in cattle infected with bovine pestivirus around the time of insemination, *Vet Rec* **133**(2): 39-43.

Paton D S, Goodey R, Brockman S and Wood L (1989). Evaluation of the quality and virologic status of the semen from bulls acutely infected with BVDV, *Vet Rec* **124**(3): 63-64.

Ramsey F K and Chivers W H (1953). Mucosal disease of cattle, *North American Veterinarian* **34**(1): 629-633.

Virakul P, Fahning M L, Joo H S and Zemjanis R (1988). Fertility of cows challenged with a cytopathic strain of bovine virus diarrhea virus during an outbreak of spontaneous infection with a noncytopathic strain, *Theriogenology* **29**(2): 441-449.

Voges H, Horner G W, Rowe S and Wellenberg G J (1999). Persistent bovine pestivirus infection of an immunocompetent bull, *Vet Microbiol* **61**: 165-175.

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RICHARD BOOTH is lecturer in veterinary extension services and infectious diseases of cattle at the RVC. He undertook his doctorate on the methods and impact of controlling and eradicating BVD from a number of Somerset farms. He has also genotyped a large number of BVD isolates in the UK and correlated this with cattle movements.