Cattle are susceptible to infection with bovine viral diarrhoea at all ages. The significance of this disease stems from its high prevalence, its clinical effects and its economic impact. This first article reviews its aetiopathogenesis and diagnostic techniques.

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Since it was first described by Olafson et al. in 1946 in the US, bovine viral diarrhoea (BVD) has become one of the most important infectious bovine diseases due to both its high prevalence in America and Europe (Houe, 1999) and its clinical effects (Gunn et al., 2005; Peterhans et al., 2010; Berends et al., 2008) and its negative economic impact on herds (Fourichon et al., 2005; Heuer et al., 2007).

**Causal agent**

The causal agent of BVD (BVDV), which also causes another disease known as mucosal disease (first found in Canada), is an RNA virus, pestivirus, which belongs to the *Flaviviridae* family. This family officially comprises four species: BVD-1, BVD-2, classic swine fever virus (CSFV) and Border disease virus (BDV) (Becher et al., 2003). Different subgenotypes are included in these species. In recent years, other pestiviruses have been isolated that are different enough not to be included in any of the above four species, and they are as yet unclassified (Neill, 2013).

**Mucosal disease is always fatal, resulting from an overinfection with a cytopathic strain of the BVD virus in a persistently infected (PI) animal.**

Examples of these viruses are the giraffe pestivirus, the antelope pestivirus or the Bungowannah virus, isolated only in Australia in domestic pigs. Then, there are other pestiviruses closely related to BVD: HoBi virus, KaHo/cont virus and Khon-Kaen virus isolated from batches of bovine serum from Brazil, cell cultures in South America and a calf in Thailand, respectively (Neill, 2013). Lastly, we have found a reference to an atypical pestivirus, proposed for acceptance as a new BVD species (it would be BVD-3) found in Italy (Decaro et al., 2011), which belongs to the group of the HoBi viruses.

In general, BVD-2 infections are more virulent than type 1 infections (Letellier et al., 2010), although there are descriptions of the type 2 virus also found in Europe, with no severe clinical cases (Barros et al., 2013; Sarrazin et al., 2013) or, by contrast, very severe cases of BVD-1 infections.

The different BVDV species are genetically and antigenically different but with some similarities, such as the fact that two biotypes are differentiated in each of them according to their behaviour in cell cultures: cytopathic (cp) and non-cytopathic (ncp) BVD viruses. Note that the biotype is unrelated to the virulence of the disease.
Clinical signs and transmission

It is also now known that mucosal disease is always fatal, resulting from superinfection with a cytopathic strain of the BVD virus in an animal persistently infected (PI) by a non-cytopathic strain. The ncp virus that persistently affects a PI animal can also mutate, creating a cytopathic strain and causing mucosal disease. PI animals are always infected since foetal life with non-cytopathic strains of the virus that crossed the placenta during pregnancy. At this stage of pregnancy, the foetus is not yet immune-competent and does not recognise the virus as extraneous.

PI animals can present clinical signs such as intermittent diarrhoea, pneumonia, high incidence of miscellaneous infections, delayed growth (Baker, 1995; Voges et al., 2006), etc., such that a malfunction of the immune system is suspected, possibly due to chronic interferon production. However, the existence of some normal PI animals that even manage to reproduce shows that some of these persistent infections are harmless. Note also that a PI cow always gives birth to PI calves (Meyling et al., 1990).

What all PIs do, irrespective of their origin, is expel the virus into the environment in large quantities, and they are the main epidemiological source of BVD infection (Matsuno et al., 2007). Therefore, all BVD control plans, whether regional or herd-specific, should include attempts to eliminate all PIs.

Months, or even years, later, if not previously eliminated, the PI animal will finally develop mucosal disease from overinfection (either by external infection or mutation of the virus) with a cytopathic strain of the BVD virus. This disease involves fever, dysentery, lesions in the oral and interdigital mucous membranes, ulcers in different parts of the digestive mucosa and lesions, especially on Peyer’s patches.

It is believed that 60% of the animals that live in endemic BVD areas not subject to control programmes come into contact with the virus at some time and become “temporarily” or “acutely” infected. They are temporarily infected because they usually survive the disease, definitively eliminating the virus from their bodies and acquiring immunity, initially for life (they present anti-BVD antibodies at all times). This transient infection, however, has consequences that are occasionally very serious for the animal and for farms’ economic performance (Fourichon et al., 2005). It has also been shown that there are cases of chronic infection after an animal’s transient infection, where the virus is replicated in “privileged” parts of the body that enable it to escape the immune response, in which case it remains active despite the animal having functional antibodies against the virus. These chronic infections have been found in the testicles of a young bull where the virus was isolated years after the infection. Prolonged viral replication has also been found in circulating lymphocytes, ovarian tissue and nervous tissue (Givens and Marley, 2013).

Although the incidence of such infections is minimal, as is their epidemiological and clinical significance, they can be very important in regions or countries in the last stages of eradicating the disease, where atypical or uncommon forms of maintaining the infection become radical to prevent it from recurring.

According to the age of the infected animal and its pregnancy status, the infection can give rise to different syndromes. It can be subclinical (Peterhans et al., 2010), and it can increase the incidence of other common diseases in cattle, such as pneumonia and mastitis, due to the virus’s immunosuppressive effect (Berends et al., 2008). Different reproductive symptoms
have also been described and found with more or less intensity (infertility, early embryonic death, miscarriages, etc.).

**Diagnosis of BVD in reproductive problems**

There are many laboratory techniques for determining both the virus itself (antigen) and the immune reaction that develops in animals that have been infected or vaccinated (antibodies) (Lanyon et al., 2013).

But diagnosis based on clinical judgment when faced with a case of BVD is more complex, due to the diversity of symptoms and, in particular, the variety of their intensity and scientific evidence. It has to be suspected whenever there are groups of miscarriages and/or malformed calves, and likewise when there is an excessive increase in stillbirths or neonatal death (the first 24 hours), or high neonatal mortality in general (Gates et al., 2013).

In the case of deficient reproductive efficiency (without miscarriages/stillbirths or neonatal mortality) it is much more difficult to conclude that it is due to BVD. Although the virus has been shown to be capable of this, based on scientific evidence, there are cases of herds with PI animals detected with no obvious effect on reproduction. As mentioned earlier, it depends a great deal on the type of virus, the strain or its virulence, intra-herd prevalence, intra-herd biocontainment and biosafety and the immune status of the farm. In any case, this disease should always be included in differential diagnoses regarding poor reproductive efficiency.

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If the objective is to clarify whether a series of reproductive problems on a farm are due to acute (also called transient) BVD infection, we have to be able to detect seroconversion in the animals (series of determinations of antibodies in blood, where they can be absent in the first sample, present in the second, or scarcer in the first and more abundant in the second sample). Another option is to detect viraemic animals (by determining the virus in the blood of affected animals).

RT-PCR techniques enable us to detect the virus in the blood of viraemic animals, as they are highly sensitive techniques. However, to ensure that it is a transient infection (and not a PI) the analysis must be repeated at least 19 days later, and the second sample would be negative for the antigen if it actually was a transient or acute infection (Meyling et al., 1990). On the other hand, an animal that has an acute BVD infection becomes seropositive (i.e. presents antibodies in blood) approximately 2-3 weeks post-infection. Therefore, if antibodies are determined three weeks after the antigen-positive sample, this would also show that it is an acute BVD infection.

In the case of miscarriages, with or without malformations, detection of the virus in foetal tissue is evidence of foetal infection, and is the presence of the virus in foetal fluids (Njaa et al., 2000). The seroconversion of the miscarried mother in a period of 4-6 weeks also indicates infection. However, cows that miscarry a PI calf can present a drop in antibodies and be treated as if there were no seroconversion (Brownlie et al., 1984), thereby leading to incorrect conclusions.

In general, the sole interpretation of a herd’s antibodies, even in paired samples, tends to be difficult. The vaccination history also has to be taken into consideration (vaccinations also give
rise to antibodies, which makes interpretation more complicated). However, finding the virus is always indicative of active BVD infection.

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