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REVIEW

BVDV control and eradication in Europe —an update

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Abstract

Infections with bovine viral diarrhoea virus (BVDV) are endemic in cattle populations worldwide and result in major economic losses. For long, attempts to control BVDV were limited to prophylactic vaccination practices, implemented primarily to reduce or prevent clinical disease on a herd basis. However, the benefit of preventing clinical disease in transiently infected animals is negligible when considering the overall losses of the disease. Another more systematic strategy to control evolved during the 1990s within eradication programmes in the Scandinavian countries. This was based on an initial determination of herd BVDV status, followed by implementation of systematic zoo-sanitary measures at a regional or national scale (without the use of vaccines) to prevent introduction of BVDV in non-infected herds, and to reduce the prevalence of infected herds by identification and elimination of PI animals. These programmes have been very successful, and all of the Scandinavian countries are currently either free, or almost free from BVDV. Today control programmes are underway in several European countries. This short review discusses the general model of BVDV control, and gives an overview of strategies used within, and the current status of, the ongoing control programmes in Europe.

Introduction

Bovine Viral Diarrhoea Virus (BVDV) is the denomination of a heterogeneous group of viruses in the family *Flaviviridae*, genus *Pestivirus* with two accepted genotypes or species (BVDV-1 and -2), which are economically important pathogens that primarily infect ruminants. Infections with BVDV are endemic in cattle populations worldwide and result in major economic losses (Houe, 2003). These losses are a result of high prevalence in combination with the negative effects on reproduction and the general health condition in affected herds. For long, control of BVDV was limited to vaccination practices, implemented on a herd-to-herd basis. During the 1990s, however, a more systematic approach toward BVDV control based on thorough knowledge of BVD epidemiology, and without the use of vaccines, was launched in the Scandinavian countries, aiming at eradication (Lindberg and Alenius, 1999). This approach showed to be successful, and the Scandinavian countries are now considered free from the disease, and today control programmes are underway in several European countries (Graham *et al.*, 2011;

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Moennig *et al.*, 2005b; Presi *et al.*, 2011; Rossmanith *et al.*, 2010).

This short review discusses the general model of BVDV control, and gives an overview of strategies used within, and the current status of, the ongoing control programmes in Europe.

Prevention of PI animals- the key to successful BVDV control

When a naïve pregnant cow is infected with BVDV in early pregnancy, the offspring may be born persistently infected (PI). This PI calf will be immunotolerant to BVDV, in general seronegative, and will shed large quantities of virus throughout its life (Coria and McClurkin, 1978; McClurkin *et al.*, 1984). The PI is often born weak and undersized, but may also appear normal at birth. Due to an impaired immune system it is particularly susceptible to other infections, which partly explains the high mortality during young age, compared to non-infected calves (Houe, 1992, 1999). Some PI animals, however, remain clinically unaffected and may breed satisfactorily (McClurkin *et al.*, 1979), and will then transmit the infection to the foetus, which will always be PI. In most bovine population the prevalence of PIs are estimated to be around 1%, although variation occurs (Houe, 1995).

Transmission

PI animals are the main source of infection within the infected herd, because they shed virus in very high concentrations in all bodily fluids throughout their life. Transiently infected animals may be a source of horizontal infection, and a few reports suggest that BVDV may persist in a herd in absence of PI animals (Moen *et al.*, 2005; Moerman *et al.*, 1993). However, because they shed comparably lower amounts of virus and only for a few days during acute infection (Brownlie *et al.*, 1987), their importance for viral transmission and persistence of the infection within the herd is limited (Lindberg and Houe, 2005; Niskanen *et al.*, 2002). The key role of the PI animal for within herd maintenance of infection is further supported by vast empirical evidence from the Scandinavian BVDV control schemes showing that virus circulation essentially stops as soon as the last PI animal is eliminated from the herd (Lindberg and Alenius, 1999).

The main route of spread of BVDV between herds is through trade or contact with infected animals, particularly PIs, or through trade with dams carrying PI foetuses (PI carriers). In addition, infection can be introduced to a susceptible herd by indirect means through the use of contaminated equipment or tools such as noose tongs, injectables, needles or rectal gloves (Lang-Ree *et al.*, 1994; Niskanen and Lindberg, 2003), or through the use of biological by-products produced using contaminated foetal bovine sera such as live vaccines (Barkema *et al.*, 2001; Falcone *et al.*, 1999), or through contaminated or infected embryos or semen (Givens and Waldrop, 2004). Wildlife reservoirs have been suggested as a possible source of transmission of BVDV (Anderson and Rowe, 1998; Pizarro-Lucero *et al.*, 2005), but even though persistent infections in non-bovine hosts have been confirmed (Pizarro-Lucero *et al.*, 2005; Vilcek *et al.*, 2000), the importance of this source is unclear (Lindberg and Houe, 2005; Walz *et al.*, 2010).

When a PI animal is born or introduced into a herd the infection will spread efficiently and result in transient infections in naïve in-contact animals. Seroconversion will occur resulting in natural immunity, which generally is considered lifelong (Lindberg and Houe, 2005). BVDV serology therefore provides a convenient means of monitoring introduction and infection of BVDV in previously free herds.

Self-clearance

Experiences from the Swedish BVDV control programme have shown that self-clearance, i.e. the process whereby an infection is eliminated from a population without intervention, is an important and frequent phenomenon that works in favour of BVDV control (Lindberg and Alenius, 1999), and this is supported by observations in studies from other parts of the world (Kampa *et al.*, 2008; Mainar-Jaime *et al.*, 2001; Ståhl *et al.*, 2008). Self-clearance occurs when PI animals do not succeed in establishing additional persistent infections before they are removed from the herd (due to death, trade or culling). The phenomenon is thought to be more frequent in smaller herds, as a result of quickly established herd immunity due to the efficient spread of virus from PI animals to the surrounding group, but also occur in larger herds possibly explained by an increased risk for early death in PI animals due to more intensive production and harder rearing conditions (Lindberg and Houe, 2005). Consequently, in any BVDV infected population (regardless of the herd-level BVDV seroprevalence), and at any given point of time, a large proportion of the herds will be free from infection due to self-clearance.

The general model of control

For long, attempts to control BVDV and reduce the losses were limited to prophylactic vaccination practices, implemented primarily to reduce or prevent clinical disease on a herd basis. However, the benefit of preventing clinical disease in transiently infected animals is negligible when considering the overall losses (Brock 2004). During the 1990s a systematic strategy to control BVDV, based on thorough knowledge of the epidemiology of the disease and therefore focused on prevention of foetal infection in early gestation, evolved within eradication programmes in the Scandinavian countries. This strategy, sometimes referred to as the general model of BVDV control, is based on the three central elements 1) biosecurity, to prevent introduction of infection into free herds; 2) elimination of PI animals in infected herds to reduce virus circulation; and 3) continuous monitoring of free herds for early detection of reinfection (Lindberg and Alenius, 1999).

Biosecurity

Biosecurity, in our experience, constitutes the most central element of BVDV control, which if implemented systematically, will lead to a reduction in BVDV prevalence without additional interventions due to self-clearance. In this context it refers to all measures that serve to prevent reinfection of free herds. Consequently, it not only includes essential measures taken on farm to prevent introduction of the virus, but also formal regulations put in place to break transmission between herds, i.e. to stop risky behaviour such as trade with PI animals or PI carriers (Lindberg *et al.*, 2006). A high level of awareness among farmers and other stakeholders is a prerequisite to ensure a necessary level of compliance, and a system whereby herds can be correctly identified and certified as BVDV free is needed. In the Scandinavian model certification of freedom is based on demonstration of absence of BVDV infection by repeated sampling with consistently low antibody or antibody-negative test results, employing herd-level tests (Lindberg and Alenius, 1999).

Elimination of PI animals in infected herds

The PI animal is the main source of virus and consequently the main target for control within infected herds. PIs are generally seronegative, which within the Swedish scheme has been used as a means of identification by individual serological testing followed by virus testing of seronegative individuals. This system not only serves to correctly identify the PIs, but also provides serological status on all individuals within the herd, including non-immune dams, which is the only group in which new PI foetuses

can be established to make the infection persist in the herd (Lindberg and Alenius, 1999). Other strategies for PI identification through direct virus detection, such as antigen testing of new born calves (using e.g. ear-notch samples) will not detect this important group.

Monitoring

Continuous monitoring of all herds is necessary to monitor programme progress, but even more to detect changes in BVDV status at an early stage, i.e. to ensure that herds certified as free remain free. In the Scandinavian schemes cost-efficient and sensitive monitoring has been achieved employing serological tests at the herd-level (Lindberg and Alenius, 1999).

The role of vaccination

Modern vaccination programmes are designed not only to prevent clinical disease, but also to protect against viremia and to prevent foetal infection, and several challenge studies indicate that inactivated as well as live vaccines may prevent foetal infection under controlled experimental conditions (Frey *et al.*, 2002; Meyer *et al.*, 2011; Patel *et al.*, 2002). However, the efficacy of these vaccines to protect foetuses against infection under field conditions have been questioned (O'Rourke, 2002), and field observations, where PI calves have been born in vaccinated herds, support this concern (Gaede *et al.*, 2004; Graham *et al.*, 2004; Van Campen *et al.*, 2000). And because 100% efficacy and coverage is needed to prevent the infection from being established, if it is introduced, vaccination has, despite the widespread use, failed to reduce the incidence and prevalence of BVDV (Lindberg and Houe, 2005), partly also explained by the often raised concern that vaccination may create a false sense of security, creating an opportunity for biosecurity breakdown.

In the context of systematic BVDV control, vaccination has been described as an optional element in areas where the risk of re-introduction into free herds is perceived as very high, but always as a complement to the three necessary elements (Moennig *et al.*, 2005a; Moennig *et al.*, 2005b). The value of this optional element, however, still remains to be assessed.

Molecular tracing- an additional valuable tool during BVDV control

Although the major routes of BVDV transmission are well known, cases of new infections appear in spite of strict biosecurity measures in areas with a systematic control. Within the Swedish BVDV scheme such cases are followed up through farmer interviews and questionnaires to identify risky behaviour (Lindberg and Alenius, 1999). Still, in our experience, in 40–50% of these cases where new infections are detected in previously free herds, the route of transmission remains unidentified. To tackle this problem molecular tracing, in which viral genome sequences are used for phylogenetic analysis to seek epidemiological relationship between old/existing and new cases, was introduced during the late phase of the Swedish programme (Ståhl *et al.*, 2005). Today, genome sequences for all strains isolated since late 2002 are available, which has provided a unique possibility to trace chains of infection and to survey the national BVDV situation. The approach has been valuable in many cases where suspected direct and indirect routes of transmission have been supported by the phylogenetic analysis, and equally important it has been possible to rule out suspected sources of infection. A similar approach has been implemented within the Swiss eradication programme (Stalder *et al.*, 2011).

The current situation in Europe

The model used within the Scandinavian BVDV control schemes has been very successful.

Despite different conditions at the start of the projects in terms of legal support, and regardless of initial prevalences of herds with PI animals, it took all countries approximately 10 years to reach their final stages (Hult and Lindberg, 2005; Nyberg *et al.*, 2004; Rikula *et al.*, 2005). Today, 5–6 years later, all of them are free, or almost free from BVDV. The number of reintroductions of infection into free herds has continuously decreased, limited to isolated cases during the last few years. To our knowledge, no cases have been reported from Finland or Norway, and only two from Denmark, one of which was due to import of a BVDV vaccinated PI carrier from a non-free country (Uttenthal, personal communication). In Sweden two cases were detected in 2010 and one in 2011, all due to direct or indirect contact with herds still under investigation, with suspected routes of transmission supported by molecular epidemiological investigations (Ståhl *et al.*, 2005).

Once proven that BVDV eradication could be achieved in a cost efficient way, a number of more or less sustainable regional programmes followed in Europe, such as in Lower Austria (Rossmanith *et al.*, 2005), on the Shetland Islands (Synge *et al.*, 1999), on Orkney (Truyers *et al.*, 2010), in Brittany in France (Joly *et al.*, 2005), and in Lower Saxony in Germany (Gaede *et al.*, 2004). In recent years some of these have developed into national schemes, and a number of additional European countries have followed.

Austria

Following the same approach as the Scandinavian forerunners, a regional programme was launched in Lower Austria in 1997. The programme which initially was voluntary was in 2004 made compulsory and extended to the entire country (Rossmanith *et al.*, 2010). The progress of the Austrian programme follows the timeline of the Scandinavian, and in 2008, eleven years after the start of the regional programme, 92% of all herds in Lower Austria were certified as free from BVDV, and the prevalence of herds with PI animals was estimated at 0.16% (Rossmanith *et al.*, 2010).

Switzerland

A national Swiss BVDV eradication campaign was launched in 2008 using an alternative approach. The compulsory programme is based on identification and elimination of PI animals through antigen testing of all newborn calves, without the use of serological testing (Presi *et al.*, 2011). The rationale behind the chosen approach was the very high initial seroprevalence, high cattle density and level of cattle movements, and the use of shared summer grazing in mountain pastures. In phase one- the eradication phase- all cattle in the country were sampled (ear-notch or blood) and tested for antigen. 1.5 million cattle were tested and more than 12 000 PI animals were detected, confirmed and eliminated. In phase two- the calf phase- all calves (≈ 700 000), which were in utero during the first testing, were tested within five days of birth, and around 5000 PI calves were detected and eliminated. The third phase—the surveillance phase—is ongoing and carried out in accordance with the principles used in phase two. To date, in less than 3 years around 3.5 million animals have been tested during the three phases, and the prevalence of PIs among newborn calves has decreased with 95% (Di Labio, 2011). A move from a costly and logistically challenging surveillance system using individual antigen testing of all newborn calves, to a long-term system using serological herd-level tests is foreseen to start during 2012.

Germany

Following a successful regional programme in Lower Saxony (Gaede *et al.*, 2004), a mandatory control scheme was introduced in all German states on January 1st 2011 (FLI, 2011). The programme is based on testing of all calves, with direct virus detection on ear-notch samples using ELISA or PCR. Confirmed PI animals should be eliminated within seven days, and movements of

PIs are prohibited. In contrast to other systematic BVDV control schemes in Europe, voluntary vaccination is being used as an additional biosecurity element. A two-step vaccination strategy systematically targeting seronegative cattle in BVDV free herds has been suggested. The strategy includes a first immunization with an inactivated vaccine followed by a second administration with a modified live virus vaccine four weeks later, and combines the advantages of inactivated and modified live vaccines and the disadvantages of both vaccines are minimised. (Moennig *et al.*, 2005a).

Scotland and Ireland

In Scotland a national control scheme was recently launched, following the regional programmes in the Shetland Islands and Orkney. A voluntary phase is currently ongoing in which financial support for testing of cattle in breeding herds is provided by the government. In a second and third phase, which will be compulsory, testing of all cattle herds will be required and movement restrictions will apply to herds infected with BVDV. Phase two and phase three will be introduced in late 2011 and late 2012, respectively (No author, 2011; Scottish Governement, 2011).

Also Ireland is aiming at BVDV eradication with a scheme scheduled to be launched in 2012. After a one year voluntary initial phase the compulsory phase is foreseen to be introduced in 2013. The scheme will initially target PI animals using direct virus detection on ear-notches (year 1–3) followed by a surveillance phase (Barrett *et al.*, 2011; Graham *et al.*, 2011).

Atypical pestiviruses

The general model and ongoing programmes are based on knowledge of epidemiology, transmission patterns, and genetic and antigenic diversity of the two widespread species BVDV-1 and -2. During the last few years however, atypical pestiviruses have emerged in various parts of the world (Cortez *et al.*, 2006; Decaro *et al.*, 2011; Schirrmeier *et al.*, 2004; Ståhl *et al.*, 2007) The risk for introduction into naïve animal populations of these "new" viruses, and implications for disease control and on ability of current diagnostic and vaccination strategies for early detection and prevention is unclear. Of particular concern in relation to BVDV control is the group of atypical bovine pestiviruses also referred to as HoBi-like or BVDV-3 (Decaro *et al.*, 2011; Liu *et al.*, 2009b; Schirrmeier *et al.*, 2004; Stalder *et al.*, 2005; Ståhl *et al.*, 2007), which are regularly detected in batches of foetal calf serum (FCS) of South American origin (Liu *et al.*, 2009a; Ståhl *et al.*, 2010). As FCS is used to produce vaccines and other biological products, the global trade with potentially infected FCS gives the potential for transboundary spread. In live cattle atypical bovine pestiviruses had, until recently, only been reported from Brazil and Thailand (Cortez *et al.*, 2006; Ståhl *et al.*, 2007), but this year (2011) an outbreak of severe respiratory disease in calves caused by an atypical bovine pestivirus was described in Italy (Decaro *et al.*, 2011). This first finding of atypical bovine pestiviruses in European cattle is of significant importance and confirms the concern that this group of viruses is widespread, and now established on at least three continents. Moreover it demonstrates, for the first time, that atypical pestiviruses are capable of causing disease, even death, in calves under field conditions, and possibly have consequences for ongoing BVDV control and eradication programmes.

Conclusion

It is now well established that area-wide BVDV control and eradication is possible, even in large and dense cattle populations. Comprehensive control concepts have evolved over the years, and diagnostic tools for large scale monitoring of herd status and for rapid identification of PI animals

are available. The success of the Scandinavian schemes has encouraged a number of regions and countries in EU, and several countries are now aiming at eradication. Systematic BVDV control, with biosecurity as a central part, will with no doubt significantly improve the general cattle health in EU during the years to come.

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