




Global knowledge gaps in the prevention and control of bovine viral diarrhoea (BVD) virus

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Abstract

The significant economic impacts of bovine viral diarrhoea (BVD) virus have prompted many countries worldwide to embark on regional or national BVD eradication programmes. Unlike other infectious diseases, BVD control is highly feasible in cattle production systems because the pathogenesis is well understood and there are effective tools to break the disease transmission cycle at the farm and industry levels. Coordinated control approaches typically involve directly testing populations for virus or serological screening of cattle herds to identify those with recent exposure to BVD, testing individual animals within affected herds to identify and eliminate persistently infected (PI) cattle, and implementing biosecurity measures such as double-fencing shared farm boundaries, vaccinating susceptible breeding cattle, improving visitor and equipment hygiene practices, and maintaining closed herds to prevent further disease transmission. As highlighted by the recent DISCONTTOOLS review conducted by a panel of internationally recognized experts, knowledge gaps in the control measures are primarily centred around the practical application of existing tools rather than the need for creation of new tools. Further research is required to: (a) determine the most cost effective and socially acceptable means of applying BVD control measures in different cattle production systems; (b) identify the most effective ways to build widespread support for implementing BVD control measures from the bottom-up through farmer engagement and from the top-down through national policy; and (c) to develop strategies to prevent the reintroduction of BVD into disease-free regions by managing the risks associated with the movements of animals, personnel and equipment. Stronger collaboration between epidemiologists, economists and social scientists will be essential for progressing efforts to eradicate BVD from more countries worldwide.

KEYWORDS

bovine viral diarrhoea virus, control, diagnostics, genetic diversity, pathogenesis, vaccination

1 | INTRODUCTION

Bovine viral diarrhoea (BVD) virus is an infectious disease of cattle that, in the absence of control programmes, is endemic in most cattle producing countries. The disease causes significant economic impacts to infected herds through its direct effects on reproductive performance, milk production and animal growth (Houe, 1999). The disease has also been associated with a period of immunosuppression in infected animals, resulting in increased susceptibility to secondary infections. In addition, a large proportion of persistently infected (PI) animals suffers from ill thrift and/or develop fatal mucosal disease highlighting the significant animal welfare implications. Further to this, in the absence of national control programmes, producers must bear the ongoing costs of preventative testing and vaccination if they want to reduce the production losses associated with BVD.

As part of the larger DISCONTTOOLS initiative to identify critical gaps in the current research knowledge for 52 animal diseases (O'Brien, Scudamore, Charlier, & Delavergne, 2016), an international panel of BVD experts, composed of members from academia, government institutes and industry, reviewed the existing scientific literature and identified research knowledge gaps that could help reduce the global burden of BVD. Following the recent DISCONTTOOLS supplement, where peer-reviewed papers on research gaps were produced for 15 infectious diseases in production animals (Charlier & Barkema, 2018), this manuscript provides a summary of key findings about BVD including (a) genetic diversity, (b) pathogenesis, (c) transmission, (d) diagnostic testing, (e) vaccination and (f) control. Within each section, both the existing knowledge, knowledge gaps and directions for future research are reviewed.

Despite the many socio-economic benefits of controlling BVD in cattle production systems (Piniór et al., 2017) and the availability of effective control measures (Lindberg & Alenius, 1999), only a small number of countries have so far attempted national BVD eradication (Ståhl & Alenius, 2012). This suggests problems in translating fundamental BVD science into real-world action against the disease. As such, this review finishes by discussing what further research is needed to benefit future BVD eradication approaches.

2 | GENETIC DIVERSITY

Bovine viral diarrhoea is a disease of cattle caused by one of three *Pestivirus* species; bovine viral diarrhoea virus 1 (BVDV-1), bovine viral diarrhoea virus 2 (BVDV-2) and HoBi-like virus (often referred to as BVDV-3 or bovine atypical pestivirus; Bauermann, Ridpath, Weiblen, & Flores, 2013). Belonging to the family *Flaviviridae*, bovine pestiviruses are single-stranded, enveloped RNA viruses similar to classical swine fever virus (CSFV) in pigs and border disease virus (BDV) in sheep. Phylogenetic analysis of the three bovine pestiviruses has further classified them into subgroups (sub-genotypes) and identified at least 21 BVDV-1 (1a–1u), three BVDV-2 and four HoBi-like subgroups (Jenckel et al., 2014; Yesilbag, Alpay, & Becher, 2017).

Bovine pestiviruses can exist as two biotypes; non-cytopathic (ncp) or cytopathic (cp). For TI animals, the immune response has been shown to differ following infection with cp and ncp bovine pestivirus strains, and that there is a faster and more efficient clearance of cp strains compared to ncp strains in these animals (Peterhans, Bachofen, Stalder, & Schweizer, 2010). However, irrespective of the pestivirus strain present, the ncp biotype has been shown to predominate in the field. In PI animals, mutation of the persisting ncp strain along with genomic insertion can occur, resulting in a population of mutated cp viruses. This leads to both the ncp and cp biotypes circulating in a PI animal and will result in the development of mucosal disease (MD), which is invariably lethal for the animal (Decaro et al., 2014; Peterhans & Schweizer, 2010; Peterhans et al., 2010).

Both ncp BVDV-1 and BVDV-2 have been isolated following outbreaks of severe transient disease associated with haemorrhage; however, severe transient disease has only been reproduced under controlled conditions with ncp BVDV-2 strains. It should be noted that highly virulent BVDV-2 strains are in the minority in nature and that the majority of BVDV-2 strains are no more virulent than the BVDV-1 or HoBi-like virus strains. The understanding of virulence factors and the difference in virulence between bovine pestiviruses are however, not yet fully understood.

How widespread each of the three bovine pestiviruses is in cattle populations has been shown to be invariably dependent on geographical location (Bauermann, Flores, & Ridpath, 2012). Both BVDV-1 and BVDV-2 have been identified as more geographically dispersed than the HoBi-like viruses, with BVDV-1 and BVDV-2 identified on all continents that support domestic or wild ruminant herds. The only exception to this is the apparent absence of BVDV-2 in Australia and New Zealand (Ridpath, Fulton, Kirkland, & Neill, 2010), which is thought to be due to the geographical isolation of both countries as well as their strict import restrictions. In comparison, HoBi-like viruses have, so far, only been reported in South America, Europe and Asia. Further to this, a high prevalence of these HoBi-like pestivirus has been identified in water buffalo from southern America, and has led to the hypothesis that this virus might primarily be a bubaline pathogen rather than a cattle pathogen (Bauermann et al., 2013).

While virus isolates from the main *Pestivirus* species, including BVDV, CSFV and BDV, exhibit considerable antigenic and biological diversity, several other emerging pestiviruses, originating from non-bovine species, have been described during recent years. These emerging pestiviruses include; “Antelope”, “Bungowanah”, “Giraffe”, “Aydin-like”, “Rat” and “Atypical porcine” pestiviruses (Smith et al., 2017). The host tropism of these emerging viruses has not been fully established and it is unknown if they can infect bovines and cause clinical presentations similar to those seen with BVD. Similarly, it is unknown at what rate bovine pestiviruses evolve and the impact different management factors and host species have on the evolution of bovine pestiviruses.

2.1 | Future research

Currently there is a limited understanding of the global distribution of bovine pestivirus strains and the reason behind the non-uniform

occurrence of genotypes. Systematic surveillance and characterization of pestiviruses at the global level should be carried out, with particular focus on areas that have been poorly investigated and that may have a major influence on other parts of the world, for example, due to export of foetal bovine serum (FBS) or semen. Furthermore, a greater understanding of virulence and the virulence factors associated with different *Pestivirus* species/subgroups is needed in order to fully understand the effect of infection on both the individual animal and within a population. It is also evident that there is a need for further investigation of the host tropism and clinical importance of recognized and emerging pestiviruses in both ruminant and non-ruminant species. This is essential as a means to identify the potential for reservoir populations of these pestiviruses, which could impact the effectiveness of current and future control efforts.

3 | PATHOGENESIS

Cattle of any age are susceptible to transient infections (TI) with bovine pestiviruses, as a result of horizontal transmission from infected animals or contaminated fomites (Thurmond, 2005). The incubation period of bovine *Pestiviruses*, upon infection, is between 6 and 12 days post-exposure but can fluctuate depending on the strain of the virus, its virulence and the virus dose transmitted (Evermann & Barrington, 2005). Once infected, TI animals shed low levels of virus in body secretions and excretions from days 3 to 15 post infection, although shedding has been shown to last for up to 3 weeks (Thurmond, 2005). Once TI animals are no longer infectious and viral shedding is complete, a serological antibody and T cell response is stimulated and confers lifelong immunity for TI animals against the infecting virus strain (Brodersen, 2014; Evermann & Barrington, 2005; Lanyon, Hill, Reichel, & Brownlie, 2014).

The clinical manifestation of transient BVD infections can be varied and is acknowledged to be dependent on the infecting viral strain as well as the age, immunological status and reproductive status of the animal when infected. Naïve calves and non-pregnant adult cattle transiently infected with BVD typically present with no or only mild clinical signs such as; fever, decreased appetite and diarrhoea (Grooms, 2004). However, transient infections also inhibit production and will almost always result in a decrease in milk production in adult cattle or a decrease in growth rates in infected calves and young stock. Naïve bulls that become transiently infected close to mating can also have reduced fertility and can serve as a reservoir of virus for naïve dams (Brock, Grooms, & Givens, 2005; Houe, 2005; Schweizer & Peterhans, 2014).

Transient BVD infections have been shown to cause a reduction in circulating white blood cells (WBC) between 3 and 14 days after infection (Bolin, McClurkin, & Coria, 1985; Liebler-Tenorio, Ridpath, & Neill, 2004). This reduction in WBC is associated with immunosuppression and the increased susceptibility of infected animals to secondary infections, such as mastitis and bovine respiratory disease complex (BRDC; Grissett, White, & Larson, 2015; Kapil, Walz, Wilkerson, & Minocha, 2005). Mortality as a result of transient BVD

infections is uncommon, however mortality rates exceeding 50% have been recorded in outbreaks with BVDV-2 strains which induce haemorrhagic syndrome (Gethmann et al., 2015; Pellerin, van den Hurk, Lecomte, & Tijssen, 1994). However, where BVD outbreaks occur in conjunction with secondary infections, as seen with bovine respiratory disease complex (BRDC), mortality rates have been shown to increase (Kapil et al., 2005). While it is understood that infections with BVD lead to an increased susceptibility to other infectious disease, the mechanisms associated with immune suppression and the pathogen synergy bovine pestiviruses have with other infectious pathogens is unclear and needs further investigation.

It is clear that transient BVD infections can have significant negative effects on production and immune function in infected animals. However, transient infection of naïve dams during pregnancy will result in more severe effects. The unique ability of pestiviruses to cross the placenta and infect the developing foetus has been shown to lead to a wide array of reproductive losses. When a dam becomes transiently infected prior to mating or during early gestation (0–100 days of gestation), infection can result in reduced conception rates and foetal loss, either as a result of early embryonic death, abortion or absorption (Pinior et al., 2017; Richter et al., 2017). While foetal death is most common with BVD infections which develop during early gestation, foetal death can occur at any time throughout pregnancy following transient infection of the dam (Grooms, 2004). When BVD infections develop during mid to late gestation (approximately 100–180 days of gestation), the birth of weak calves or calves born with significant congenital or physical malformations, such as ocular or cerebellar lesions and skeletal malformations are possible (Brownlie, 1990; Grooms, 2004) due to infection developing during the period of organogenesis. The extent of the malformations observed at birth is dependent upon which organ systems were developing at the time of foetal infection. Similarly, if the dam becomes infected prior to foetal immunocompetence (between 30 and 125 days of gestation) the calf develops innate and adaptive immunotolerance to the infecting BVDV strain and will be born persistently infected.

Persistently infected animals excrete large quantities of virus in most bodily fluids, throughout their lives and are, as a result, critical for the maintenance and circulation of bovine pestiviruses in the field. Persistently infected animals often present as weak and unthrifty calves but they can also appear clinically normal and healthy without obvious signs of illness, often making it hard to identify PI animals without the use of diagnostic testing. Persistently BVDV infected animals are predisposed to secondary infections due to reduced immune function, and tend to have significantly reduced growth and production performance compared to their peers (Kapil et al., 2005; Peterhans, Jungi, & Schweizer, 2003). As a result, the lifespan of PI animals is significantly shorter than other cattle due to their increased susceptibility to other diseases, the increased likelihood of culling due to poor performance or death due to mucosal disease, the result of co-infection with both the ncp and cp strains of the virus (Houe, 1992; Houe, 1993; Peterhans et al., 2010).

Although the impacts of BVD infection have been shown to be varied and in many instances, severe, the overall impact of bovine

pestiviruses from a production and welfare point of view is somehow still not clear. The effect of congenital infection on calf development (especially neuroinvasion and neuropathology) and production have not been well studied or quantified, particularly in regard to beef farming systems. Instead, most research has focussed on the influence of pestiviral infections on reproductive disorders and not on the overall economic losses in each of the different production systems.

In addition, it has been reported that many non-bovine species are susceptible to infections with BVDV-1, BVDV-2 and HoBi-like pestivirus. Antibodies to these viruses have been detected in several domestic non-bovine species, including sheep (Evans, Lanyon, Sims, & Reichel, 2015), goats (Bachofen et al., 2013), water buffalo (Evans, Cockcroft, & Reichel, 2016), camelids (Foster et al., 2005) and pigs (Tao et al., 2013). Similarly, persistently BVDV infections have been reported in sheep (Evans, Reichel, Hemmatzadeh, & Cockcroft, 2017), goats (Loken, Bjerkas, & Larsen, 1991) and alpaca (Carman et al., 2005). Experimental and natural infection of sheep and goats, with various BVDV subgroups, have reproduced reproductive and clinical outcomes resembling those induced by outbreaks of BVD in cattle (Decaro et al., 2015; Evans, Reichel, et al., 2017) and BDV in sheep (Nettleton, Gilray, Russo, & Dliissi, 1998). Despite the similarities in disease presentation in non-bovine hosts, the full extent of the impacts caused by bovine pestiviruses in these species is not yet fully understood. In particular, the risk posed by infections in these non-bovine species to cattle has yet to be quantified and is an important area of research considering the broadening global uptake of national eradication programmes for BVD.

3.1 | Future research

While many of the large scale implications relating to bovine pestivirus infections in cattle are understood, further research into the virus life cycle including the involvement of tissue-specific host cell factors, and the role of the innate and cellular immunity in the defence against all biotypes of bovine pestiviruses, for example, Hobi-like virus, are required. Such studies are fundamental in order to understand aspects such as the mechanism and extent of immunopathogenesis and immunosuppression in infected animals, the role of neutralizing antibodies versus cell-mediated immunity in foetal protection, virus transmission and species specificity, to name a few. Finally, longitudinal studies on the effect of production in endemically infected herds are needed, both on an individual and population level. The focus of these studies should incorporate not only the reproductive effects but also the effects of transient and foetal infections with bovine pestiviruses on general calf and herd health for both dairy and beef farming systems.

4 | TRANSMISSION

The persistence and spread of BVD in a population (herd) can be achieved through either horizontal or vertical transmission.

Persistently infected animals have long been regarded as the major reservoir of bovine pestiviruses since they shed large quantities of virus through almost all bodily excretions and secretions, for the entirety of their lives (Van Campen & Frolich, 2001). Horizontal transmission from PIs to seronegative, susceptible cattle has been shown to occur readily, both under field and experimental conditions (Fulton et al., 2005; Houe, 1999; Lindberg & Alenius, 1999). In fact, infection of susceptible cattle has been reported to develop only after 1 hr of contact with a PI (Tråvén, Alenius, Fossum, & Larsson, 1991). Persistently infected animals of any age are considered highly infectious carriers of virus, however it has been hypothesized that the presence of maternal antibodies, through colostral ingestion, may temporarily reduce the viral shedding rates of PI calves during the first few months of life (Meyling, Houe, & Jensen, 1990). It has been reported that the presence of maternal antibodies in PI animals can inhibit the accurate detection of young PI animals, referred to as the "colostral antibody gap" (Fux & Wolf, 2012), however to what extent maternal antibodies have on the viral load and subsequent infectivity of PI animals remains unknown.

Vertical transmission of BVD occurs when bovine pestiviruses infect susceptible, pregnant females and the virus crosses the placenta, establishing infection within the developing foetus. When vertical transmission occurs prior to 125 days of gestation then a PI calf can develop. Pregnant dams carrying PI calves are often referred to as "Trojan Dams" and currently, the identification of these cows is difficult (Lindberg, Groenendaal, Alenius, & Emanuelson, 2001). There is limited information available on the contribution of Trojan dams on the spread of infection between herds, but one study has indicated that they may account for approximately 10% of PI births in the absence of effective control measures (Reardon et al., 2018).

Situations that favour the spread of bovine pestiviruses between herds include: animal trade (purchase of PIs or Trojan Dams), common pasturing (including cattle and domestic small ruminants), grouping of animals from different sources (such as in sale barns and feedlots), contact between domestic and wild species and other cattle management strategies that increases the likelihood of between-herd contacts. The risk of pestivirus transmission through shared grazing and calving lands is largely unknown although essential to understand. This is of particular importance for the many European countries which have implemented control or eradication programmes for BVD but where shared grazing is a common management practice for cattle and small ruminants, potentially leading to transmission within or between species.

Bovine pestiviruses have also been shown to spread due to indirect contact with infected animals through contaminated bedding, fomites, equipment, machinery and personnel including veterinarians (Gunn, 1993; Moen, Sol, & Sampimon, 2005; Niskanen & Lindberg, 2003), the use of contaminated biological products such as semen, vaccines or FBS and non-bovine reservoir hosts. There is very little information available regarding the contamination rates of personnel, vehicles and equipment after visiting BVD positive farms. However, survival of these viruses even for a short period outside the host suggests that fomites are a potential source of transmission that

need further attention. There is limited evidence to suggest that vectors, such as flies and other biting insects, play a significant role in the passive transmission of BVD viruses (Chamorro et al., 2011; Gunn, 1993). The prolonged survival of bovine pestiviruses in the environment and on equipment/clothing is largely unknown although previous work suggests these viruses can survive in the environment anywhere from 3 days to 3 weeks (Botner & Belsham, 2012; Niskanen & Lindberg, 2003), but are dependent on environmental factors, such as temperature (Niskanen & Lindberg, 2003). Understanding what conditions favour survival of bovine pestiviruses, and for how long they can survive outside of a host, will help in understanding the risk of indirect sources to the spread of BVD within and between herds.

While PI animals are considered the major source of infection in a herd, TI cattle are also, for a short period of time, infective to susceptible individuals. The length of time TI animals are infectious can vary based on the health, stress level and age of the animal as well as the presence of other pathogens (Castrucci, Ferrari, Traldi, & Tartaglione, 1992; Fulton et al., 2000; Richer, Marois, & Lamontagne, 1988). However, it has been reported that TI animals may typically shed low-levels of virus. Despite the short duration for viral excretion in TI animals, it has been reported that it may be sufficient at sustaining infection within a herd in the absence of a PI animal (Collins, Heaney, Thomas, & Brownlie, 2009; Moen et al., 2005) although other experimental studies do not support this (Nickell, White, Larson, Renter, & Sanderson, 2011; Niskanen, Lindberg, & Traven, 2002; Sarrazin et al., 2014). Outbreaks of BVD pestiviruses have also occurred due to the persistence of the virus in the reproductive organs, ovaries and testes, of TI animals (Collins et al., 2009; Niskanen, Alenius, et al., 2002; Strong et al., 2015). While the risk of transmission by TI animals is considered much lower than the risk posed by PI animals, the full extent of viral shedding and persistence of virus in TIs and their ability to maintain infection within a population needs further investigation.

4.1 | Future research

While the main sources of horizontal and vertical transmission of bovine pestiviruses are generally well understood there are a number of other potential sources which need further clarification. This includes further research into the environmental stability of each of the viruses under different conditions (e.g., temperature, humidity, matrix) and their survival outside of the host. This is essential in understanding the role of fomites on the spread of these viruses to susceptible hosts as well as when trying to convince farmers and veterinarians on the importance of implementing good biosecurity measures.

Semen from infected cattle, frozen colostrum, transplanted embryos, contaminated live vaccines and cell lines and other biologicals products using contaminated FBS have been identified as possible transmission sources (Falcone et al., 2003; Gregg et al., 2009; Makoschey, van Gelder, Keijsers, & Goovaerts, 2003). The general use of contaminated biological products is primarily a risk factor for long distance/high impact transmission rather than within herd spread. Currently, however, the only restriction on biological

products is the ban on trading BVD contaminated semen from infected bulls. Further work is also required in the use of contaminated FBS in vaccines and reproductive technologies and highlighting the threat posed by contaminated biological products on the spread of these viruses to cleared herds and countries.

Lastly, the detection of bovine pestiviruses in several domestic and wild ungulates raises questions as to whether non-bovine ruminants are incidental hosts, or reservoirs of these viruses (Nelson, Duprau, Wolff, & Evermann, 2016). Recent preliminary work on the transmission of BVD from infected sheep, both PI and TI, has reported transmission to be poor (Evans, Hemmatzadeh, Reichel, & Cockcroft, 2018; Evans, Moffat, Hemmatzadeh, & Cockcroft, 2017), however further work is needed in this field. Understanding the epidemiological importance of non-bovine hosts in the spread of bovine pestiviruses is essential, particularly in countries where co-grazing of cattle and other susceptible species is common or those that have large populations of wild ruminants (i.e., Australia and some European countries).

5 | DIAGNOSTIC TESTING

Effectively differentiating between animals that are susceptible to infection, undergoing TI, recovered from TI or PI is critical in the management and control of bovine pestiviruses. Current diagnostic testing for bovine pestiviruses is used to identify either virus-specific antibodies (Ab), virus-specific antigen (Ag), RNA or the virus itself (Saliki & Dubovi, 2004).

5.1 | Antibody testing

Virus-specific antibody testing is predominantly used to distinguish between animals which have previously been exposed to the virus (or viral antigens in the case of inactivated vaccines) and have circulating antibodies, and animals which are naïve, and consequently susceptible to infection. In control programs, antibody testing is commonly used as a screening tool for herds to identify those which have been exposed and those which are naïve. Diagnostic tests for identifying Abs to bovine pestiviruses include enzyme linked immunosorbent assay (ELISA), virus neutralization test (VNT) or, less often, agarose gel immunodiffusion (AGID) and indirect immunofluorescent test (IFAT).

Testing by VNT has long been considered the gold standard for bovine pestivirus Ab detection due to its ability to differentiate between pestivirus species based on the results of cross-neutralization testing. However, VNT requires that research reagents and cells be screened and remain free of pestivirus contamination and is time consuming and expensive to run. In comparison, blocking or indirect ELISAs have become more commercially available and are now routinely used due to being highly sensitive/specific and their ability to process large numbers. Antibody ELISAs have been validated for use on serum, plasma and milk samples, either individual or pooled. However, variation in cross-reactivity across *pestivirus* species (Bauermaier et al., 2012) can affect sensitivity and ELISAs cannot

differentiate between vaccinated and naturally derived antibodies. In comparison the AGID has been reported to differentiate between vaccinated and natural antibodies (Kirkland & Mackintosh, 2006) although, similar to VNT, it is more time consuming to run and requires more infrastructure than the ELISA. Currently the use of AGID, VNT and IFAT is limited and they are rapidly being replaced by the Ab ELISA.

Individuals that test negative for antibodies to BVD, and related pestiviruses, are often considered naïve and susceptible to BVD infections. However, animals which are persistently infected with BVD will typically also test negative for BVD-specific Abs. Similarly, animals which test positive for antibodies are generally considered not to be PI. However, Abs to BVD will be detected in young PI animals which acquired colostral Abs, or in PI animals which have been exposed to a bovine pestivirus that is sufficiently heterologous from the one that caused the original persistent infection (Fulton et al., 2003). As such, caution needs to be taken when interpreting individual Ab results from actively infected herds and, in circumstances other than for surveillance of herds, Ab testing should be used in conjunction with Ag or virus testing.

5.2 | Antigen/virus testing

Identifying animals persistently infected with bovine pestiviruses is achieved by testing for viral antigen, RNA or the infecting virus itself. Virus isolation (VI) has long been considered the gold standard in this area and can be undertaken on a wide range of biological samples, most commonly whole blood, serum, buffy coat and spleen, however, due to the cost, time requirements and levels of expertise needed to perform VI, it is rarely used in surveillance programmes. Methods more commonly used in these situations include antigen capture ELISAs (ACE) which can be used to test blood, milk and tissue samples, real-time polymerase chain reaction (RT-PCR) used to test blood, milk, semen and tissue samples and immunohistochemistry used to test fixed tissue samples such as ear notches.

A positive virus or viral antigen result typically signifies that an animal is persistently infected; however, TI animals undergo a short period of viral excretion approximately 4–15 days after infection and during this time may also test positive for virus. In order to be able to accurately differentiate between TI and PI animals, repeated testing is necessary. A second positive result, at least 3 weeks after initial testing will confirm persistent infection. While animals which test positive on post-mortem or on submitted tissue samples are more likely to be PI rather than TI, no viral based test, based on a single sample, can be absolutely relied upon to differentiate between persistent and transient infection (Bauermann et al., 2014; Fulton et al., 2006; Hilbe et al., 2007) and as such re-testing is recommended, particularly in test-and-cull situations.

5.3 | Future research

Many of today's surveillance programmes use pooled sampling or representative individual sampling from a population, instead of

testing each individual animal on a property, as a means to reduce costs. Often, surveillance programmes for dairy herds are based on Ab or PCR testing of bulk milk tank samples as these samples can be easily collected, and are an effective method of screening all animals in the milking herd at once and has been shown to have a positive correlation with the infection status of the herd (Lanyon, McCoy, Bergman, & Reichel, 2014). However, while the pooling of samples has been employed in many testing programmes in an effort to lower test costs, pooling has been shown to reduce the sensitivity of the diagnostic tests used. Similarly, the thresholds used by laboratories to classify a herd as negative, exposed or actively infected can also influence the sensitivity and specificity of diagnostic tests to accurately identify a herd's infection status. Reduced sensitivity, when using pooled samples, increases the risk of false negatives due to the dilution of positive samples, as a result of negative and positive samples combined in pools, and needs to be factored in when designing surveillance programmes (Munoz-Zanzi, Thurmond, Hietala, & Johnson, 2006). Further work on the use of pooled samples for surveillance testing, particularly in regard to improving testing protocols for beef herds or where bulk milk tank samples are not available, is needed.

In addition, one major source for the introduction of BVD into a naïve herd is through the purchase of "Trojan Dams", seropositive dams carrying PI foetuses. To date there is no test, that does not require the collection of foetal tissue or amniotic fluid, which is able to identify Trojan animals from other TI or recovered individuals. Further work needs to be undertaken to determine a means of identifying Trojan Dams prior to the birth of a PI calf. Trojan Dams are important in the spread and persistence of BVD and being able to accurately identify PI calves prior to birth will provide significant improvements to control efforts.

Finally, many of the commercially available diagnostic tests are unable to differentiate between BVDV-1, BVDV-2 and HoBi-like viruses. From an epidemiological standpoint the development of a diagnostic test that is able to distinguish between different viral species would be useful. However, since the goal of eradication efforts was to eliminate all PI animals, regardless of the infecting species or strain, the development of a single test that can identify animals infected with all bovine *Pestivirus* species and subgroups would be more beneficial, cost effective for eradication efforts.

6 | VACCINATION

Current BVD vaccines are prepared using conventional cell lines and are based on BVDV-1 and BVDV-2 strains as, to the authors knowledge, there are no vaccines licensed for the prevention of infection with HoBi-like viruses. Both modified live vaccines (MLV) and inactivated vaccines are available globally, although the use of vaccines in some countries is not licensed in order to avoid interference with serological testing (i.e., Sweden, Norway, Denmark, Austria and Switzerland). Recently a new live double deleted vaccine has been approved in both the EU and non-EU countries, which can be used

at any stage of pregnancy irrespective of vaccination history, and covers both BVDV species (EMA (2015) Bovela EPAR safety document).

Vaccines against BVD viruses are used as a means to (a) protect susceptible animals from transient infections and (b) protect the foetus from infection and prevent the development of PI animals. As such, many current vaccination programmes only vaccinate replacement breeding cattle with a two-step vaccination protocol (Moennig et al., 2005). However, it has recently been shown that vaccinating calves against BVD can result in markedly different immune responses and improved growth rates compared to unvaccinated calves which are exposed to PI cattle (Grooms, Brock, Bolin, Groteleschen, & Cortese, 2014). These findings suggest that susceptible cattle of both young and breeding age should be vaccinated against BVD as a means to managing the production and reproductive losses associated with transient BVD infections.

While non-systematic vaccination strategies are widely used there is currently no proof that these programs result in a sustainable decrease in disease prevalence or clinical impact. This lack of data highlights that there are clearly many issues with the currently available vaccine options. Firstly, it has been reported that foetal protection is not 100%, despite this being the major driving factor for many vaccination programmes. The ability of bovine pestiviruses to cross the placenta and cause reproductive disorders in the foetus is a major mechanism of pathogenicity for these viruses; however, the action of neutralizing antibodies versus cell-mediated immunity in foetal protection is not well understood. Increasing our understanding of these mechanisms for foetal protection is critical in producing vaccines effective in preventing the production of PI animals. Secondly, it is not known what level of cross protection there is between BVD species and subgroups when using current BVD vaccines, an issue which has been raised in geographical areas where multiple circulating strains and subgroups are present. Lastly, there is a significant confusion relating to the application of vaccines and which groups of cattle to vaccinate. Should farmers vaccinate all animals or just breeding groups? Finding a cost effective and efficient approach to vaccination use is critical.

Misunderstandings surrounding the effects and transmission potential of BVD have led to many farms implementing “natural vaccination”, a questionable method for protecting herds against BVD. This is where PI animals are left in the herd to act as “natural vaccinators” whereby they cause transient infections to develop in susceptible cattle so that they develop a natural and lifelong immunity to BVD. This method of protecting against BVD is considered an inferior option to vaccination for several reasons. Firstly, not all susceptible animals may be exposed to the virus prior to the breeding season, this puts animals at risk of producing PI calves thus allowing the virus to persist within the herd. Secondly, TI animals still experience production losses such as decreased milk yields, slower growth rates and suppressed immune function. Thirdly, natural vaccination requires the deliberate retention of a PI animal in the herd which is often unable to be fully isolated from pregnant animals, resulting in the accidental establishment of further PIs. Fourthly, PI animals have the propensity

to die and makes it a poor long-term control strategy. Finally, BVD is an immunosuppressive virus, and “natural vaccination” does not induce the same level of humoral and cell-mediated immunity which can be reached through vaccination, in particular with newly developed vaccines (Platt, Kesl, Guidarini, Wang, & Roth, 2017).

6.1 | Future research

While vaccination is common in many BVD management programmes, both at the herd and national level, it is not effective in controlling bovine pestiviruses alone. Vaccination has to be performed in conjunction with testing, culling of PI animals and improving biosecurity protocols in order to have the optimum impact. Therefore, for vaccination to be a stronger contributor to control efforts further work needs to be undertaken in a number of areas. However, herds that are using vaccination as part of their control efforts are unable to use less expensive antibody-based screening tests, since current antibody tests are unable to differentiate between naturally acquired antibodies and those as a result of vaccination. Therefore, there is a need to better understand how vaccination and herd screening tests can be optimally combined in future control efforts. A better understanding of the transplacental transmission of ncp BVD viruses would be beneficial in order to improve the efficacy of foetal protection of vaccines. Identifying and producing vaccines which are capable of protecting cattle from multiple strains and subgroups of BVD viruses are critical due to many geographical regions having more than one circulating strain present. Finally, the production of DIVA vaccines and serological assays which can differentiate between vaccine-induced antibodies and naturally occurring antibodies is critical, particularly due to the essential and ongoing screening of herds in the final stages of any control programme.

7 | CONTROL

Bovine viral diarrhoea has been placed on the OIE's list of notifiable diseases, mainly as a result of its potential for international spread. While there are currently no formal reporting requirements for BVD, countries with national or regional control programmes may have certain regulations for affiliated farmers that effectively restrict trade with animals of positive suspect or unknown BVD status (Marschik et al., 2018). In addition, international trade regulations have been made in many countries surrounding artificial insemination (AI) stations and semen from bulls (Council Directive 88/407/EEC).

The cost of BVD virus infections has been estimated up to 680 US dollar (USD) per animal in an infected herd (Houe, 2003). Richter et al. showed that the BVD production losses between and within countries were largely heterogeneous with respect to the monetary level and type of losses. Extent of infection, clinical outcomes present, mortality, morbidity, premature culling, stillbirth, abortion and reinfection had a significant influence on the monetary level of production losses. As a result of the significant financial impact of BVD on cattle producers, many countries including Norway, Sweden,

Denmark, Finland, Austria, Switzerland, Ireland, Scotland, England, Wales, Germany Northern Ireland, Belgium, the Netherlands and the US (such as those in Colorado, Alabama, Georgia, Mississippi, Montana, Oregon, Washington, New York and the Upper Peninsula of Michigan) have implemented compulsory or voluntary programmes aimed at controlling or eradicating BVD.

The fundamental principle of any BVD control and eradication programme is to reduce the prevalence of PI animals in a population and prevent the creation of new PI animals. This can be achieved by; (a) Test-and-Cull, to identify and remove PI animals; (b) Improvements to Biosecurity, to reduce virus transmission in to a population and/or (c) Vaccination, to protect the foetus from infection and thus reduce PI development (Lindberg et al., 2006). The degree with which the disease is reduced is different for control compared to eradication (Houe, Lindberg, & Moennig, 2006). Control programmes aim to reduce disease prevalence to a relatively low and manageable level while eradication programmes aim to provide a continued absence of the disease in the population (Houe et al., 2006). Both goals, in regard to BVD, have been shown to be achievable (Scharnböck et al., 2018) and can be undertaken either at the national, regional or individual farm level.

Controlling BVD at the farm level would ideally result in the use of a closed herd policy including the strict control of semen (and embryos in herds where embryo transfer is used). The effectiveness of a closed herd policy will depend on the prevalence of the virus in the surrounding areas and livestock market, as well as the compliance of the farm with biosecurity measures such as sourcing animals from herds confirmed to be free from BVD or pre-purchase testing. Where a closed herd policy is unachievable, additional bioexclusion measures, to prevent introduction by other direct (purchased PI animals, dams carrying PI foetuses or transiently infected animals) or indirect transmission pathways (e.g. boundary contacts, personnel) are required. This can include double-fencing on boundary fences, quarantining newly purchased animals and the cleaning of equipment and vehicles shared across properties. Although the testing of newly purchased animals, for BVD, is a good practice it is unable to identify dams carrying PI foetuses. As such, the introduction of pregnant animals of unknown BVD status is best avoided. Vaccination can be used in conjunction with improvements to biosecurity to further protect breeding animals from infection prior to or during pregnancy, and reduce the potential for PI development.

An overview of the currently implemented BVD control efforts, worldwide, is provided on the OIE website (OIE, 2012). In addition, a study by Scharnböck et al. (2018) shows the worldwide distribution of BVD during the last 45 years within and between countries at national, regional and farm level and highlights the decreased of PI, TI, and Ab prevalences during the period. The highest BVD prevalences were identified in countries that had failed to implement any BVD intervention programmes (including vaccination; Scharnböck et al., 2018). However, despite the different pre-conditions of countries, in terms of initial prevalence, herd density, regulatory support, the success of worldwide BVD control and/or eradication programmes, reduction in the overall prevalence of BVD was evident.

The success of BVD programmes has prompted some countries to change from BVD control/eradication programmes to surveillance testing strategies (Marschik et al., 2018). Nonetheless, discontinuation of control efforts should be treated with caution as a seronegative cattle population will be fully susceptible to BVD virus and thus the movement of untested livestock needs to be controlled (Scharnböck et al., 2018).

7.1 | Future research

At the individual herd level there is a need to identify the most cost-effective diagnostic test and management strategies for individual herds, or herd types, and compare this to the resulting increase in complexity of programme management. These studies should include evaluation of the efficacy/cost-efficiency of different vaccines and vaccination strategies and tailor on-farm biosecurity recommendations to the disease risks identified on that farm.

There is also a need to identify the cost-benefit association of different BVD control/eradication programme types at the national level. Identifying how BVD control improved other areas of animal health and management, such as productivity, reduced calf mortality, morbidity and antimicrobial usage, should be addressed. The impact of BVD targeted biosecurity measures on other diseases and animal health issues should also be identified and quantified. Similarly, reports on control methods that were successful, as well as those which hindered control efforts, and why, need to be made publicly available in order to assist future BVD control efforts in countries yet to implement such programmes. Furthermore, the impact of controls on trade, both within and between countries, should be evaluated.

The development of a formal means to review and compare the success rates for different control/eradication strategies over time, both including and excluding the use of vaccination strategies, would be beneficial. There is also a need for more case-control studies to measure the benefits and costs of intervention activities (Burgstaller et al., 2016), although the challenge of separating the impact of BVDV from other concurrent animal health issues is recognized.

There is also a need for well-designed socio-economic studies to be undertaken in order to better understand farmers' behavioural motivation (including attitude to risk taking) to (a) adopt BVD control voluntarily at the individual herd level and (b) comply with mandatory national legislation. These studies also need to consider factors which drive or constrain other stakeholder groups, such as industry bodies, to adopt BVD control strategies particularly when progressing to national-level control. There is a further need to reassess these factors several years after the start of eradication programmes to investigate and accommodate changes in attitudes, beliefs, and practices over time.

8 | DISCUSSION

As highlighted by this review, the main knowledge gaps in the control of BVD worldwide relates to the application of existing tools

rather than the development of new tools. Currently the diagnostic tests available for BVD have excellent performance for identifying existing PI cattle despite there being no reliable tests to identify Trojan dams. However, the risks posed by Trojan Dams can be managed (a) by testing calves shortly after birth and (b) using vaccination as a means to prevent the creation of new PI calves in situations where the risk of BVD exposure during pregnancy cannot be eliminated. As such, it is not unreasonable to expect to eliminate PI animals from a herd in only 1–2 years.

However, the implementation of national BVD control programmes requires a significant amount of infrastructure including centralized national animal demographic databases that are capable of recording the identity of individual animals and farms as well as animal movement patterns between farms and linking with diagnostic laboratory testing databases in order to maintain accurate records of animal and herd BVD status (Tratalos, Graham, & More, 2017). Previous studies have shown that in some countries there are issues with the quality and completeness of national animal demographic databases particularly with movements to and from temporary grazing locations (Büttner, Salau, & Krieter, 2018; Green & Kao, 2007; Jewell, van Andel, Vink, & McFadden, 2016; Vernon, Webb, & Heath, 2010). There are also known issues with linking diagnostic laboratory testing data together because of poor quality identification data provided by veterinarians on the submission forms as well as differences in how the laboratories report testing results (Driskell & Ridpath, 2006). Without complete data, it becomes difficult to perform accurate contact tracing in low prevalence situations. Molecular epidemiology has recently emerged as a promising tool for investigating transmission pathways, by comparing the genetic relatedness of BVD strains isolated from infected farms (Stahl et al., 2005; Stalder et al., 2016), however is yet to be including in National BVD control efforts.

Another critical factor for achieving national BVD eradication is the lack of awareness about the disease and the economic losses associated with infection because the clinical signs are non-specific and farms may not experience as significant production losses in endemically infected herds. It can therefore be difficult to convince producers of the economic benefits of eradicating BVD, especially if they are asked to bear the costs of implementing BVD control programmes in their herds as part of a nationally regulated programme. Even if farmers are technically required to control BVD by law, it is still important to have good relationships with regulatory authorities to ensure that in addition to complying with testing requirements, good practices are being followed on farm such as administering vaccinations using approved protocols, improving herd biosecurity to prevent inward or outward BVD transmission, and accurately reporting animal movements. There is also a strong need for further research into how these protocols can be communicated to animal health decision-makers on farm in a manner which may improve the likelihood of appropriate uptake.

Although there are currently no restrictions on international trade based on BVD status, this may become a greater issue as more and more countries achieve disease freedom. The risks from live

animal trade can be virtually eliminated by conducting pre-export screening to prevent movements of PI animals or animals that may be carrying a PI calf as well as implementing post-import quarantine to monitor closely for transient infections. There is also a substantial global trade of biological products like vaccines, semen, embryos, bovine cell lines, and biologics derived from bovine foetal serum, which could pose a significant risk to the re-introduction of BVD into a previously cleared country. Given that the economic consequences of an outbreak in a completely immunologically naïve population could be devastating, there is a need to conduct more formal risk analyses to determine how best to manage these products.

9 | CONCLUSION

As evidenced by the many successful regional and national BVD control and eradication programmes already implemented throughout Europe, it is clear that there is a technical capacity to permanently eradicate BVD from cattle populations worldwide. The primary challenges remain (a) determining the most cost effective and socially acceptable means of applying BVD control measures in each unique cattle production system at both the farm level and industry level, (b) building support to implement BVD control measures from the bottom-up through farmer engagement and from the top-down through national policy, and (c) preventing the re-introduction of BVD into disease-free regions by strategically managing the risks associated with the movements of animals, personnel, and equipment. Stronger collaboration between epidemiologists, virologists, economists, and social scientists will be required to fill in these research knowledge gaps for each country considering national BVD eradication programme.

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CONFLICT OF INTEREST

There are no conflicts of interest.

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REFERENCES

- Bachofen, C., Vogt, H. R., Stalder, H., Mathys, T., Zanoni, R., Hilbe, M., ... Peterhans, E. (2013). Persistent infections after natural transmission of bovine viral diarrhoea virus from cattle to goats among goats.

- Veterinary Research*, 44, 32–42. <https://doi.org/10.1186/1297-9716-44-32>
- Bauermann, F. V., Falkenberg, S. M., Ley, B. V., Decaro, N., Brodersen, B. W., Harmon, A., ... Ridpath, J. F. (2014). Generation of calves persistently infected with HoBi-like pestivirus and comparison of methods for detection of these persistent infections. *Journal of Clinical Microbiology*, 52, 3845–3852. <https://doi.org/10.1128/jcm.01563-14>
- Bauermann, F. V., Flores, E. F., & Ridpath, J. F. (2012). Antigenic relationships between Bovine viral diarrhoea virus 1 and 2 and HoBi virus: Possible impacts on diagnosis and control. *Journal of Veterinary Diagnostic Investigation*, 24, 253–261. <https://doi.org/10.1177/1040638711435144>
- Bauermann, F. V., Ridpath, J. F., Weiblen, R., & Flores, E. F. (2013). HoBi-like viruses: An emerging group of pestiviruses. *Journal of Veterinary Diagnostic Investigation*, 25, 6–15. <https://doi.org/10.1177/1040638712473103>
- Bolin, S. R., McClurkin, A. W., & Coria, M. F. (1985). Effects of bovine viral diarrhoea virus on the percentages and absolute numbers of circulating B and T lymphocytes in cattle. *American journal of veterinary research*, 46, 884–886.
- Botner, A., & Belsham, G. J. (2012). Virus survival in slurry: Analysis of the stability of foot-and-mouth disease, classical swine fever, bovine viral diarrhoea and swine influenza viruses. *Veterinary Microbiology*, 157, 41–49. <https://doi.org/10.1016/j.vetmic.2011.12.010>
- Brock, K. V., Grooms, D. L., & Givens, M. D. (2005). Reproductive disease and persistent infections. In S. M. Goyal, & J. F. Ridpath (Eds.), *Bovine viral diarrhoea virus: Diagnosis, management and control* (pp. 145–156). Ames, IA: Blackwell Publishing. <https://doi.org/10.1002/9780470344453>
- Brodersen, B. W. (2014). Bovine viral diarrhoea virus infections: Manifestations of infection and recent advances in understanding pathogenesis and control. *Veterinary pathology*, 51, 453–464. <https://doi.org/10.1177/0300985813520250>
- Brownlie, J. (1990). The pathogenesis of bovine virus diarrhoea virus infections. *Revue scientifique et technique*, 9, 43–59. <https://doi.org/10.20506/rst.9.1.491>
- Burgstaller, J., Obritzhauser, W., Kuchling, S., Kopacka, I., Pinior, B., & Kofer, J. (2016). The effect of bovine viral diarrhoea virus on fertility in dairy cows: Two case-control studies in the province of Styria, Austria. *Berliner und Munchener Tierarztliche Wochenschrift*, 129, 103–110.
- Büttner, K., Salau, J., & Krieter, J. (2018). Effects of data quality in an animal trade network and their impact on centrality parameters. *Social Networks*, 54, 73–81. <https://doi.org/10.1016/j.socnet.2018.01.001>
- Carman, S., Carr, N., DeLay, J., Baxi, M., Deregt, D., & Hazlett, M. (2005). Bovine viral diarrhoea virus in alpaca: Abortion and persistent infection. *Journal of Veterinary Diagnostic Investigation*, 17, 589–593. <https://doi.org/10.1177/104063870501700613>
- Castrucci, G., Ferrari, M., Traldi, V., & Tartaglione, E. (1992). Effects in calves of mixed infections with bovine viral diarrhoea virus and several other bovine viruses. *Comparative Immunology, Microbiology and Infectious Diseases*, 15, 261–270. [https://doi.org/10.1016/0147-9571\(92\)90005-C](https://doi.org/10.1016/0147-9571(92)90005-C)
- Chamorro, M. F., Passler, T., Givens, M. D., Edmondson, M. A., Wolfe, D. F., & Walz, P. H. (2011). Evaluation of transmission of bovine viral diarrhoea virus (BVDV) between persistently infected and naive cattle by the horn fly (*Haematobia irritans*). *Veterinary Research Communications*, 35, 123–129. <https://doi.org/10.1007/s11259-010-9453-7>
- Charlier, J., & Barkema, H. W. (2018). DISCONTTOOLS supplement: Current research gaps for advancing control of infectious diseases in production animals. *Transboundary and Emerging Diseases*, 65, 5–8. <https://doi.org/10.1111/tbed.12878>
- Collins, M. E., Heaney, J., Thomas, C. J., & Brownlie, J. (2009). Infectivity of pestivirus following persistence of acute infection. *Veterinary Microbiology*, 138, 289–296. <https://doi.org/10.1016/j.vetmic.2009.04.022>
- Decaro, N., Lanave, G., Lucente, M. S., Mari, V., Varello, K., Losurdo, M., ... Buonavoglia, C. (2014). Mucosal disease-like syndrome in a calf persistently infected by Hobi-like pestivirus. *Journal of Clinical Microbiology*, 52, 2946–2954. <https://doi.org/10.1128/jcm.00986-14>
- Decaro, N., Losurdo, M., Larocca, V., Lucente, M. S., Mari, V., Varello, K., ... Buonavoglia, C. (2015). HoBi-like pestivirus experimental infection in pregnant ewes: Reproductive disorders and generation of persistently infected lambs. *Veterinary Microbiology*, 178, 173–180. <https://doi.org/10.1016/j.vetmic.2015.05.011>
- Driskell, E. A., & Ridpath, J. F. (2006). A survey of bovine viral diarrhoea virus testing in diagnostic laboratories in the United States from 2004 to 2005. *Journal of veterinary diagnostic investigation*, 18, 600–605. <https://doi.org/10.1177/104063870601800615>
- Evans, C. A., Cockcroft, P. D., & Reichel, M. P. (2016). Antibodies to bovine viral diarrhoea virus (BVDV) in water buffalo (*Bubalus bubalis*) and cattle from the Northern Territory of Australia. *Australian Veterinary Journal*, 94, 423–426. <https://doi.org/10.1111/avj.12517>
- Evans, C. A., Hemmatzadeh, F., Reichel, M. P., & Cockcroft, P. D. (2018). Natural transmission of bovine viral diarrhoea virus-1c from a persistently infected neonate lamb to naïve sheep and cattle. *Veterinary Record*, 182, 1–5. <https://doi.org/10.1136/vr.104468>
- Evans, C. A., Lanyon, S. R., Sims, S. K., & Reichel, M. P. (2015). Reproductive performance in experimentally BVDV infected ewes and seroconversion rates in sheep co-mingled with BVDV PI calves. *Small Ruminant Research*, 123, 314–319. <https://doi.org/10.1016/j.smallrumres.2014.11.018>
- Evans, C. A., Moffat, J. L., Hemmatzadeh, F., & Cockcroft, P. D. (2017). The risk of transmission from sheep experimentally infected with BVDV-1c during the acute phase to BVDV naïve sheep. *Small Ruminant Research*, 15, 5–8. <https://doi.org/10.1016/j.smallrumres.2017.04.022>
- Evans, C. A., Reichel, M. P., Hemmatzadeh, F., & Cockcroft, P. D. (2017). Clinical responses and reproductive outcomes in pregnant ewes experimentally infected with bovine viral diarrhoea virus (Type-1c) between days 59 and 69 of gestation. *Small Ruminant Research*, 149, 121–127. <https://doi.org/10.1016/j.smallrumres.2017.01.012>
- Evermann, J. F., & Barrington, G. M. (2005). Clinical features. In S. M. Goyal, & J. F. Ridpath (Eds.), *Bovine viral diarrhoea virus: Diagnosis, management and control* (pp. 105–119). Ames, IA: Blackwell Publishing. <https://doi.org/10.1002/9780470344453>
- Falcone, E., Cordioli, P., Tarantino, M., Muscillo, M., Sala, G., La Rosa, G., ... Tollis, M. (2003). Experimental infection of calves with bovine viral diarrhoea virus type-2 (BVDV-2) isolated from a contaminated vaccine. *Veterinary Research Communications*, 27, 577–589. <https://doi.org/doi>
- Foster, A. P., Houlihan, M., Higgins, R. J., Errington, J., Iyata, G., & Wakeley, P. R. (2005). BVD virus in a British alpaca. *The Veterinary record*, 156, 718–719. <https://doi.org/doi>
- Fulton, R. W., Briggs, R. E., Ridpath, J. F., Saliki, J. T., Confer, A. W., Payton, M. E., ... Walker, D. A. (2005). Transmission of bovine viral diarrhoea virus 1b to susceptible and vaccinated calves by exposure to persistently infected calves. *Canadian Journal of Veterinary Research*, 69, 161–169.
- Fulton, R. W., Hessman, B., Johnson, B. J., Ridpath, J. F., Saliki, J. T., Burge, L. J., ... Payton, M. E. (2006). Evaluation of diagnostic tests used for detection of bovine viral diarrhoea virus and prevalence of subtypes 1a, 1b, and 2a in persistently infected cattle entering a feedlot. *Journal of the American Veterinary Medical Association*, 228, 578–584. <https://doi.org/10.2460/javma.228.4.578>
- Fulton, R. W., Purdy, C. W., Confer, A. W., Saliki, J. T., Loan, R. W., Briggs, R. E., & Burge, L. J. (2000). Bovine viral diarrhoea viral infections in feeder calves with respiratory disease: Interactions with *Pasteurella* spp., parainfluenza-3 virus, and bovine respiratory syncytial virus. *Canadian Journal of Veterinary Research*, 64, 151–159.
- Fulton, R. W., Step, D. L., Ridpath, J. F., Saliki, J. T., Confer, A. W., Johnson, B. J., ... Payton, M. E. (2003). Response of calves persistently

- infected with noncytopathic bovine viral diarrhoea virus (BVDV) sub-type 1b after vaccination with heterologous BVDV strains in modified live virus vaccines and Mannheimia haemolytica bacterin-toxoid. *Vaccine*, 21, 2980–2985. [https://doi.org/10.1016/S0264-410X\(03\)00118-X](https://doi.org/10.1016/S0264-410X(03)00118-X)
- Fux, R., & Wolf, G. (2012). Transient elimination of circulating bovine viral diarrhoea virus by colostral antibodies in persistently infected calves: A pitfall for BVDV-eradication programs? *Veterinary Microbiology*, 161, 13–19. <https://doi.org/10.1016/j.vetmic.2012.07.001>
- Gethmann, J., Homeier, T., Holsteg, M., Schirrmeier, H., Sasserath, M., Hoffmann, B., ... Conraths, F. J. (2015). BVD-2 outbreak leads to high losses in cattle farms in Western Germany. *Heliyon*, 1, e00019. <https://doi.org/10.1016/j.heliyon.2015.e00019>
- Green, D. M., & Kao, R. R. (2007). Data quality of the Cattle Tracing System in Great Britain. *Veterinary Record*, 161, 439–443. <https://doi.org/10.1136/vr.161.13.439>
- Gregg, K., Chen, S. H., Sadeghieh, S., Guerra, T., Xiang, T., Meredith, J., & Polejaeva, I. (2009). Experimental risk assessment of bovine viral diarrhoea virus transmission via in vitro embryo production using somatic cell nucleus transfer. *Theriogenology*, 72, 99–110. <https://doi.org/10.1016/j.theriogenology.2009.02.005>
- Grissett, G. P., White, B. J., & Larson, R. L. (2015). Structured literature review of responses of cattle to viral and bacterial pathogens causing bovine respiratory disease complex. *Journal of Veterinary Internal Medicine*, 29, 770–780. <https://doi.org/10.1111/jvim.12597>
- Grooms, D. L. (2004). Reproductive consequences of infection with bovine viral diarrhoea virus. *Veterinary Clinics of North America: Food Animal Practice*, 20, 5–19. <https://doi.org/10.1016/j.cvfa.2003.11.006>
- Grooms, D. L., Brock, K. V., Bolin, S. R., Grotelueschen, D. M., & Cortese, V. S. (2014). Effect of constant exposure to cattle persistently infected with bovine viral diarrhoea virus on morbidity and mortality rates and performance of feedlot cattle. *Journal of the American Veterinary Medical Association*, 244, 212–224. <https://doi.org/10.2460/javma.244.2.212>
- Gunn, H. M. (1993). Role of fomites and flies in the transmission of bovine viral diarrhoea virus. *The Veterinary record*, 132, 584–585. <https://doi.org/10.1136/vr.132.23.584>
- Hilbe, M., Stalder, H., Peterhans, E., Haessig, M., Nussbaumer, M., Egli, C., ... Ehrensperger, F. (2007). Comparison of five diagnostic methods for detecting bovine viral diarrhoea virus infection in calves. *Journal of Veterinary Diagnostic Investigation*, 19, 28–34. <https://doi.org/10.1177/104063870701900105>
- Houe, H. (1992). Age distribution of animals persistently infected with bovine diarrhoea virus in twenty-two Danish dairy herds. *Canadian Journal of Veterinary Research*, 56, 194–198. <https://doi.org/doi>
- Houe, H. (1993). Survivorship of animals persistently infected with bovine virus diarrhoea virus (BVDV). *Preventive Veterinary Medicine*, 15, 275–283. [https://doi.org/10.1016/0167-5877\(93\)90099-F](https://doi.org/10.1016/0167-5877(93)90099-F)
- Houe, H. (1999). Epidemiological features and economical importance of bovine virus diarrhoea virus (BVDV) infections. *Veterinary Microbiology*, 64, 89–107. [https://doi.org/10.1016/S0378-1135\(98\)00262-4](https://doi.org/10.1016/S0378-1135(98)00262-4)
- Houe, H. (2003). Economic impact of BVDV infection in dairies. *Biologicals*, 31, 137–143. [https://doi.org/10.1016/S1045-1056\(03\)00030-7](https://doi.org/10.1016/S1045-1056(03)00030-7)
- Houe, H. (2005). Risk assessment. In S. M. Goyal, & J. F. Ridpath (Eds.), *Bovine viral diarrhoea virus: Diagnosis, management and control* (pp. 35–64). Ames, IA: Blackwell Publishing. <https://doi.org/10.1002/9780470344453>
- Houe, H., Lindberg, A., & Moennig, V. (2006). Test strategies in bovine viral diarrhoea virus control and eradication campaigns in Europe. *Journal of Veterinary Diagnostic Investigation*, 18, 427–436. <https://doi.org/10.1177/104063870601800501>
- Jenckel, M., Hoper, D., Schirrmeier, H., Reimann, I., Goller, K. V., Hoffmann, B., & Beer, M. (2014). Mixed triple: Allied viruses in unique recent isolates of highly virulent type 2 bovine viral diarrhoea virus detected by deep sequencing. *Journal of Virology*, 88, 6983–6992. <https://doi.org/10.1128/JVI.00620-14>
- Jewell, C. P., van Andel, M., Vink, W. D., & McFadden, A. M. J. (2016). Compatibility between livestock databases used for quantitative biosecurity response in New Zealand. *New Zealand Veterinary Journal*, 64, 158–164. <https://doi.org/10.1080/00480169.2015.1117955>
- Kapil, S., Walz, P. H., Wilkerson, M., & Minocha, H. (2005). Immunity and Immunosuppression. In S. M. Goyal, & J. F. Ridpath (Eds.), *Bovine viral diarrhoea virus: Diagnosis, management and control* (pp. 157–170). Ames, IA: Blackwell Publishing. <https://doi.org/10.1002/9780470344453>
- Kirkland, P. D., & Mackintosh, S. G. (2006) *Ruminant pestivirus infections*. Australia and New Zealand Standard Diagnostic Procedures April 2006 (pp. 1–30). Camden, NSW: Elizabeth Macarthur Agricultural Institute.
- Lanyon, S. R., Hill, F. I., Reichel, M. P., & Brownlie, J. (2014). Bovine viral diarrhoea: Pathogenesis and diagnosis. *The Veterinary Journal*, 199, 201–209. <https://doi.org/10.1016/j.tvjl.2013.07.024>
- Lanyon, S. R., McCoy, R., Bergman, E., & Reichel, M. P. (2014). Milk as a diagnostic sample for a commercially available ELISA to identify bovine viral diarrhoea (BVD) antibodies in dairy herds. *Australian Veterinary Journal*, 92, 269–273. <https://doi.org/10.1111/avj.12188>
- Liebler-Tenorio, E. M., Ridpath, J. E., & Neill, J. D. (2004). Distribution of viral antigen and tissue lesions in persistent and acute infection with the homologous strain of noncytopathic bovine viral diarrhoea virus. *Journal of Veterinary Diagnostic Investigation*, 16, 388–396. <https://doi.org/10.1177/104063870401600504>
- Lindberg, A., & Alenius, S. (1999). Principles for eradication of bovine viral diarrhoea virus (BVDV) infections in cattle populations. *Veterinary Microbiology*, 64, 197–222. [https://doi.org/10.1016/S0378-1135\(98\)00270-3](https://doi.org/10.1016/S0378-1135(98)00270-3)
- Lindberg, A., Brownlie, J., Gunn, G. J., Houe, H., Moennig, V., Saatkamp, H. W., ... Valle, P. S. (2006). The control of bovine viral diarrhoea virus in Europe: Today and in the future. *Revue Scientifique et Technique/Office International Des Epizooties*, 25, 961–979.
- Lindberg, A., Groenendaal, H., Alenius, S., & Emanuelson, U. (2001). Validation of a test for dams carrying foetuses persistently infected with bovine viral diarrhoea virus based on determination of antibody levels in late pregnancy. *Preventive Veterinary Medicine*, 51, 199–214. [https://doi.org/10.1016/S0167-5877\(01\)00229-X](https://doi.org/10.1016/S0167-5877(01)00229-X)
- Loken, T., Bjerkaas, I., & Larsen, H. J. (1991). Experimental pestivirus infections in newborn goat kids. *Journal of Comparative Pathology*, 103, 277–288. [https://doi.org/10.1016/s0021-9975\(08\)80048-5](https://doi.org/10.1016/s0021-9975(08)80048-5)
- Makoschey, B., van Gelder, P. T., Keijsers, V., & Goovaerts, D. (2003). Bovine viral diarrhoea virus antigen in foetal calf serum batches and consequences of such contamination for vaccine production. *Biologicals*, 31, 203–208. [https://doi.org/10.1016/S1045-1056\(03\)00058-7](https://doi.org/10.1016/S1045-1056(03)00058-7)
- Marschik, T., Obritzhauser, W., Wagner, P., Richter, V., Mayerhofer, M., Egger-Danner, C., ... Pinior, B. (2018). A cost-benefit analysis and the potential trade effects of the bovine viral diarrhoea eradication programme in Styria, Austria. *The Veterinary Journal*, 231, 19–29. <https://doi.org/10.1016/j.tvjl.2017.11.010>
- Meyling, A., Houe, H., & Jensen, A. M. (1990). Epidemiology of bovine virus diarrhoea virus. *Revue scientifique et technique*, 9, 75–93. <https://doi.org/10.20506/rst.9.1.489>
- Moën, A., Sol, J., & Sampimon, O. (2005). Indication of transmission of BVDV in the absence of persistently infected (PI) animals. *Preventive Veterinary Medicine*, 72, 93–98. <https://doi.org/215-219>, [10.1016/j.prevetmed.2005.08.014](https://doi.org/10.1016/j.prevetmed.2005.08.014)
- Moennig, V., Eicken, K., Flebbe, U., Frey, H. R., Grummer, B., Haas, L., ... Liess, B. (2005). Implementation of two-step vaccination in the control of bovine viral diarrhoea (BVD). *Preventive Veterinary Medicine*, 72, 109–114. <https://doi.org/10.1016/j.prevetmed.2005.08.011>
- Munoz-Zanzi, C., Thurmond, M., Hietala, S., & Johnson, W. (2006). Factors affecting sensitivity and specificity of pooled-sample testing for

- diagnosis of low prevalence infections. *Preventive Veterinary Medicine*, 74, 309–322. <https://doi.org/10.1016/j.prevetmed.2005.12.006>
- Nelson, D. D., Duprau, J. L., Wolff, P. L., & Evermann, J. F. (2016). Persistent bovine viral diarrhoea virus infection in domestic and wild small ruminants and camelids including the mountain goat (*Oreamnos americanus*). *Front Microbiol*, 6, 1415. <https://doi.org/10.3389/fmicb.2015.01415>.
- Nettleton, P. F., Gilray, J. A., Russo, P., & Dliissi, E. (1998). Border disease in sheep and goats. *Veterinary Research*, 29, 327–340.
- Nickell, J. S., White, B. J., Larson, R. L., Renter, D. G., & Sanderson, M. W. (2011). A simulation model to quantify the value of implementing whole-herd Bovine viral diarrhoea virus testing strategies in beef cow-calf herds. *Journal of Veterinary Diagnostic Investigation*, 23, 194–205. <https://doi.org/10.1177/104063871102300202>
- Niskanen, R., Alenius, S., Belak, K., Baule, C., Belak, S., Voges, H., & Gustafsson, H. (2002). Insemination of susceptible heifers with semen from a non-viraemic bull with persistent bovine virus diarrhoea virus infection localized in the testes. *Reproduction in Domestic Animals*, 37, 171–175. <https://doi.org/10.1046/j.1439-0531.2002.00353.x>
- Niskanen, R., & Lindberg, A. (2003). Transmission of bovine viral diarrhoea virus by unhygienic vaccination procedures, ambient air, and from contaminated pens. *The Veterinary Journal*, 165, 125–130. [https://doi.org/10.1016/s1090-0233\(02\)00161-2](https://doi.org/10.1016/s1090-0233(02)00161-2)
- Niskanen, R., Lindberg, A., & Traven, M. (2002). Failure to spread bovine virus diarrhoea virus infection from primarily infected calves despite concurrent infection with bovine coronavirus. *The Veterinary Journal*, 163, 251–259. <https://doi.org/10.1053/tvj.2001.0657>
- O'Brien, D., Scudamore, J., Charlier, J., & Delavergne, M. (2016). DIS-CONTROLS: A database to identify research gaps on vaccines, pharmaceuticals and diagnostics for the control of infectious diseases of animals. *BMC veterinary research*, 13, 1. <https://doi.org/10.1186/s12917-016-0931-1>
- OIE (2012) *Disease Control Measures*. Available at: http://www.oie.int/wahis_2/public/wahid.php/Diseasecontrol/controlmeasuresmap 2018).
- Pellerin, C., van den Hurk, J., Lecomte, J., & Tijssen, P. (1994). Identification of a new group of bovine viral diarrhoea virus strains associated with severe outbreaks and high mortalities. *Virology*, 203, 260–268. <https://doi.org/10.1006/viro.1994.1483>
- Peterhans, E., Bachofen, C., Stalder, H., & Schweizer, M. (2010). Cytopathic bovine viral diarrhoea viruses (BVDV): Emerging pestiviruses doomed to extinction. *Veterinary Research*, 41, 44. <https://doi.org/10.1051/vetres/2010016>
- Peterhans, E., Jungi, T. W., & Schweizer, M. (2003). BVDV and innate immunity. *Biologicals*, 31, 107–112. [https://doi.org/10.1016/S1045-1056\(03\)00024-1](https://doi.org/10.1016/S1045-1056(03)00024-1)
- Peterhans, E., & Schweizer, M. (2010). Pestiviruses: How to outmaneuver your hosts. *Veterinary Microbiology*, 142, 18–25. <https://doi.org/10.1016/j.vetmic.2009.09.038>
- Piniór, B., Firth, C. L., Richter, V., Lebl, K., Trauffler, M., Dzieciol, M., ... Kasbohrer, A. (2017). A systematic review of financial and economic assessments of bovine viral diarrhoea virus (BVDV) prevention and mitigation activities worldwide. *Preventive Veterinary Medicine*, 137, 77–92. <https://doi.org/10.1016/j.prevetmed.2016.12.014>
- Platt, R., Kesl, L., Guidarini, C., Wang, C., & Roth, J. A. (2017). Comparison of humoral and T-cell-mediated immune responses to a single dose of Bovela(R) live double deleted BVDV vaccine or to a field BVDV strain. *Veterinary Immunology and Immunopathology*, 187, 20–27. <https://doi.org/10.1016/j.vetimm.2017.03.003>
- Reardon, F., Graham, D. A., Clegg, T. A., Tratalos, J. A., O'Sullivan, P., & More, S. J. (2018). Quantifying the role of Trojan dams in the between-herd spread of bovine viral diarrhoea virus (BVDv) in Ireland. *Preventive Veterinary Medicine*, 152, 65–73. <https://doi.org/10.1016/j.prevetmed.2018.02.002>
- Richer, L., Marois, P., & Lamontagne, L. (1988). Association of bovine viral diarrhoea virus with multiple viral infections in bovine respiratory disease outbreaks. *Canadian Veterinary Journal*, 29, 713–717.
- Richter, V., Lebl, K., Baumgartner, W., Obritzhauser, W., Kasbohrer, A., & Piniór, B. (2017). A systematic worldwide review of the direct monetary losses in cattle due to bovine viral diarrhoea virus infection. *The Veterinary Journal*, 220, 80–87. <https://doi.org/10.1016/j.tvj.2017.01.005>
- Ridpath, J. F., Fulton, R. W., Kirkland, P. D., & Neill, J. D. (2010). Prevalence and antigenic differences observed between Bovine viral diarrhoea virus subgenotypes isolated from cattle in Australia and feedlots in the southwestern United States. *Journal of Veterinary Diagnostic Investigation*, 22, 184–191. <https://doi.org/10.1177/104063871002200203>
- Saliki, J. T., & Dubovi, E. J. (2004). Laboratory diagnosis of bovine viral diarrhoea virus infections. *The Veterinary Clinics of North America: Food Animal Practice*, 20, 69–83. <https://doi.org/10.1016/j.jvfa.2003.11.005>
- Sarrazin, S., Dewulf, J., Mathijs, E., Laureyns, J., Mostin, L., & Cay, A. B. (2014). Virulence comparison and quantification of horizontal bovine viral diarrhoea virus transmission following experimental infection in calves. *The Veterinary Journal*, 202, 244–249. <https://doi.org/10.1016/j.tvj.2014.07.010>
- Scharnböck, B., Roch, F. F., Richter, V., Funke, C., Firth, C., Orbitzhauser, W., ... Piniór, B. (2018). A meta-analysis of bovine viral diarrhoea virus (BVDV) prevalence in the global cattle population. *Scientific Reports*, 8, 1–15. <https://doi.org/10.1038/s41598-018-32831-2>
- Schweizer, M., & Peterhans, E. (2014). Pestiviruses. *Annual Review of Animal Biosciences*, 2, 141–163. <https://doi.org/10.1146/annurev-anima-1-022513-114209>
- Smith, D. B., Meyers, G., Bukh, J., Gould, E. A., Monath, T., Scott Muerhoff, A., ... Becher, P. (2017). Proposed revision to the taxonomy of the genus Pestivirus, family Flaviviridae. *The Journal of General Virology*, 98, 2106–2112. <https://doi.org/10.1099/jgv.0.000873>
- Stähl, K., & Alenius, S. (2012). BVDV control and eradication in Europe - an update. *The Japanese Journal of Veterinary Research*, 60, S31–S39.
- Stähl, K., Kampa, J., Baule, C., Isaksson, M., Moreno-López, J., Belák, S., ... Lindberg, A. (2005). Molecular epidemiology of bovine viral diarrhoea during the final phase of the Swedish BVD-eradication programme. *Preventive Veterinary Medicine*, 72, 103–108. <https://doi.org/10.1016/j.prevetmed.2005.01.021>
- Stalder, H., Hug, C., Zanoni, R., Vogt, H.-R., Peterhans, E., Schweizer, M., & Bachofen, C. (2016). A nationwide database linking information on the hosts with sequence data of their virus strains: A useful tool for the eradication of bovine viral diarrhoea (BVD) in Switzerland. *Virus Research*, 2018, 49–56. <https://doi.org/10.1016/j.virusres.2015.09.012>
- Strong, R., La Rocca, S. A., Paton, D., Bensaude, E., Sandvik, T., Davis, L., ... Steinbach, F. (2015). Viral dose and immunosuppression modulate the progression of acute BVDV-1 infection in calves: Evidence of long term persistence after intra-nasal infection. *PLoS ONE*, 10, e0124689. <https://doi.org/10.1371/journal.pone.0124689>
- Tao, J., Liao, J. H., Wang, Y., Zhang, X. J., Wang, J. Y., & Zhu, G. Q. (2013). Bovine viral diarrhoea virus (BVDV) infections in pigs. *Veterinary Microbiology*, 165, 185–189. <https://doi.org/10.1016/j.vetmic.2013.03.010>
- Thurmond, M. C. (2005). Virus transmission. In S. M. Goyal, & J. F. Ridpath (Eds.), *Bovine viral diarrhoea virus: Diagnosis, management and control* (pp. 91–104). Ames, IA: Blackwell Publishing. <https://doi.org/10.1002/9780470344453>
- Tratalos, J. A., Graham, D., & More, S. (2017). Patterns of calving and young stock movement in Ireland and their implications for BVD serosurveillance. *Preventive Veterinary Medicine*, 142, 30–38. <https://doi.org/10.1016/j.prevetmed.2017.04.005>
- Trávén, M., Alenius, S., Fossum, C., & Larsson, B. (1991). Primary bovine viral diarrhoea virus infection in calves following direct contact with a persistently viraemic calf. *Journal of Veterinary Medicine*, 38, 453–462.

- Van Campen, H., & Frolich, K. (2001). Pestivirus infections. In E. S. Williams, & I. K. Barker (Eds.), *Infectious diseases of wild mammals* (pp. 232–244). Ames, IA: Iowa State University Press. <https://doi.org/10.1002/9780470344880>
- Vernon, M. C., Webb, C. R., & Heath, M. F. (2010). Postal survey of contacts between cattle farms on the Isle of Lewis. *The Veterinary Record*, 166, 37–40. <https://doi.org/10.1136/vr.c69>
- Yesilbag, K., Alpay, G., & Becher, P. (2017). Variability and global distribution of subgenotypes of bovine viral diarrhoea virus. *Viruses*, 9(6), 128. <https://doi.org/10.3390/v9060128>

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