The impact of bovine viral diarrhoea virus on fertility in cattle and the protective effect of vaccination

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Published in:
Livestock

DOI:
10.12968/live.2024.29.1.9

First published: 29/01/2024

Document Version
Version created as part of publication process; publisher's layout; not normally made publicly available

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Bovine viral diarrhoea virus (BVDV) infection is associated with significant reproductive losses in cattle through the detrimental impact of both persistent and transient infection on breeding females and males. The pathology within the reproductive tract is well described, although the mechanisms that lead to reproductive failure have yet to be fully unravelled. Prolonged shedding of virus following acute infection of bulls in both the peri- and post-pubertal periods has been observed, although the significance of this in relation to reproductive failure and the spread of infection has yet to be fully explored for the UK situation. Infection and recovery lead to an immune state in the female that is protective against breeding failure and generation of persistently infected calves. Vaccination using either of the two vaccines licensed for the control of BVDV infection in breeding cattle in the UK has been shown to be protective against fetal infection. In the UK where regional and herd level eradication of BVDV is progressing against a background of endemic infection, vaccination would appear to offer stopgap mitigation against reinfection until such times as national eradication is achieved. 10.12968/live.2024.29.1.???

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Key words: Bovine viral diarrhoea virus | reproductive failure | pregnancy | vaccination

Submitted: 11 September 2023; accepted for publication following double-blind peer review: 8 November 2023

Bovine viral diarrhoea virus (BVDV) is a *Pestivirus* that can have a range of negative impacts on the health and productivity of cattle herds through effects on fertility (Lanyon et al, 2014) and immunosuppression (Chase, 2013). In total 95% of non-vaccinating dairy herds in England and Wales had antibody to BVDV in the bulk tank milk, with high antibody concentrations found in 65% of the herds (Paton et al, 1998). Using similar methodology, 20.5% of non-vaccinated Scottish dairy herds were estimated to have high levels of antibodies to BVDV in the bulk tank milk (Humphry et al, 2012). More recently, an evaluation of a voluntary BVDV control programme in England found that 13.5% of beef breeding herds and 20% of dairy herds that submitted samples for testing had at least one antibody-or virus-positive animal in the samples submitted during 2020 (Prosser et al, 2022). While this constitutes a biased sample of the English breeding herd, it nevertheless indicates that BVDV continues to be active in cattle herds throughout England.

The estimates of the financial impact of BVDV infection range from $2.40 to $687.80 per cow, depending on the number of factors contributing to the loss that were considered (Richter et al, 2017). The higher estimates included morbidity, mortality, premature culling and re-infection, and therefore gave a more comprehensive assessment of the total impact of incursion of the virus into a herd. Using meta-analysis and a modelling approach, the mean annual losses per cow were calculated as €42.14 (Pinior et al, 2019), while a modelling approach arrived at figures of $22.22 and $41.19 per cow per year for dairy and beef cows respectively in New Zealand (Han et al, 2020). The calving pattern of the herd and the stage of pregnancy in a naïve herd encountering BVDV will affect the impact on health and fertility and therefore affect the financial output (Barbudo et al, 2008). The basic reproduction

ratio (R0) can be expected to be affected by the herd size, grouping, housing and stocking density, and hence influence the cost of the outbreak. The impact of BVDV on fertility is an important part of the cost of an outbreak, and it has been estimated that more than 75% of the financial losses associated with BVDV infection are caused by infections during breeding and pregnancy (Meyling et al, 1990).

Advances in the understanding of the biology of BVDV infections led to the development and implementation of successful control and eradication programmes, initially in Scandinavian countries (Lindberg and Alenius, 1999) and subsequently in other countries or regions in Europe (Houe et al, 2006), notably Ireland (Graham et al, 2014), Germany (Wernike et al, 2017), Slovenia (Toplak et al, 2021) and Switzerland (Presi et al, 2011). In the UK, BVDV eradication programmes are well-advanced in Northern Ireland (Strain et al, 2021) and Scotland (Scottish Government, 2023) and voluntary control and herd level assurance programmes have been available throughout the UK since 1998 (CHeCS, 2023). Regional and herd-level initiatives can be expected to have a beneficial effect on the health and welfare, and therefore productivity of the herds where successful eradication is achieved. However, they create a population that remains at risk of the re-introduction of the virus when restrictions on the internal movement of cattle of unknown BVDV status end and effective boundary biosecurity can be difficult to achieve. Until national eradication of BVDV infection is achieved or more robust internal restrictions on movements of cattle are implemented, herd vaccination against the infection would seem to offer a stopgap mitigation for these naïve populations.

This article reviews the impacts of BVDV on the fertility of cattle and discusses the role vaccination has in mitigating these.

Pathogenesis of BVDV in relation to fertility

Acute or transient infection with the non-cytopathic biotype of BVDV results in viraemia within a few days that is cleared after 2 weeks as immunity develops (Howard, 1990), although more chronic infection of the male and female reproductive tracts can occur (Grooms et al, 1998b; Voges et al, 1998). During the time of transient infection, the virus can be found in the male and female reproductive tracts; there is leukopaenia with profound lymphopaenia, immunosuppression and fever (Chase et al, 2015). The impact on the immune system and the altered function of the cells in the reproductive tract are likely to alter the nature of the fluids, particularly in the female reproductive tract. This in turn may impact on fertilisation and implantation while the inhibitory effect that the virus has on the host's innate response to infection has also been found to be critical in relation to interference in the maternal recognition of pregnancy (Oguejiofor et al, 2019). Additionally, BVDV can have a direct lethal effect on the conceptus and can cause developmental abnormalities that are likely to result in congenital defects that are critical to the survival of the newborn calf. Persistent infection is a consequence of infection during the first trimester and the principal significance of the persitently infected animal is as the source of BVDV infection for other animals (Brownlie, 1990).

The effect of BVDV on female fertility

Fertility in persistently infected females

Persitently infected (PI) females frequently exhibit ovarian hypoplasia and a reduction in the number of follicles (Grooms et al, 1996). Consequently, a poor embryo yield can be expected in super ovulated PI cattle (Brock et al, 1997). The virus has been identified in the luteal cells and macrophage-like cells of the ovaries of PI cattle (Grooms et al, 1996) and detected in follicles and oocytes (Brownlie et al, 1997). However, the collection of ova or embryos from a PI cow can result in the birth of a non-PI calf when washed and transplanted into a non-PI recipient (Brock et al, 1997; Smith and Grimmer, 2000). Despite that, PI cattle will always give birth to PI cattle: the transmission of the virus from dam to calf may occur via germ line transmission or as a result of the fetus developing in an infected environment (Fray et al, 2000b).

Transient infection around conception

Infection immediately prior to breeding, at breeding or immediately post-breeding all result in reduced pregnancy rates when compared to unexposed controls (McGowan et al, 1993; Kirkland et al, 1994). Exposure to infection at 50 days prior to breeding (Rodning et al, 2012) and prior exposure and seroconversion (Virakul et al, 1988) have a protective effect on exposure to BVDV infection at breeding. Failure in conception is of greater importance when exposure occurs immediately prior to breeding, but embryonic death can occur following pre- or post-breeding exposure (McGowan et al, 1993). There appears to be multiple explanations for the reduction in breeding success at this time. BVDV can be found in the reproductive tract from 6 days post-infection (Tsuboi et al, 2011) and at 16 days post-infection (Bielanski et al, 1998). Its presence is associated with structural abnormalities in the ovary and oophoritis (Grooms et al, 1998a; McGowan et al, 2003), and necrosis of the granulosa cells and of the oocyte in mature follicles (McGowan et al, 2003). Viraemia during the pre-ovulatory phase decreases the rate of follicular growth (Grooms et al, 1998a; Fray et al, 1999) and this may persist for two oestrous cycles after infection (Grooms et al, 1998b). Despite the apparent recovery and resistance reported above, BVDV-associated oophoritis may last up to 2 months post-infection (Ssentongo et al, 1980).

BVDV infection also causes diffuse lymphocytic and plasmocytic changes in the endometrium (Archbald et al, 1973), which can be expected to result in a hostile environment in the uterus and oviducts with a consequent negative effect on fertilisation and implantation. A reduction in oestradiol concentration has been observed 4–9 days post-infection, which could impact on fertility (Fray et al, 2000a). When BVDV infection occurs at the final period of preovulatory growth, oestradiol secretion is reduced with a negative impact on the pre-ovulatory surge of luteinising hormone that in turn affects the competency of the resultant corpus luteum, thereby impacting negatively on embryo survival (Fray et al, 2002; McGowan et al, 2003).

Leukocytes have a key role in structural and functional changes that take place in the ovary during normal cyclicity (Fray et al, 2000a) and it is likely that the BVDV-induced systemic leukopaenia (Müller-Doblies et al, 2004) is reflected in the leukocyte population in the ovary and therefore ovarian function may be

further impaired. Furthermore, BVDV has the capacity to down-regulate interferon-stimulated genes in endometrial cells (Cheng et al, 2017). This works to block the interferon tau released from blastocysts and so blocks the maternal recognition of pregnancy and allows the secretion of pulses of prostaglandin F2-alpha, causing luteolysis, and so preventing implantation (Bazer, 2013).

Transient infection in established pregnancy

As discussed, infection in early pregnancy can lead to embryonic death. In the first third of pregnancy, the potential sequelae to infection include death of the conceptus and abortion, mummification, the creation of a PI calf or developmental malformation. Most calves surviving infection between 25 and 90 days of gestation will be PI. Following this the proportion of conceptuses that become PI declines. For example, 67% of calves born to cows infected at 100 days of gestation were PI (Liess et al, 1984) and the generation of PI animals has been reported as late as 125 days of gestation (Duffell and Harkness, 1985). While the explanation of the immune tolerance was previously attributed to the immaturity of the immune system, BVDV's ability to circumvent the innate immune response of the embryo in the first trimester is also of crucial importance to establish persistent infection. This is mediated by the non-structural protein Npro (Rümenapf et al, 1998) and the structural protein Erns, which has an associated RNase and is produced in excess (Schneider et al, 1993). These respectively inhibit interferon (IFN) expression and promote the degradation of the transcription factor IRF-3, blocking IFN expression in BVDV-infected cells (Peterhans and Schweizer, 2013).

During mid-gestation, infection can result in fetal death and abortion, and teratogenic effects occur more often than in the first trimester. Fetal deformities can include cerebellar hypoplasia, cataracts, and in-utero growth retardation (Lanyon et al, 2014). Experimental infection at 100 days of gestation resulted in a high proportion of animals aborting (Done et al, 1980), but previously exposed females were largely resistant when subsequently exposed to BVDV at 100 days of gestation (Duffell et al, 1984). Reports of field outbreaks indicate that where the cows are at a similar stage of gestation, as occurs in seasonal breeding or synchronised insemination programmes, a high abortion rate may occur. In one outbreak, 19 of 37 heifers aborted in the last month of gestation or gave birth prematurely to calves with congenital deformities (Blanchard et al, 2010). In another outbreak, 39 animals were pregnant during the calculated period of risk; nine aborted, one calf was born mummified at full term, three were stillborn or died in the perinatal period and one died at 1-week-old. Of the 25 surviving calves, 12 were PI. In total, 42% of the dams giving birth to live calves had retained fetal membranes compared to 3.5% of the other dams ($P<0.001$) (Larsson et al, 1994).

Impact of BVDV on bull fertility

Both persistently and transiently-infected bulls can shed BVDV in semen. However, the titres of virus shed, and the consequences of this shedding, are likely to be different for these two groups of animals.

Persistently infected bulls

PI bulls can produce semen of acceptable quality (Kirkland et al, 1994), but there are often abnormalities in the motility, density and morphology. As many as 45% of spermatozoa can have abnormalities of the head while 61% of the spermatozoa can be dead (Revell et al, 1988). The targets advised for progressive motility and normal morphology are greater than 60% and 70% respectively (Penny, 2010). Testicular hypoplasia has also been reported in PI bulls (Borel et al, 2007).

PI bulls shed high titres of virus in the semen (10^4–10^6 50% tissue culture infectious dose (TCID50 per millilitre) (Read et al, 2020), and the potential for this to spread to naïve females at service is well-established (McClurkin et al, 1979; Kirkland et al, 1994). This can occur after natural service or artificial insemination and can result in poor conception rates or early embryonic death. PI calves can also result from mating with a PI bull because of persistence of the virus in the female reproductive tract or sub-lethal infection of the conceptus (Kirkland et al, 1994).

In contrast to the poor conception rates documented above, successful conception can also occur (Wentink et al, 1989).

Transiently infected bulls

Bulls that are acutely infected with BVDV shed virus in their semen (8–66 TCID50 per millilitre), but at much lower levels than occurs in PI animals (Paton et al, 1989; Kirkland et al, 1991). During an acute infection, the semen may retain normal motility, concentration and morphology (Kirkland et al, 1991); however, a deterioration in semen quality with a slow recovery period is more likely. Abnormalities of the head have been observed in almost 80% of sperm, and motility and density are also reduced below levels consistent with normal fertility (Paton et al, 1989).

After an acute infection, the duration of virus shedding in the semen is usually brief and decreases once serum antibody is detectable (Givens et al, 2009), but persistent shedding can occur (Voges et al, 1998). It was hypothesised that infection in the peri-pubertal period created the opportunity for virus to pass through the blood–testes barrier just before closure at puberty, leading to persistent viral shedding (Voges et al, 1998). This has been reproduced in peri-pubertal bulls, two of which shed virus until 848 days after intra-nasal inoculation (Givens et al, 2009). However, bulls infected after puberty can also shed virus persistently in the semen (Givens et al, 2003) and have been found to shed virus in the semen for as long as 7 months. More recently, routine screening of unvaccinated bulls over a 5-year period found that 50% of 586 bulls entering a breeding centre were positive for antibody to BVDV. The semen from the seropositive bulls was screened for BVDV by polymerase chain reaction and five bulls were found to have BVDV RNA present for a period of 3–8 months after infection and one bull continued to produce BVDV-positive ejaculates until slaughter after 73 months. BVDV was found to be present in four of 32 ejaculates that were subjected to virus isolation. Five of the six virus-positive bulls were considered to have been infected several months after puberty (Read et al, 2020).

Despite the low titre of virus in the semen of transiently infected bulls, infection in females following insemination has occurred (Kirkland et al, 1997). Transmission of BVDV in the se-

men of transiently infected bulls, however, is less common than the transmission of virus in the semen of PI animals, and the risk of BVDV spread through using bulls that have been transiently infected with BVDV may be slight. Once these bulls cease to produce virus-contaminated ejaculates, there is no evidence that they can subsequently shed virus even if subjected to a period of stress (Walz et al, 2008).

Although the onward transmission of BVDV from transiently infected bulls is less consistent than from PI bulls, that it does occur means that it needs to be considered as a potential risk pathway. A herd outbreak in the final stages of BVDV eradication in Sweden was thought to be because of persistent testicular infection (Ståhl et al, 2005). Nothing is known about the prevalence of persistent testicular infection in bulls in the UK, and the scale of the importance of this occurrence in BVDV transmission has yet to be explored.

The impact of BVDV on herd level fertility

Demonstrating the impact of BVDV on reproduction in a herd that has experienced an outbreak is difficult, principally because identifying the period of exposure precisely is challenging and the available data on reproductive performance may be limited. For these reasons many of the reports provide little valuable information on the impact of BVDV on herd reproductive performance. However, late return to oestrus (Robert et al, 2004); reduced conception rate (Burgstaller et al, 2016); increased calving to conception interval (Arnaiz et al, 2021) and increased age at first calving (Valle et al, 2001) have all been convincingly documented in herds with active BVDV infection, while an increase in conception rate was subsequently observed in the period that followed successful herd eradication of BVDV (Burgstaller et al, 2016).

The impact of BVDV vaccination on fertility in cattle

Available vaccines

As discussed previously, while BVDV is immunosuppressive, the immunity that develops post-infection protects against subsequent infection and negative impacts on reproduction. From this it can be inferred that vaccination has the potential to prevent or reduce the impact of BVDV infection. Live vaccines are considered to stimulate a longer duration of protection (Kalaycioglu, 2007; Newcomer et al, 2017); a more rapid onset of immunity and increased antibody levels (Brock et al, 2007); and a stronger cell-mediated immunity (Woolums et al, 2013). However, modified live vaccines involve the vaccine virus replicating in the animal and carry with them the risk of adverse effects such as pyrexia, virulence and they may alter immune function (Brodersen, 2014). Vaccine-induced pyrexia may adversely affect sperm quality and the use of live cytopathic BVDV vaccine may precipitate mucosal disease when administered to a PI animal (Brodersen, 2014). Vaccinal BVDV has been found in the testicular tissue of peripubertal bulls vaccinated with a modified live vaccine 134 days previously (Givens et al, 2007), and also in the ovaries of vaccinated females (Grooms et al, 1998c). However, a live double-gene-deleted BVDV vaccine strain was not detected in the tissues of bulls 13 days post-vaccination, and it was not detected in the reproductive tissues at all. Additionally, this vaccine did not appear to induce a pyrexia (Tunney 2016), although an increase in body temperature within the physiological range is common (European Medicines Agency, 2014). Currently, in the UK, no BVDV vaccine is licensed for use in bulls.

While the differentiation of gene-deleted vaccine virus from wild virus can be easily achieved, occasional diagnostic challenges still arise. The double-gene-deleted vaccine virus has been detected in some calves born to dams vaccinated in the first trimester (Wernike et al, 2018). These calves were positive for BVDV on ear and skin samples by reverse transcription polymerase chain reaction up to 34 days after birth, but subsequently tested negative for viable BVDV on both blood and skin samples. There is no evidence of onward transmission of the vaccine virus to a naïve animal, and these calves do not present a risk to the herd. To prevent this occurrence, it is advised that pregnant animals are not vaccinated, but the individual farm circumstances need to be considered (European Medicines Agency, 2014).

Inactivated vaccines can be used in pregnant animals without the concern of pyrexia or fetal infection with the vaccinal strain. The onset of immunity is slower, at 4–6 weeks from the initial dose (Newcomer et al, 2017) and multiple doses are required.

Vaccination inevitably impacts on the ability to subsequently screen animals for exposure to infection by using antibody tests. However, because inactivated vaccines contain only trace amounts of non-structural proteins, antibody ELISAs using the non-structural proteins such as NS 3 (also known as P80) can allow for a partial differentiation of infection from vaccination assay (DIVA) (Graham et al, 2003; Alvarez et al, 2012). This approach is not available for use in animals vaccinated with modified live vaccines where antibodies to non-structural proteins of the virus are persistently high.

Efficacy of vaccination

Both modified live and inactivated vaccinations provide significant protection against BVDV, but modified live vaccines appear to provide superior fetal protection. A meta-analysis on the efficacy of BVDV vaccination in reproductive disease found that when live vaccines were used, the risk of fetal infection was reduced by almost 90% and the risk of abortion by 63%, compared to 75% and 34% for inactivated vaccines (Newcomer et al, 2015).

Given the difficulties that hinder herd-level studies examining the impact of BVDV outbreaks on reproduction, it is not surprising that there is an even greater lack where BVDV vaccination is concerned. However, one study does demonstrate successful protection. In 28 dairy herds in Galicia that experienced a BVDV breakdown having been previously demonstrably free from infection, 13 instigated a herd vaccination programme with a modified live double-gene-deleted vaccine on identification of the BVDV outbreak (Arnaiz et al, 2021). In these herds, unlike the situation in the 15 herds that did not use vaccine and experienced a significant increase in the calving to conception interval, there was no significant difference in calving to conception interval in the period of freedom before the outbreak compared to the period of the outbreak. This suggested that the vaccination had a protective impact on reproductive performance. Otherwise, there is a lack of

evidence of the efficacy of BVDV vaccination in preventing failure of conception and early embryonic death, and on the effect of vaccination at a herd level. However, given the significant reduction in fetal infection and abortion found in many experimental stuies (Newcomer et al, 2015), it is considered that vaccination at a herd level will reduce the risk of a BVDV outbreak.

Despite widespread availability of BVDV vaccination for decades, the prevalence of BVDV in countries or regions without an eradication programme remains unchanged (Moennig and Becher, 2018). Antigenic variation between and within the strains of BVDV may offer an explanation (Brodersen, 2014; Moennig and Becher, 2018). While it has been observed that protection is maximal when challenge strain matches the vaccine strain (Newcomer et al, 2015), sera from all seven calves vaccinated with a single strain inactivated vaccine were found to have virus neutralising antibody against 20 of the 22 strains of BVDV tested (Hamers et al, 2002). However, the vaccine used in that study is no longer produced, and a similar study involving the vaccines currently licensed in Europe failed to show the same level of cross protection against heterologous genotypes of BVDV (Sozzi et al, 2020).

A further factor critical to the success of a vaccination program is the correct administration of the vaccine. Many farmers fail to adhere to the vaccine manufacturers' instructions on storage and administration (Meadows, 2010). Even when vaccines are used correctly, in the face of a natural challenge model, fetal infection can still occur, but the proportion of fetuses or calves with detectable BVDV varies with choice of vaccine and vaccine protocol. In studies that involved challenge through the exposure of the vaccinated and control animals to PI cattle, there were statistically significant levels of protection afforded by vaccination when either modified live or inactivated vaccines were used (Grooms et al, 2007; Packianathan et al, 2017; Walz et al, 2017). This was assessed on the abortion rate or the detection of BVDV in the fetus or calf from exposed cattle. Nevertheless, protection was not complete, and fetal infection, or the birth of virus positive calves, was observed in each study. Currently there are only two licensed BVDV-specific vaccines for use in breeding cattle in the UK and neither featured in these studies. In contrast, using experimental intranasal challenge, no evidence of fetal infection was found in animals vaccinated with vaccines that were either licensed at the time or are currently licensed for use in the UK (Brownlie et al, 1995; Patel et al, 2002; Meyer et al, 2012).

These studies demonstrate that BVDV vaccination is effective in reducing fetal infection and can be expected to provide effective herd-level control, but that protection may not be absolute. Given the wide genetic diversity of BVDV (Yeşilbağ et al, 2017) there would appear to be a need for vaccine manufacturers to provide information on the degree of cross protection that can be expected against the different genotypes existing in any country (Yeşilbağ et al, 2017; Sozzi et al, 2020).

Conclusions

Reproductive losses make up a considerable proportion of the production losses associated with BVDV infection in cattle herds. While the pathology within the reproductive tract has been well-described, a full understanding of how this affects reproduction remains to be achieved. Chronic infection following acute infection is recognised, but the significance, particularly in relation to bulls, is yet to be adequately explored in the UK. There is evidence that natural infection results in effective immunity and both modified live and inactivated vaccines have been shown to be effective in the face of experimental challenge. Complete protection may not be achieved, but the published studies involving the current UK licensed vaccines showed they prevented abortion and the birth of virus-positive calves. The extent of cross protection against the most prevalent strains of the virus circulating within the UK is unclear. The current patchy approach to herd and regional level BVDV eradication has created a naïve population in the UK that is at risk from lack of control of cattle movements from herds with endemic infection. The available BVDV vaccines offer a way to suitably mitigate the risk of breakdowns in naïve herds until such times as national eradication or more effective control of the movement of infected cattle can be achieved. LS

Conflicts of interest

The work of the second author on this article was supported by MSD.

References

Alvarez M, Donate J, Makoschey B. Antibody responses against non-structural protein 3 of bovine viral diarrhoea virus in milk and serum samples from animals immunised with an inactivated vaccine. Vet J. 2012;191(3):371–376. https://doi.org/10.1016/j.tvjl.2011.03.004

Archbald LF, Gibson CD, Schultz RH, Fahning ML, Zemjanis R. Effects of intrauterine inoculation of bovine viral diarrhea-mucosal disease virus on uterine tubes and uterus of nonpregnant cows. Am J Vet Res. 1973;34(9):1133–1137

Arnaiz I, Cerviño M, Martínez S, Fouz R, Diéguez FJ. Bovine viral diarrhea virus (BVDV) infection: Effect on reproductive performance and milk yield in dairy herds. Vet J. 2021;277:105747. https://doi.org/10.1016/j.tvjl.2021.105747

Barbudo A, Gunn GJ, Stott AW. Combining models to examine the financial impact of infertility caused by bovine viral diarrhoea in Scottish beef suckler herds. J Agri Sci. 2008;146(6):621–632. https://doi.org/10.1017/S0021859608008113

Bazer FW. Pregnancy recognition signaling mechanisms in ruminants and pigs. J Anim Sci Biotechnol. 2013;4(1):23. https://doi.org/10.1186/2049-1891-4-23

Bielanski A, Sapp T, Lutze-Wallace C. Association of bovine embryos produced by in vitro fertilization with a noncytopathic strain of bovine viral diarrhea virus type II. Theriogenology. 1998;49(6):1231–1238. https://doi.org/10.1016/s0093-691x(98)00070-3

Blanchard PC, Ridpath JF, Walker JB, Hietala SK. An outbreak of late-term abortions, premature births, and congenital deformities associated with a bovine viral diarrhea virus 1 subtype b that induces thrombocytopenia. J Vet Diagn Invest. 2010;22(1):128–131. https://doi.org/10.1177/104063871002200127

Borel N, Janett F, Teankum K, Zlinszky K, Iten C, Hilbe M. Testicular hypoplasia in a bull persistently infected with bovine diarrhoea virus. J Comp Pathol. 2007;137(2-3):169–173. https://doi.org/10.1016/j.jcpa.2007.06.002

Brock KV, Lapin DR, Skrade DR. Embryo transfer from donor cattle persistently infected with bovine viral diarrhea virus. Theriogenology. 1997;47(4):837–844. https://doi.org/10.1016/s0093-691x(97)00039-3

Brock KV, Widel P, Walz P, Walz HL. Onset of protection from experimental infection with type 2 bovine viral diarrhea virus following vaccination with a modified-live vaccine. Vet Ther. 2007;8(1):88–96

Brodersen BW. Bovine viral diarrhea virus infections: manifestations of infection and recent advances in understanding pathogenesis and control. Vet Pathol. 2014;51(2):453–464. https://doi.org/10.1177/0300985813520250

Brownlie J. Pathogenesis of mucosal disease and molecular aspects of bovine virus diarrhoea virus. Vet Microbiol. 1990;23(1-4):371–382. https://doi.org/10.1016/0378-1135(90)90169-v

Brownlie J, Booth PJ, Stevens DA, Collins ME. Expression of non-cytopathogenic bovine viral diarrhoea virus (BVDV) in oocytes and follicles of persistently infected cattle. Vet Rec. 1997;141(13):335–337. https://doi.org/10.1136/vr.141.13.335

Brownlie J, Clarke MC, Hooper LB, Bell GD. Protection of the bovine fetus from bovine viral diarrhoea virus by means of a new inactivated vaccine. Vet Rec. 1995;137(3):58–62. https://doi.org/10.1136/vr.137.3.58

Burgstaller J, Obritzhauser W, Kuchling S, Kopacka I, Pinior B, Köfer J. The effect of bovine viral diarrhoea virus on fertility in dairy cows: two case-control studies in the province of Styria, Austria. Berl Munch Tierarztl Wochenschr. 2016;129(3-4):103–110

Chase CC. The impact of BVDV infection on adaptive immunity. Biologicals. 2013;41(1):52–60. https://doi.org/10.1016/j.biologicals.2012.09.009

Chase CC, Thakur N, Darweesh MF, Morarie-Kane SE, Rajput MK. Immune response to bovine viral diarrhea virus--looking at newly defined targets. Anim Health Res Rev. 2015;16(1):4–14. https://doi.org/10.1017/S1466252315000110

CHeCS. Checs technical document 2021. 2023. https://checs.co.uk/wp-content/uploads/2021/10/CHECS-Technical-Document-2021-FINAL.pdf (accessed

19 December 2023)
Cheng Z, Chauhan L, Barry AT et al. Acute bovine viral diarrhea virus infection inhibits expression of interferon tau-stimulated genes in bovine endometrium. Biol Reprod. 2017;96(6):1142–1153. https://doi.org/10.1093/biolre/iox056
Done JT, Terlecki S, Richardson C, et al. Bovine virus diarrhoea-mucosal disease virus: pathogenicity for the fetal calf following maternal infection. Vet Rec. 1980;106(23):473–479. https://doi.org/10.1136/vr.106.23.473
Duffell SJ, Harkness JW. Bovine virus diarrhoea-mucosal disease infection in cattle. Vet Rec. 1985;117(10):240–245. https://doi.org/10.1136/vr.117.10.240
Duffell SJ, Sharp MW, Winkler CE et al. Bovine virus diarrhoea-mucosal disease virus-induced fetopathy in cattle: Efficacy of prophylactic maternal pre-exposure. Vet Rec. 1984;114(23):558–561. https://doi.org/10.1136/vr.114.23.558
European Medicines Agency. Bovela lyophilisate and solvent for suspension of injection for cattle. 2014. https://www.ema.europa.eu/en/documents/product-information/bovela-epar-product-information_en.pdf (accessed 19 December 2023)
Fray MD, Mann GE, Bleach EC, Knight PG, Clarke MC, Charleston B. Modulation of sex hormone secretion in cows by acute infection with bovine viral diarrhoea virus. Reproduction. 2002;123(2):281–289
Fray MD, Mann GE, Clarke MC, Charleston B. Bovine viral diarrhea virus: its effects on estradiol, progesterone and prostaglandin secretion in the cow. Theriogenology. 1999;51(8):1533–1546. https://doi.org/10.1016/s0093-691x(99)00096-5
Fray MD, Mann GE, Clarke MC, Charleston B. Bovine viral diarrhoea virus: its effects on ovarian function in the cow. Vet Microbiol. 2000a;77(1-2):185–194. https://doi.org/10.1016/s0378-1135(00)00275-3
Fray MD, Paton DJ, Alenius S. The effects of bovine viral diarrhoea virus on cattle reproduction in relation to disease control. Anim Reprod Sci. 2000b;60-61:615-627. https://doi.org/10.1016/s0378-4320(00)00082-8
Givens MD, Heath AM, Brock KV, Brodersen BW, Carson RL, Stringfellow DA. Detection of bovine viral diarrhea virus in semen obtained after inoculation of seronegative postpubertal bulls. Am J Vet Res. 2003;64(4):428–434. https://doi.org/10.2460/ajvr.2003.64.428
Givens MD, Riddell KP, Edmondson MA et al. Epidemiology of prolonged testicular infections with bovine viral diarrhea virus. Vet Microbiol. 2009;139(1-2):42–51. https://doi.org/10.1016/j.vetmic.2009.04.029
Givens MD, Riddell KP, Walz PH et al. Noncytopathic bovine viral diarrhea virus can persist in testicular tissue after vaccination of peri-pubertal bulls but prevents subsequent infection. Vaccine. 2007;25(5):867–876. https://doi.org/10.1016/j.vaccine.2006.09.037
Graham DA, German A, Mawhinney K, Goodall EA. Antibody responses of naive cattle to two inactivated bovine viral diarrhoea virus vaccines, measured by indirect and blocking ELISAS and virus neutralisation. Vet Rec. 2003;152(26):795–800. https://doi.org/10.1136/vr.152.26.795
Graham DA, Lynch M, Coughlan S, et al. Development and review of the voluntary phase of a national BVD eradication programme in Ireland. Vet Rec. 2014;174(3):67. https://doi.org/10.1136/vr.101814
Grooms DL, Bolin SR, Coe PH, Borges RJ, Coutu CE. Fetal protection against continual exposure to bovine viral diarrhea virus following administration of a vaccine containing an inactivated bovine viral diarrhea virus fraction to cattle. Am J Vet Res. 2007;68(12):1417–1422. https://doi.org/10.2460/ajvr.68.12.1417
Grooms DL, Brock KV, Pate JL, Day ML. Changes in ovarian follicles following acute infection with bovine viral diarrhea virus. Theriogenology. 1998a;49(3):595–605. https://doi.org/10.1016/s0093-691x(98)00010-7
Grooms DL, Brock KV, Ward LA. Detection of bovine viral diarrhea virus in the ovaries of cattle acutely infected with bovine viral diarrhea virus. J Vet Diagn Invest. 1998b;10(2):125–129. https://doi.org/10.1177/104063879801000201
Grooms DL, Brock KV, Ward LA. Detection of cytopathic bovine viral diarrhea virus in the ovaries of cattle following immunization with a modified live bovine viral diarrhea virus vaccine. J Vet Diagn Invest. 1998c;10(2):130–134. https://doi.org/10.1177/104063879801000202
Grooms DL, Ward LA, Brock KV. Morphologic changes and immunohistochemical detection of viral antigen in ovaries from cattle persistently infected with bovine viral diarrhea virus. Am J Vet Res. 1996;57(6):830–833
Hamers C, Di Valentin E, Lecomte C et al. Virus neutralising antibodies against 22 bovine viral diarrhoea virus isolates in vaccinated calves. Vet J. 2002;163(1):61–67. https://doi.org/10.1053/tvjl.2001.0638
Han JH, Weston JF, Heuer C, Gates MC. Modelling the economics of bovine viral diarrhoea virus control in pastoral dairy and beef cattle herds. Prev Vet Med. 2020;182:105092. https://doi.org/10.1016/j.prevetmed.2020.105092
Houe H, Lindberg A, Moennig V. Test strategies in bovine viral diarrhea virus control and eradication campaigns in Europe. J Vet Diagn Invest. 2006;18(5):427–436. https://doi.org/10.1177/104063870601800501
Howard CJ. Immunological responses to bovine virus diarrhoea virus infections. Rev Sci Tech. 1990;9(1):95–103. https://doi.org/10.20506/rst.9.1.488
Humphry RW, Brülisauer F, McKendrick IJ, Nettleton PF, Gunn GJ. Prevalence of antibodies to bovine viral diarrhoea virus in bulk tank milk and associated risk factors in Scottish dairy herds. Vet Rec. 2012;171(18):445. https://doi.org/10.1136/vr.100542
Kalaycioglu AT. Bovine viral diarrhoea virus (BVDV) diversity and vaccination. A review. Vet Q. 2007;29(2):60–67. https://doi.org/10.1080/01652176.2007.9695228
Kirkland PD, Mackintosh SG, Moyle A. The outcome of widespread use of semen from a bull persistently infected with pestivirus. Vet Rec. 1994;135(22):527–529. https://doi.org/10.1136/vr.135.22.527
Kirkland PD, McGowan MR, Mackintosh SG, Moyle A. Insemination of cattle with semen from a bull transiently infected with pestivirus. Vet Rec. 1997;140(5):124–127. https://doi.org/10.1136/vr.140.5.124
Kirkland PD, Richards SG, Rothwell JT, Stanley DF. Replication of bovine viral diarrhoea virus in the bovine reproductive tract and excretion of virus in semen during acute and chronic infections. Vet Rec. 1991;128(25):587–590. https://doi.org/10.1136/vr.128.25.587
Lanyon SR, Hill FI, Reichel MP, Brownlie J. Bovine viral diarrhoea: pathogenesis and diagnosis. Vet J. 2014;199(2):201–209. https://doi.org/10.1016/j.tvjl.2013.07.024
Larsson B, Niskanen R, Alenius S. Natural infection with bovine virus diarrhea virus in a dairy-herd - a spectrum of symptoms including early reproductive failure and retained placenta. Anim Reprod Sci. 1994;36(1-2):37–48. https://doi.org/10.1016/0378-4320(94)90052-3
Liess B, Orban S, Frey HR, Trautwein G, Wiefel W, Blindow H. Studies on transplacental transmissibility of a bovine virus diarrhoea (BVD) vaccine virus in cattle. II. Inoculation of pregnant cows without detectable neutralizing antibodies to BVD virus 90-229 days before parturition (51st to 190th day of gestation). Zentralbl Veterinarmed B. 1984;31(9):669–681
Lindberg AL, Alenius S. Principles for eradication of bovine viral diarrhoea virus (BVDV) infections in cattle populations. Vet Microbiol. 1999;64(2-3):197–222. https://doi.org/10.1016/s0378-1135(98)00270-3
McClurkin AW, Coria MF, Cutlip RC. Reproductive performance of apparently healthy cattle persistently infected with bovine viral diarrhea virus. J Am Vet Med Assoc. 1979;174(10):1116–1119
McGowan MR, Kafi M, Kirkland PD et al. Studies of the pathogenesis of bovine pestivirus-induced ovarian dysfunction in superovulated dairy cattle. Theriogenology. 2003;59(3-4):1051–1066. https://doi.org/10.1016/s0093-691x(02)01136-6
McGowan MR, Kirkland PD, Rodwell BJ, Kerr DR, Carroll CL. A field investigation of the effects of bovine viral diarrhea virus infection around the time of insemination on the reproductive performance of cattle. Theriogenology. 1993;39(2):443–449. https://doi.org/10.1016/0093-691x(93)90387-k
Meadows D. A study to investigate the use and application of BVDV vaccine in uk cattle. Cattle Practice. 2010;18:202–215
Meyer G, Deplanche M, Roux D et al. Fetal protection against bovine viral diarrhoea type 1 virus infection after one administration of a live-attenuated vaccine. Vet J. 2012;192(2):242–245. https://doi.org/10.1016/j.tvjl.2011.05.011
Meyling A, Houe H, Jensen AM. Epidemiology of bovine virus diarrhoea virus. Rev Sci Tech. 1990;9(1):75–93. https://doi.org/10.20506/rst.9.1.489
Moennig V, Becher P. Control of bovine viral diarrhea. Pathogens. 2018;7(1):29. https://doi.org/10.3390/pathogens7010029
Müller-Doblies D, Arquint A, Schaller P et al. Innate immune responses of calves during transient infection with a noncytopathic strain of bovine viral diarrhea virus. Clin Diagn Lab Immunol. 2004;11(2):302–312. https://doi.org/10.1128/cdli.11.2.302-312.2004
Newcomer BW, Chamorro MF, Walz PH. Vaccination of cattle against bovine viral diarrhea virus. Vet Microbiol. 2017;206:78–83. https://doi.org/10.1016/j.vetmic.2017.04.003
Newcomer BW, Walz PH, Givens MD, Wilson AE. Efficacy of bovine viral diarrhea virus vaccination to prevent reproductive disease: a meta-analysis. Theriogenology. 2015;83(3):360–365.e1. https://doi.org/10.1016/j.theriogenology.2014.09.028
Oguejiofor CF, Thomas C, Cheng Z, Wathes DC. Mechanisms linking bovine viral

KEY POINTS

- Reproductive failure is considered to account for more than 75% of the financial losses associated with bovine viral diarrhoea virus (BVDV) infection.
- During acute infection, BVDV is responsible for a range of pathologies and can be found throughout the male and female reproductive tracts.
- Infection around breeding can result in failure in conception and embryonic death. Later infection can cause death of the conceptus, the generation of persistent infection or fetal developmental defects.
- Transient infection in bulls both during the peri-pubertal and post-pubertal phases can lead to chronic shedding of the virus in semen, despite the development of immunity, and while this is a relatively rare occurrence associated with low virus titres in the ejaculates, the importance in relation to fertility and the spread of infection is unknown in the UK situation.
- The published studies on the BVDV vaccines licensed in the UK indicate that they are protective against abortion and fetal infection, but this can be expected to be most effective when protecting against virus strains that are closely related to the vaccine strain.
- Given that there are regional and herd-level BVDV eradication programmes in place in the UK against a background of endemic infection, herd vaccination offers a way to mitigate the risk of BVDV in herds that have eradicated the infection.

diarrhea virus (BVDV) infection with infertility in cattle. Anim Health Res Rev. 2019;20(1):72–85. https://doi.org/10.1017/S1466252319000057
Packianathan R, Clough WJ, Hodge A, et al. Prevention of fetal infection in heifers challenged with bovine viral diarrhoea virus type 1a by vaccination with a type 1c or type 1a vaccine. N Z Vet J. 2017;65(3):134–139. https://doi.org/10.1080/00480169.2017.1291376
Patel JR, Shilleto RW, Williams J, Alexander DC. Prevention of transplacental infection of bovine foetus by bovine viral diarrhoea virus through vaccination. Arch Virol. 2002;147(12):2453–2463. https://doi.org/10.1007/s00705-002-0878-3
Paton DJ, Christiansen KH, Alenius S, Cranwell MP, Pritchard GC, Drew TW. Prevalence of antibodies to bovine virus diarrhoea virus and other viruses in bulk tank milk in England and Wales. Vet Rec. 1998;142(15):385–391. https://doi.org/10.1136/vr.142.15.385
Paton DJ, Goodey R, Brockman S, Wood L. Evaluation of the quality and virological status of semen from bulls acutely infected with BVDV. Vet Rec. 1989;124(3):63–64. https://doi.org/10.1136/vr.124.3.63
Penny C. The bcva's bull pre-breeding examination certificate. Vet Record. 2010;167(15):551–554
Peterhans E, Schweizer M. BVDV: a pestivirus inducing tolerance of the innate immune response. Biologicals. 2013;41(1):39–51. https://doi.org/10.1016/j.biologicals.2012.07.006
Pinior B, Garcia S, Minviel JJ, Raboisson D. Epidemiological factors and mitigation measures influencing production losses in cattle due to bovine viral diarrhoea virus infection: A meta-analysis. Transbound Emerg Dis. 2019;66(6):2426–2439. https://doi.org/10.1111/tbed.13300
Presi P, Struchen R, Knight-Jones T, Scholl S, Heim D. Bovine viral diarrhea (BVD) eradication in Switzerland--experiences of the first two years. Prev Vet Med. 2011;99(2-4):112–121. https://doi.org/10.1016/j.prevetmed.2011.01.012
Prosser NS, Hill EM, Armstrong D et al. Descriptive analysis of national bovine viral diarrhoea test data in England (2016-2020). Vet Rec. 2022;191(5):e1854. https://doi.org/10.1002/vetr.1854
Read AJ, Gestier S, Parrish K et al. Prolonged detection of bovine viral diarrhoea virus infection in the semen of bulls. Viruses. 2020;12(6):674. https://doi.org/10.3390/v12060674
Revell SG, Chasey D, Drew TW, Edwards S. Some observations on the semen of bulls persistently infected with bovine virus diarrhoea virus. Vet Rec. 1988;123(5):122–125. https://doi.org/10.1136/vr.123.5.122
Richter V, Lebl K, Baumgartner W, Obritzhauser W, Käsbohrer A, Pinior B. A systematic worldwide review of the direct monetary losses in cattle due to bovine viral diarrhoea virus infection. Vet J. 2017;220:80–87. https://doi.org/10.1016/j.tvjl.2017.01.005
Robert A, Beaudeau F, Seegers H, Joly A, Philipot JM. Large scale assessment of the effect associated with bovine viral diarrhoea virus infection on fertility of dairy cows in 6149 dairy herds in Brittany (Western France). Theriogenology. 2004;61(1):117–127. https://doi.org/10.1016/s0093-691x(03)00182-1
Rodning SP, Givens MD, Marley MS et al. Reproductive and economic impact following controlled introduction of cattle persistently infected with bovine viral diarrhea virus into a naive group of heifers. Theriogenology. 2012;78(7):1508–1516. https://doi.org/10.1016/j.theriogenology.2012.05.031
Rümenapf T, Stark R, Heimann M, Thiel HJ. N-terminal protease of pestiviruses: identification of putative catalytic residues by site-directed mutagenesis. J Virol. 1998;72(3):2544–2547. https://doi.org/10.1128/JVI.72.3.2544-2547.1998
Schneider R, Unger G, Stark R, Schneider-Scherzer E, Thiel HJ. Identification of a structural glycoprotein of an RNA virus as a ribonuclease. Science. 1993;261(5125):1169–1171. https://doi.org/10.1126/science.8356450
Scottish Government. Scottish BVD eradication programme. 2023. https://www.gov.scot/publications/scottish-bvd-eradication-scheme/ (accessed 19 December 2023)
Smith AK, Grimmer SP. Birth of a BVDV-free calf from a persistently infected embryo transfer donor. Vet Rec. 2000;146(2):49–50. https://doi.org/10.1136/vr.146.2.49
Sozzi E, Righi C, Boldini M, et al. Cross-reactivity antibody response after vaccination with modified live and killed bovine viral diarrhoea virus (bvd) vaccines. Vaccines (Basel). 2020;8(3):374. https://doi.org/10.3390/vaccines8030374
Ssentongo YK, Johnson RH, Smith JR. Association of bovine viral diarrhoea-mucosal disease virus with ovaritis in cattle. Aust Vet J. 1980;56(6):272–273. https://doi.org/10.1111/j.1751-0813.1980.tb05722.x
Ståhl K, Kampa J, Baule C et al. Molecular epidemiology of bovine viral diarrhoea during the final phase of the Swedish BVD-eradication programme. Prev Vet Med. 2005;72(1-2):103–219. https://doi.org/10.1016/j.prevetmed.2005.01.021
Strain S, Verner S, Campbell E, Hodnik JJ, Santman-Berends IMGA. The Northern Ireland control programmes for infectious cattle diseases not regulated by the EU. Front Vet Sci. 2021;8:694197. https://doi.org/10.3389/fvets.2021.694197
Toplak I, Hostnik P, Černe D, Mrkun J, Starič J. The principles of the voluntary programme for the control and elimination of bovine viral diarrhoea virus (bvdv) from infected herds in Slovenia. Front Vet Sci. 2021;8:676473. https://doi.org/10.3389/fvets.2021.676473
Tsuboi T, Osawa T, Kimura K, Kubo M, Haritani M. Experimental infection of early pregnant cows with bovine viral diarrhea virus: transmission of virus to the reproductive tract and conceptus. Res Vet Sci. 2011;90(1):174–178. https://doi.org/10.1016/j.rvsc.2010.04.024
Tunney O. Bulls and bvd. Cattle Practice. 2016;24:23–27
Valle PS, Martin SW, Skjerve E. Time to first calving and calving interval in bovine virus diarrhoea virus (BVDV) sero-converted dairy herds in Norway. Prev Vet Med. 2001;51(1-2):17–36. https://doi.org/10.1016/s0167-5877(01)00204-5
Virakul P, Fahning ML, Joo HS, Zemjanis R. Fertility of cows challenged with a cytopathic strain of bovine viral diarrhea virus during an outbreak of spontaneous infection with a noncytopathic strain. Theriogenology. 1988;29(2):441–449. https://doi.org/10.1016/0093-691x(88)90246-4
Voges H, Horner GW, Rowe S, Wellenberg GJ. Persistent bovine pestivirus infection localized in the testes of an immuno-competent, non-viraemic bull. Vet Microbiol. 1998;61(3):165–175. https://doi.org/10.1016/s0378-1135(98)00177-1
Walz PH, Givens MD, Cochran A, Navarre CB. Effect of dexamethasone administration on bulls with a localized testicular infection with bovine viral diarrhea virus. Can J Vet Res. 2008;72(1):56–62
Walz PH, Givens MD, Rodning SP et al. Evaluation of reproductive protection against bovine viral diarrhea virus and bovine herpesvirus-1 afforded by annual revaccination with modified-live viral or combination modified-live/killed viral vaccines after primary vaccination with modified-live viral vaccine. Vaccine. 2017;35(7):1046–1054. https://doi.org/10.1016/j.vaccine.2017.01.006
Wentink GH, Remmen JL, van Exsel AC. Pregnancy rate of heifers bred by an immunotolerant bull persistently infected with bovine viral diarrhoea virus. Vet Q. 1989;11(3):171–174. https://doi.org/10.1080/01652176.1989.9694217
Wernike K, Gethmann J, Schirrmeier H, Schröder R, Conraths FJ, Beer M. Six years (2011-2016) of mandatory nationwide bovine viral diarrhea control in Germany-a success story. Pathogens. 2017;6(4):50. https://doi.org/10.3390/pathogens6040050
Wernike K, Michelitsch A, Aebischer A et al. The occurrence of a commercial Npro and Erns double mutant BVDV-1 live-vaccine strain in newborn calves. Viruses. 2018;10(5):274. https://doi.org/10.3390/v10050274
Woolums AR, Berghaus RD, Berghaus LJ et al. Effect of calf age and administration route of initial multivalent modified-live virus vaccine on humoral and cell-mediated immune responses following subsequent administration of a booster vaccination at weaning in beef calves. Am J Vet Res. 2013;74(2):343–354. https://doi.org/10.2460/ajvr.74.2.343
Yeşilbağ K, Alpay G, Becher P. Variability and global distribution of subgenotypes of bovine viral diarrhea virus. Viruses. 2017;9(6):128. https://doi.org/10.3390/v9060128