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Importance of Viral Disease in Dairy Cow Fertility

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ABSTRACT

Many viral diseases are endemic in cattle populations worldwide. The ability of many viruses to cross the placenta and cause abortions and fetal malformations is well understood. There is also significant evidence that viral infections have additional actions in dairy cows, which are reflected in reduced conception rates. These effects are, however, highly dependent on the time at which an individual animal first contracts the disease and are less easy to quantify. This paper reviews the evidence relating to five viruses that can affect fertility, together with their potential mechanisms of action. Acute infection with non-cytopathic bovine viral diarrhea virus (BVDV) in mid-gestation increases abortion rates or causes the birth of persistently infected calves. BVDV infections closer to the time of breeding can have direct effects on the ovaries and uterine endometrium, which cause estrous cycle irregularities and early embryo mortality. Fertility may also be reduced by BVDV-induced immunosuppression, which increases the susceptibility to bacterial infections. Bovine herpesvirus (BHV)-1 is most common in pre-pubertal heifers, and can slow their growth, delay breeding, and increase the age at first calving. Previously infected animals subsequently show reduced fertility. Although this may be associated with lung damage, ovarian lesions have also been reported. Both BHV-1 and BHV-4 remain latent in the host following initial infection and may be reactivated later by stress, for example associated with calving and early lactation. While BHV-4 infection alone may not reduce fertility, it appears to act as a co-factor with established bacterial pathogens such as *Escherichia coli* and *Trueperella pyogenes* to promote the development of endometritis and delay uterine repair mechanisms after calving. Both Schmallenberg virus (SBV) and bluetongue virus (BTV) are transmitted by insect vectors and lead to increased abortion rates and congenital malformations. BTV-8 also impairs the development of hatched blastocysts; furthermore, infection around the time of breeding with either virus appears to reduce conception rates. Although the reductions in conception rates are often difficult to quantify, they are nevertheless sufficient to cause economic losses, which help to justify the benefits of vaccination and eradication schemes.

1. Introduction

Although viral disease remains a major cause of financial loss to the modern cattle industry, its potential impact on fertility is generally underestimated, and the main mechanisms of action are often unclear. Factors including trade globalization, increases in herd size, and environmental change have contributed to the spread of existing pathogens and the introduction of disease into regions and animal populations that were previously free of it [1]. Poor fertility and udder health/milk quality remain the two major causes of concern among dairy producers [2]. In terms of fertility, the ability of viruses to cause abortions and fetal malformations has probably received the most attention [3]. The outcome is generally dependent on the stage of pregnancy during which the initial infection occurs. The effects of viral diseases on reproductive performance are, however, much more pervasive and can have many subtle effects through reductions in conception rates and increased risk of culling through failure to conceive in a timely fashion. Excluding fertilization failure, approximately 40% of bovine embryos die in the first three weeks after service or insemination, with cows returning to estrus after 21–24 d. A further 10%–20% of embryos are lost between days 24–60 of gestation [4]. In comparison, abortion rates on cattle farms are usually quite low (5%–10%) and have many potential etiologies that are often difficult to diagnose reliably [5]. In addition to the loss of the fetus,

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an abortion does, however, often have adverse effects on the fate of the dam. Depending on the stage of gestation when it occurs, the cow either may need to be rebred (thus increasing her calving interval) or may start the next lactation prematurely. In one study, for example, 4.8% of 7768 Holstein heifers aborted. This increased their risk of leaving the herd without completing a first lactation 2.73 times. One third of the animals which did not complete a first lactation either died or had to be culled within 50 d of calving [6]. The present short review focuses on five different viral infections showing a variety of mechanisms that can have an impact on dairy cow fertility.

2. Bovine viral diarrhea virus

Bovine viral diarrhea virus (BVDV) is discussed first and in the most detail, as its effects on fertility have been the most widely studied; thus, more is understood about its potential underlying mechanisms. BVDV is a Flaviviridae pestivirus that is endemic in many countries worldwide, with a prevalence of 40%–90% in individual cattle and 28%–66% in cattle herds [7,8]. It comprises a single-stranded, positive-sense RNA genome that is classified by sequence differences as type 1 or 2 (BVDV-1 or BVDV-2). There is also a third type, BVDV-3 (a Hobi-like, atypical pestivirus). The virus exists as either non-cytopathogenic (ncp) or cytopathogenic (cp) biotypes, with the ncp biotype causing the majority of field losses [9]. BVDV exhibits vertical transmission from mother to fetus, has a broad tissue tropism, and can infect the host either transiently or persistently [10]. Such RNA viruses display significant genetic variation, facilitating the emergence of new species [11]. Mammalian cells normally produce type I interferons (IFNs) in response to viral infection, which then trigger a cascade of antiviral pathways. BVDV causes immunosuppression through its ability to inhibit IFN production, thereby delaying the host's responses and enhancing the ability of the virus to complete its replication cycle [12,13].

BVDV infection generally occurs via the oronasal route, but direct transmission to the reproductive tract via semen or embryo transfer is also possible [14,15]. Acutely infected animals usually eliminate the virus within 10–14 d, but transmissible virus can persist for much longer in some animals that have apparently recovered [16]. In rare cases, bulls develop a persistent infection of the testes—an immune-privileged site. More commonly, BVDV is detectable by reverse transcription polymerase chain reaction (RT-PCR) in semen for some months after an initial acute infection, although the continued risk of viral transmission appears to be unlikely after nine weeks [15]. Fetal infection with ncp BVDV before the development of immune competence (i.e., prior to gestation day 120) results in early embryonic death, later abortion, or the birth of an immunotolerant calf that is persistently infected (PI) [17]. The PI calf can continuously shed virus from all secretions, and is therefore a major source of infection within a herd.

The effects of acute BVDV infection vary extensively depending on both biotype and virulence, and this can lead to either avoidance or initiation of apoptotic and innate immune responses. Ncp BVDV can dampen innate immune responses in several ways [13,18]. The virus is first detected by toll-like receptor (TLR)-3 or TLR-7/TLR-8 located in intracellular compartments or by cytoplasmic pattern-recognition receptors (RIG-I, DDX58), which detect single-stranded RNA. The downstream signaling pathway from TLR-3 involves the IFN regulatory factor (IRF)-3 and IRF-7, which usually upregulate the transcription of type I IFNs. The BVDV protein N^{pro} targets IRF-3 toward proteasomal degradation, thus inhibiting downstream signaling and preventing the IFN rise [18]. Guanylate-binding protein 4 (GBP4), an IFN-inducible GTPase, can also inhibit this pathway while leaving NF-κB signaling intact [19]. In addition, the secreted BVDV structural protein E^{rns} degrades viral RNA through its extracellular function as a ribonuclease [20].

Many of the economic losses attributed to BVDV are due to suboptimal fertility, in addition to causing abortion and fetal deformity at later stages of gestation [10,17]. BVDV-induced immunosuppression increases susceptibility to other diseases, which may then also affect fertility. Conception rates fell by up to 44% following experimental infections with BVDV either 9 d before or 4 d after insemination [21]. The review by Fray et al. [22] cited many similar results that have been reported following ncp BVDV infection in the field, in spite of the occasional report to the contrary. Since then, Rüfenacht et al. [23] measured fertility parameters in Swiss dairy herds with a high prevalence of BVDV using individual seroconversion measurements to assess the time of likely exposure. Infection during the first 45 d of gestation did not influence non-return rates, but infection in mid-gestation was associated with an increased abortion rate from 6.1% to 15.8%. The timing of exposure is clearly critical, as Rodning et al. [24] reported that when PI animals were introduced to naïve heifers 50 d prior to the start of breeding, they developed active immunity and there was no adverse effect on reproductive performance. Newcomer et al. [25] undertook a meta-analysis of 46 studies to determine the potential benefits of vaccination against BVDV on three reproductive outcomes. Vaccinated cows experienced a reduction in both abortion and fetal infection rates of nearly 45% and 85%, respectively, compared with unvaccinated cohorts, while the risk of becoming pregnant was smaller but nevertheless improved by about 5%. It is likely that a change of this magnitude would fail to reach significance in smaller studies due to a lack of statistical power.

A variety of mechanisms have been suggested to account for such reductions in fertility via effects on the ovary, uterus, and early embryo. BVDV antigen was detectable in ovaries 60 d after acute infection [26] and in oocytes and follicular cells of PI heifers [27]. Animals infected with BVDV develop oophoritis [26] and have impaired ovulation and ovarian steroidogenesis [27–29]. When heifers were infected with acute ncp BVDV, follicular growth patterns were affected through the subsequent two estrous cycles, including reduced growth of dominant follicles [30]. Similarly, when heifers were infected 9 d before a synchronized estrus, luteinizing hormone (LH) pulsatility was decreased, there was a delay from ovulation to the progesterone rise, and subsequent progesterone levels were lower [28,31]. These results align with studies showing that various types of stress can either delay or inhibit ovulation mechanisms [32,33], while both heat stress and intramammary infection can reduce follicular steroidogenesis, disrupt follicular dominance, and reduce the pre-ovulatory LH surge [34]. Any acute infection occurring at this critical stage of the estrous cycle is likely to have a similar effect.

The uterine endometrium is also recognized as a major site for BVDV infection [17,29]. BVDV was found in the uterus 7–16 d after infecting heifers with BVDV by either intravenous inoculation or by breeding to a PI bull [14,35], while ncp BVDV was isolated from uterocervical mucus 24 d after initial infection [22]. BVDV antigen was also detected in macrophage-like cells of the endometrium in 23% of 65 cows examined in a slaughterhouse survey [36]. There is good evidence for two mechanisms by which the uterine presence of BVDV may have detrimental effects on fertility: first, by predisposing cows toward the development of endometritis; and second, by interference with the establishment of pregnancy. The bovine uterus is colonized with many bacterial species following calving in over 90% of cows [37]. These bacteria should be cleared rapidly using mucosal defense systems and an innate immune response involving endometrial epithelial and stromal cells in addition to professional immune cells [38,39]. This early innate response is crucial to avoid the development of uterine disease; nevertheless, many dairy cows do develop metritis and/or endometritis (estimated at around 40% and 20% of all animals, respectively) [38]. In cultured bovine endometrial cells, experimental infection with ncp BVDV inhibited a variety of immune pathways normally activated in response to a challenge with bacterial lipopolysaccharide (LPS), including downregulation of many interferon-stimulated genes (ISGs), which are an important part of uterine defense mechanisms [40,41]. Infection with ncp BVDV was also able to switch endometrial prostaglandin production from prostaglandin (PG)$F_{2\alpha}$ to PGE_2 [42]. $PGF_{2\alpha}$ is recognized as an immune enhancer, while PGE_2 acts as an immune suppressor and is luteotrophic [43,44]; therefore, this switch may also reduce the endometrial immune response to bacteria and increase the likelihood of a cow developing a persistent corpus luteum [45], which is often found in association with uterine disease [46].

Maternal recognition of pregnancy in cows is achieved through the production of interferon tau (IFNT) by the trophectoderm of the elongating conceptus [47,48], which inhibits the development of endometrial oxytocin receptors, thereby preventing luteolysis [49,50]. IFNT is a type I IFN that is structurally related to IFN-α and IFN-β but lacks viral responsive elements in its promoter and is therefore not upregulated by viral infection [51]. IFNT does, however, bind to the same IFN-α/IFN-β receptor on the uterine endometrium. Together with progesterone, IFNT programs the uterine endometrium to develop a receptive environment for implantation, including upregulation of many ISGs [50,52,53]. These are likely to have crucial roles in the establishment of pregnancy via modulation of uterine immunity, stromal remodeling, hyperplasia of the endometrial glands, and development of the uterine vasculature [52,54]. Acute infection with ncp BVDV alone has been shown to have a limited influence on endometrial gene expression *in vitro* [40]. However, infection did interfere with the ISG regulatory IRF-STAT1 and STAT2 pathways to inhibit IFNT-induced ISG expression including *ISG15*, *HERC5*, *USP18* (involved in protein modification via ISGylation), *DDX58*, *IFIH1* (cytosolic detection of viral RNA) and *IFIT3*, *MX2*, *RSAD2*, and *SAMD9* (immune regulators with antiviral activity) [41]. Upregulation of the endometrial ISGylation pathway is an important process in early pregnancy that is conserved across mammalian species [55]. Therefore, dysregulation of the antiviral IFN response by BVDV can undoubtedly interfere with IFNT signaling in the endometrium, suggesting another mechanism whereby infection in early gestation may reduce conception rates.

There has been considerable research on the effects of BVDV on bovine embryos following concern that naïve cows might develop BVDV following embryo-transfer procedures. Embryos produced using both *in vivo* and *in vitro* techniques have been infected with either ncp or cp virus at all stages from oocyte to hatched blastocyst. The affinity of BVDV for *in vivo*-derived embryos varied according to the strain of BVDV [56,57]. Uterine inoculation with ncp BVDV-1 in the medium used for embryo transfer on day 7 of a synchronized estrous cycle resulted in 6/10 heifers becoming pregnant 30 d later, but these pregnancies had been lost within the following 30 d [58]. Although BVDV replicated efficiently in cumulus cells surrounding bovine oocytes, this did not affect the development of the blastocysts subsequently produced by *in vitro* fertilization [59]. Similarly, when oocytes, zygotes, 8-cell embryos, morulae, and hatched blastocysts were infected with either ncp or cp virus, development was only adversely affected with cp BVDV and when the zona pellucida was not present [60]. In a more recent study, cumulus-oocyte complexes were infected with BVDV-1, BVDV-2, or BVDV-3 at different doses [57]. BVDV-1 had no effect on the embryos that did develop, and BVDV-2 infection actually increased cleavage rates but did not affect blastocyst rates. In both cases, however, the degenerate embryos tested positive. Overall, the oocytes infected with BVDV-1 and BVDV-2 developed normally but carried the virus. BVDV-3 (Hobi-like virus) reduced both cleavage and blastocyst rates, so would be expected to cause pre-implantation embryo loss *in vivo*. Bielanski et al. [35] used semen from a PI bull on superovulated cows, collected day 7 embryos, and transferred washed embryos to clean recipients. Although BVDV was detected in the pre-transfer embryos, it did not infect the new host. From this work, it was concluded that the risk of transmission of BVDV to host cows via embryo transfer was minimal providing correct washing procedures were applied, as recommended by International Embryo Transfer Society guidelines [61]. This resulted in low copy numbers of virus, as measured by a sensitive quantitative polymerase chain reaction (qPCR) technique [62].

In summary, acute ncp BVDV infection causes intracellular changes to ovarian and endometrial tissues through combined effects on pathways regulating immunity. These effects can reduce cow fertility by causing estrous cycle irregularities, early embryo mortality, and immunosuppression. Infections during mid-gestation increase abortion rates or may give rise to the birth of PI calves.

3. Bovine herpesvirus-1

Infectious bovine rhinotracheitis (IBR) is a highly contagious respiratory disease caused by bovine herpesvirus (BHV)-1 that is characterized by acute inflammation of the upper respiratory tract. BHV-1 is a virus of the family Herpesviridae and subfamily Alphaherpesvirinae. Although some countries have achieved IBR eradication [63], the disease remains endemic in dairy herds in many parts of the world, including Britain and Ireland [8,64]. A recent meta-analysis found a pooled prevalence of BHV-1 of 40% in Chinese cattle [65]. It is a major contributing factor in calf pneumonia, which remains the most common cause of mortality and morbidity in dairy calves between 1 and 5 months of age [66]. BHV-1 can also cause conjunctivitis, abortions, encephalitis, and generalized systemic infections [5,63]. After the first infection, the virus is never fully eliminated, remaining latent in nerve cells of the brain. From there, it can be reactivated in times of stress, mediated via increased glucocorticoids [67–69]. BHV-1 is only one of a diverse range of pathogens that can contribute to bovine respiratory disease (BRD) including several other viruses (i.e., bovine respiratory syncytial virus (BRSV), parainfluenza III virus (PI3), BVDV, and corona viruses), bacteria (e.g., *Mannheimia haemolytica*, *Haemophilus somnus*, *Pasteurella* spp., and *Mycoplasma*), and fungal genera (e.g., *Aspergillus*) [70].

Numerous epidemiology studies in various countries around the world have determined that up to 46% of calves contract BRD [70,71]. For the calves that survive, there is mounting evidence of longer term consequences of juvenile disease on adult performance [72,73]. BRD-affected animals have reduced growth rates [71,74], which in turn delay the age at first breeding and first calving. This is often associated with bronchopneumonic lesions and pleural adhesions [75]. For example, first parity was delayed by a median of six months in heifers that had BRD in the first three months of life [76]. Bach [74] reported that calves experiencing four episodes of BRD before first calving had 1.87 ± 0.14 greater odds of failing to complete their first lactation in comparison with healthy calves. Another study found that calving intervals were increased by 12% in mature cows that had experienced severe BRD as calves during their first three months [77,78]. In Irish herds with a seasonal calving pattern that were identified as positive by a bulk tank BHV-1 enzyme linked immunosorbent assay (ELISA), the three-week calving rate was significantly lower in multiparous cows in comparison with BHV-1 negative herds [79]. Two related epidemiology studies in Ethiopia found significantly higher rates of uterine infection and retained fetal membranes in cows that were seropositive for BHV-1 [80,81]. A meta-analysis of over 7500 animals showed an overall decrease in abortion risk of 60% in pregnant cattle vaccinated against BHV-1[82].

A number of studies have investigated the effects of treating cattle with modified live IBR vaccine around the time of breeding. Heifers inoculated at estrus [83], the day after [84], or on days 7 or 14 post-breeding [85] developed mild oophoritis characterized by foci of necrosis, a few necrotic follicles, and mononuclear cell accumulation in the corpus luteum. Heifers inoculated on days 21 or 28 post-breeding did not have lesions in the corpus luteum, but there were numerous necrotic follicles [85]. Such lesions were not found in ovaries from which BHV-1 was not isolated [84]. Vaccination at estrus was followed by a reduction in circulating progesterone [84,86]; conception rates were also reduced [86,87]. Although this review relates primarily to cows, there is evidence that young bulls exposed to BHV-1 at about six months of age had reduced sperm quality six months later [88]. Givens [89] recently reviewed the effects of a number of viral diseases on bulls and the transmission risks of these diseases via semen.

In summary, a high proportion of dairy calves experience BRD, which is often associated with BHV-1 infection. This slows growth, leading to an increased age at first calving. Fertility, risk of culling, and abortion rates are all subsequently increased. Information on the direct effects on the reproductive tract is sparse, but there is some evidence that infection can have a direct effect on ovarian function.

4. Bovine herpesvirus-4

BHV-4 is a double-stranded DNA virus that is highly prevalent in some dairy herds and has been associated with reduced fertility [90,91]. In common with other herpes viruses, it can remain latent in the host following an initial infection in several cell types including macrophages. This results in a persistent infection [92], which can be reactivated *in vitro* by glucocorticoids [93,94]. There is evidence from measuring seroconversion that it can also be reactivated *in vivo* during the periparturient period [95] and in association with clinical metritis [96].

Like BVDV, BHV-4 can readily infect the uterus and has been associated with metritis and endometritis; however, its role in fertility is somewhat unclear, as it has often also been found in control cows that did not have uterine infection. In addition, tested cows were usually also positive for recognized bacterial pathogens including *Escherichia coli*, *Trueperella pyogenes*, *Streptococcus* spp., and *Histophilus somni* [97–100]. Nevertheless, there is evidence that BHV-4 can be associated with reduced fertility. A comparison between cows requiring one or two inseminations to conceive and those needing more than two inseminations found a higher prevalence of BHV-4 in the cows requiring more inseminations [101]. Klamminger et al. [100] also recorded reduced risks of infected animals either being inseminated before 80 d after calving or conceiving within 200 d.

Unlike ncp BVDV, BHV-4 is cytopathic, and infection can kill endometrial epithelial and stromal cells [102,103]. Accumulating evidence supports the view that BHV-4 can act as a co-factor with established uterine pathogens to promote the development of endometritis [99,104,105]. Replication of BHV-4 depends on immediate early gene 2 (*IE2*) transactivation, and it has been shown that this promoter is upregulated by PGE_2, tumor necrosis factor-α (TNF-α), *Escherichia coli*, and LPS, all of which are associated with bacterial infection of the endometrium [104,106]. BHV-4 in turn activates the interleukin (IL)-8 gene promoter in endometrial cells [103,107]. This is a key chemokine that attracts granulocytes to the uterus. In a recent study, Tebaldi et al. [108] measured global gene transcription caused by the BHV-4 infection of cultured bovine endometrial stromal cells. In addition to IL-8, another main pathway that was activated involved the upregulation of matrix metalloproteinase (MMP)-1. MMPs are involved in the remodeling of the post-partum endometrium [109]. They are also important in controlling the balance of immune responses. On the one hand, their proteolytic activity can promote immune cell migration and activate cytokines such as IL-1, IL-8, TNF-α, and defensins [110]. On the other hand, over-activation of MMPs has been associated with many immunopathological outcomes (reviewed in Ref. [108]).

In summary, the evidence to date suggests that BHV-4 infections are quite common in dairy cows. The virus on its own probably does not cause clinical uterine disease, but it can be reactivated from latency in the endometrium following calving and then act together with bacterial pathogens to increase the risk of uterine disease by disrupting innate immunity and impairing uterine repair mechanisms.

5. Schmallenberg virus

Schmallenberg virus (SBV) first emerged in Europe in 2011. Phylogenetic analysis showed that it belongs to the Simbu serogroup of the genus *Orthobunyavirus* [111]. SBV is transmitted by *Culicoides* midges and affects both domestic and wild ruminants including sheep, goats, and cattle. The clinical signs of disease in adult cows are quite mild and include fever, a drop in milk yield, and diarrhea with peak viremia 4–7 d post-infection [112]. SBV can both persist in and cross the placenta to replicate in the fetus itself [113]. Depending on the time of exposure, this may result in abortion or severe congenital malformations causing dystocia and the birth of non-viable calves [114,115]. A case control study on Swiss dairy farms found that the abortion rate increased to 6.5% in 2012 when the SBV infection started, in comparison with a rate of 3.7% the year before [116].

While these effects on the fetus are the most obvious sign of disease, there is also evidence for adverse effects on the establishment of pregnancy and/or early embryo development. Similar to BVDV, it is possible that SBV infection during early pregnancy may disrupt IFNT production, thus compromising the survival of the conceptus. Like BVDV, SBV uses a non-structural protein (in this case NSs) that degrades cellular RNA polymerase II, resulting in the inhibition of type I IFN production and an increase in virulence [117]. The impact of the 2011 epidemic on the productivity of dairy cattle in the Netherlands and parts of Germany was assessed at the herd level in a study by Veldhuis et al. [118], who compared milk production, fertility, and mortality during the epidemic with those from an earlier reference period. In both countries, there was a small but demonstrable decline in fertility parameters during the epidemic, including a significant increase in the number of repeat inseminations required and a decrease of about 5% in the 56-day non-return rate (from 61.5% to 55.7%). A further analysis was undertaken based on the effects of SBV on Swiss dairy cows [119]. This was analyzed at the individual animal level and similarly found that the number of inseminations per cow was higher during the epidemic for cows showing clinical signs of infection in comparison with non-clinical animals from case and control herds. In this study, the non-return rate was not affected, although this may have been influenced by farms with affected animals stopping their services during the period of active infection.

6. Bluetongue virus

Bluetongue virus (BTV) is an important *Orbivirus* virus infection of both domestic and wild ruminants. Its geographical distribution is primarily dependent on the distribution of *Culicoides* midges, which are the insect vectors [120]. Many serotypes of BTV exist, including the BTV-8 strain, which is currently circulating in Europe [121]. In addition to potentially causing high morbidity and mortality and reduced milk production, BTV affects reproductive performance in dairy cows [122,123]. The virus can cross the placenta, and bovine fetuses infected before 130 d of gestation develop fatal malformations of the central nervous system [124]. Later studies on BTV-8 also found a higher incidence of congenital malformations in newborn calves [122]. Cows that were seropositive for BTV in a Californian study were significantly older at first calving [125]. Fetal mortality increased during an outbreak of BTV-8 in Belgium in 2007 [126]. An early epidemiological study provided evidence for lower conception rates and longer calving-to-conception intervals in cattle [124]. More recently, this was confirmed from data obtained after an outbreak of BTV-8 in the Netherlands [127]. This study found that infected cows were five times more likely to return to service within 56 d after their first artificial insemination (AI) and required 1.7 times more inseminations. Using a different analytical approach, Nusinovici et al. [123] provided evidence that French cows infected with BTV-8 experienced reduced fertility if they had been inseminated from four weeks before until five weeks after the date of disease detection within the herd. Together, these studies provide good evidence that BTV-8 infection prevents initial conception and/or has an adverse effect on early embryos.

Experimental infection of pre-implantation cattle embryos was only cytopathic in embryos with damaged zona pellucidae; there was no evidence of BTV transmission to the early embryo in viremic donors [128]. Days 8–9 hatched blastocysts were, however, susceptible to BTV-8 infection, showing growth arrest and increased apoptosis [129]. There is again evidence that BTV has the ability to inhibit IFN synthesis. In this case, viral NS4 protein is able to counteract the host's immune response by downregulating the expression of type I IFN and ISGs [130]. As discussed above for BVDV, this may potentially negate the signals normally associated with the maternal recognition of pregnancy.

7. Conclusions and future developments

This literature review confirms that many common viral infections of cattle have adverse effects on dairy cow fertility. Abortions and fetal abnormalities are easy to quantify, although in many cases the causal factor remains unknown. In contrast, reductions in conception rates are much more difficult to detect reliably. The effects are dependent on the exact stage of the reproductive cycle when the animal becomes infected, and are influenced by herd and season. Some viruses can remain latent, and reactivation around calving is likely in association with the metabolic stress of early lactation. Others have synergistic actions with other infectious agents, either directly or indirectly by promoting immunosuppression in the host. This may interrupt reproductive processes such as ovulation and implantation as well as predisposing the animals to bacterial infections of the reproductive tract. Determination of significant effects on fertility rates in the field is dependent on having significant power in the study to detect potentially small changes. It is also complicated by our inability to capture reliable data on many other factors that influence fertility, such as the previous disease and vaccination history and the current metabolic status of individual cows. *In vitro* studies using primarily uterine endometrial cells and embryos have provided useful evidence on mechanisms of action. However, very few studies have made a thorough examination of the effects on the reproductive tract of viral infection *in vivo*. This is understandable, given the costs involved and the practicalities of maintaining infectious cows in containment facilities over a sufficient period of time. Despite these limitations, the available data do strongly suggest that viral disease plays a key but currently under-recognized role in reducing cow fertility.

Given the importance of viral diseases in global cattle production, attempts to eradicate—or at least reduce—the prevalence of such diseases is vital. Rigorous quarantine procedures can help prevent the spread of novel diseases between countries. National measures can incentivize farmers to increase their use of regular testing and vaccination. Local regulatory organizations must remain vigilant to detect novel viral diseases or variant strains of existing viruses as rapidly as possible after their emergence. Disease monitoring may also be facilitated by new technologies, such as a computational approach to pathogen discovery based on bioinformatic analysis of RNA sequencing data from whole blood [131]. Such measures should pay dividends by improving conception rates and longevity within the dairy herd.

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Compliance with ethics guidelines

D. Claire Wathes, Chike F. Oguejiofor, Carole Thomas, and Zhangrui Cheng declare that they have no conflict of interest or financial conflicts to disclose.

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