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Review

Border disease in cattle

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ABSTRACT

Within the family *Flaviviridae*, viruses within the genus *Pestivirus*, such as Border disease virus (BDV) of sheep, can cause great economic losses in farm animals. Originally, the taxonomic classification of pestiviruses was based on the host species they were isolated from, but today, it is known that many pestiviruses exhibit a broad species tropism. This review provides an overview of BDV infection in cattle. The clinical, hematological and pathological–anatomical findings in bovines that were transiently or persistently infected with BDV largely resemble those in cattle infected with the closely related pestivirus bovine viral diarrhoea virus (BVDV). Accordingly, the diagnosis of BDV infection can be challenging, as it must be differentiated from various pestiviruses in cattle. The latter is very relevant in countries with control programs to eradicate BVDV in *Bovidae*, as in most circumstances, pestivirus infections in sheep, which act as reservoir for BDV, are not included in the eradication scheme. Interspecies transmission of BDV between sheep and cattle occurs regularly, but BDV in cattle appears to be of minor general importance. Nevertheless, BDV outbreaks at farm or local level can be very costly.

Introduction

Border disease virus (BDV) belongs to the genus *Pestivirus* in the family *Flaviviridae*, together with bovine viral diarrhoea virus types 1 (BVDV-1) and 2 (BVDV-2) and classical swine fever virus (CSFV). Border disease virus, BVDV-1 and BVDV-2 constitute the ruminant pestiviruses (Nettleton and Entrican, 1995). It was recently proposed by the Flaviviridae Study Group of the International Committee for the Taxonomy of Viruses (ICTV) that the original species BVDV-1, BVDV-2, CSFV and BDV be renamed as Pestivirus A, B, C and D, respectively (Smith et al., 2017). Other and hitherto unclassified pestiviruses have been isolated from giraffes (Giraffe 1 pestivirus, Pestivirus G), cattle (Atypical ruminant pestiviruses or Hobi-like viruses, Pestivirus H), antelopes (Pronghorn antelope pestivirus, Pestivirus E), piglets (Bungowannah virus, Pestivirus F; atypical porcine pestivirus, Pestivirus K; Linda virus, no new species proposed yet) and small ruminants (Aydin-like pestivirus, Pestivirus I; Tunisian sheep pestiviruses, no new species proposed yet). In rats (Pestivirus J) and possibly bats (no new species proposed yet), pestivirus sequences have been detected although virus isolates have not been obtained (Smith et al., 2017). It was previously assumed that BVDV-1 and BVDV-2 were limited to cattle, BDV to small ruminants, and CSFV to pigs. However, it has since been shown that pestiviruses can be transmitted among various domesticated species as well as between domesticated and wildlife species (Passler and Walz, 2010). For example, BDV can also infect cattle (Becher et al., 1997; Krametter-Frötscher et al., 2008a, 2010a; Strong et al., 2010; McFadden et al., 2012; Frei, 2014; Braun et al., 2013a, 2014, 2015a; Kaiser et al., 2017), pigs (Kawanishi et al., 2014; Rosell et al., 2014; Stalder et al., 2017) and chamois (*Rupicapra pyrenaica pyrenaica*; Serrano et al., 2015). In addition, antibodies reacting with BDV were also detected in hares (*Lepus europaeus*; Colom-Cadena et al., 2016).

Even though BDV infection in cattle is not a new phenomenon, it has largely gone unnoticed because BVDV, which is very closely related to BDV, is much more common in cattle. The pathogenesis of BVD is very complex, and clinical diagnosis is not straightforward. Bovine viral diarrhoea has been subject to mandatory eradication programs in several countries (Greiser-Wilke et al., 2003; Ståhl and Alenius, 2012; Schweizer and Peterhans, 2014; Moennig and Becher, 2015; Kaiser et al., 2017) and as a result,

Abbreviations: AGID, agarose gel immunodiffusion; BDV, Border disease virus; BVD, bovine viral diarrhoea; BVDV, bovine viral diarrhoea virus; CT, computer tomography; Cp, cytopathic; CSFV, classical swine fever virus; Ct, cycle threshold; ELISA, enzyme-linked immunosorbent assay; IHC, immunohistochemistry; Ncp, non-cytopathic; N^{Pro}, n-terminal protease region; OD, optical density; ORF, open reading frame; RNA, ribonucleic acid; RT-PCR, real-time polymerase chain reaction; SNT, serum neutralisation test; TCID, tissue culture infective dose; UTR, untranslated region.

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Border disease, which can spread from sheep and other small ruminants to cattle, has gained importance for two reasons: Firstly, the clinical course of BDV infection is often similar to that of BVDV infection and secondly, laboratory differentiation of BDV and BVDV infection is arduous. This problem applies to several European countries including Sweden (Ståhl and Alenius, 2012), Germany (Wernike et al., 2017), Austria (Rossmanith et al., 2010) and Switzerland (Presi and Heim, 2010; Kaiser et al., 2017). In the context of BVD eradication in cattle, sheep persistently infected with BDV pose a significant risk to cattle because direct contact can cause transient BDV infection in cattle, and persistent BDV infection of the fetus can occur in pregnant cattle infected between days 40 and 120 of gestation. In addition, the fact that BVDV can also be transmitted from cattle to sheep and then potentially back to cattle makes a very strong argument that small ruminants cannot be ignored in an eradication program.

The first reports on border disease in cattle have been published in the last century (Gibbons et al., 1974; Vannier et al., 1988; Nettleton, 1990; Løken et al., 1991; Carlsson and Belák, 1994). Indeed, the pestivirus published in these studies was not genetically typed and therefore it was not known whether the causative agent was actually BDV or BVDV. The name BDV has been used in that time for all pestivirus detected in sheep and goats. Hence, it was unknown whether a BDV, BVDV-1 or BVDV-2 or other pestiviruses were responsible in cattle for the infections described in the papers mentioned above. In the following section, only the papers where BDV has been genetically typed are reviewed. This review presents a detailed account of BDV infection of cattle.

Classification of Border disease viruses

Pestiviruses comprise a multitude of virus species (Fig. 1(a); Ridpath et al., 1994; Hamers et al., 2001; Becher et al., 2003; Stalder et al., 2005; Liu et al., 2009; Peterhans et al., 2010; Yeşilbağ et al., 2017). They contain a (+)-sense, single-stranded RNA encoding a single open reading frame (ORF) with untranslated regions (UTR) at the 5′- and 3′-ends (Nettleton and Entrican, 1995; Nettleton and Willoughby, 2008). The 5′UTR of the pestivirus genome is highly conserved. This genome region, in addition to the region of the non-structural protein N^{pro}, is therefore routinely used for classification of pestiviruses into species and subgenotypes (Becher et al., 2003; Giangaspero and Harasawa, 2014; Giammarioli et al., 2015) as well as for designing primers for amplification and identification by RT-PCR (Nettleton and Willoughby, 2008; Stalder et al., 2016). Accordingly, new subgenotypes of Border disease viruses were proposed in recent years (e.g., Arnal et al. 2004; Dubois et al., 2008; Oguzoglu et al., 2009; Peterhans et al., 2010; Giammarioli et al., 2011), and to date, at least eight subgenotypes referred to as BDV-1 to BDV-8 were assigned to the species of Border disease viruses (Peletto et al., 2016; Fig. 1(b)).

Border disease virus-1 has been isolated in the USA, the United Kingdom and New Zealand (Becher et al., 1994; Sullivan et al., 1997; Vilček et al., 1998); BDV-2 in Germany (Becher et al., 2003); BDV-3 in France (Dubois et al., 2008), Austria (Krametter-Frötscher et al., 2010a), Switzerland (Stalder et al., 2005), China (Mao et al., 2015), India (Mishra et al., 2016) and Italy (Giammarioli et al., 2015); BDV-4 in Spain (Arnal et al., 2004; Valdazo-Gonzáles et al., 2007; Luzzago et al., 2016); BDV-5 in France (Dubois et al., 2008) and Italy (Giammarioli et al., 2015); BDV-6 in France (Dubois et al., 2008); BDV-7 in Italy (Giammarioli et al., 2015; Peletto et al., 2016); and BDV-8 in Switzerland (Peterhans et al., 2010; Stalder et al., 2017) and Italy (Peletto et al., 2016; Caruso et al., 2017). The latter subgenotype was first isolated in Switzerland as an unclassified BDV subgenotype that was provisionally named BD Switzerland or BDSwiss (Peterhans et al., 2010; Stalder et al., 2017), which turned out to be very similar to BDV-8 later isolated in Italy (Peletto et al., 2016). Analogous to BVDV, the species BDV can exist as a cytopathic (cp) and a non-cytopathic (ncp) biotype (Becher et al., 1996) as defined by their effect in cultured cells. The cp virus emerges from the persisting ncp virus within the host (Becher et al., 1996; Nettleton and Willoughby, 2008), with probably similar types of mutations leading to replication independent of the limiting host factor (Jiv; Isken et al., 2018). The ncp biotype may be transmitted horizontally or vertically and is isolated much more frequently than the cp biotype (Nettleton and Entrican, 1995; Peterhans et al., 2010).

Distribution and epidemiology of BDV infection in cattle

Naturally occurring BDV infection of cattle has been reported in England and Wales (Cranwell et al., 2007; Strong et al., 2010), Austria (Hornberg et al., 2009; Krametter-Frötscher et al., 2009), Italy (Schirrmeier et al., 2008), New Zealand (McFadden et al., 2012), Switzerland (Schenk, 2012; Frei et al., 2014), Spain (Paniagua et al., 2016) and Mexico (Gómez-Romero et al., 2018). Border disease virus can be transmitted from sheep to cattle naturally or under experimental conditions (Becher et al., 1997; Cranwell et al., 2007; Krametter-Frötscher et al., 2008a; Hornberg et al., 2009; Reichle, 2009; Krametter-Frötscher et al., 2010b; Strong et al., 2010; McFadden et al., 2012; Braun et al., 2014; Frei, 2014; Schoepf et al., 2016) and from cattle persistently infected with BDV to pestivirus-naive cattle (McFadden et al., 2012; Braun et al., 2015a, 2015b, 2018). The most important factor in BDV transmission in cattle is direct contact between sheep persistently infected with BDV and cattle (Krametter-Frötscher et al., 2010a; Strong et al., 2010; Schenk, 2012; Braun et al., 2014), which can occur when sheep and cattle are housed together in the same barn or on pastures (Krametter-Frötscher et al., 2010a; Schenk, 2012; Braun et al., 2013b). In Switzerland, the latter occurs commonly on alpine community pastures in the summer. Sheep and cattle were co-housed in the same barn in two of three Italian herds that had calves born persistently infected with BDV in South Tyrol (Schirrmeier et al., 2008), and a report from Austria described abortions in several ewes and one cow after the addition of a persistently infected ram to the flock (Krametter-Frötscher et al., 2008a, 2008b) with seroconversion in the cow being confirmed using serum neutralisation. A retrospective study from Austria examined 232 calves that had tested positive for pestivirus in the mandatory BVDV eradication program. Blood and ear notch samples from 13 of these calves from 13 farms, which were all mixed farms with cattle, sheep and/or goats, were classified as BDV-positive (Schoepf et al., 2016). During routine testing in conjunction with the mandatory BVD eradication program in Switzerland, three herds were identified with a calf persistently infected with BDV, and this gave rise to further pestivirus investigations (Schenk, 2012). The first herd had no sheep but there was a BDV-infected ewe on the neighbouring farm. Because there was no contact between the sheep and the cattle and because the same BDV subgenotype (BDSwiss) was isolated from the ewe and the calf, transmission of the virus from the ewe to the calf's dam was suspected to have occurred by a vector such as a person, dog or a bird, although this could not be confirmed. Each of the other two farms had one sheep persistently infected with BDV, and both herds had several cattle with positive SNT (serum neutralisation test) titres against BDV. On one of the farms, sheep and cattle had nose-to-nose contact, and on the other farm, ewes were brought to the cow barn for lambing. To examine the role of alpine community summer pasturing in BDV transmission from sheep to cattle, 1170 sheep destined for one of four alpine community pastures were tested for BDV infection using RT-PCR, and 923 cattle, intended for the same pastures, underwent serological testing for pestivirus antibodies (Büchi, 2009; Braun et al., 2013a).

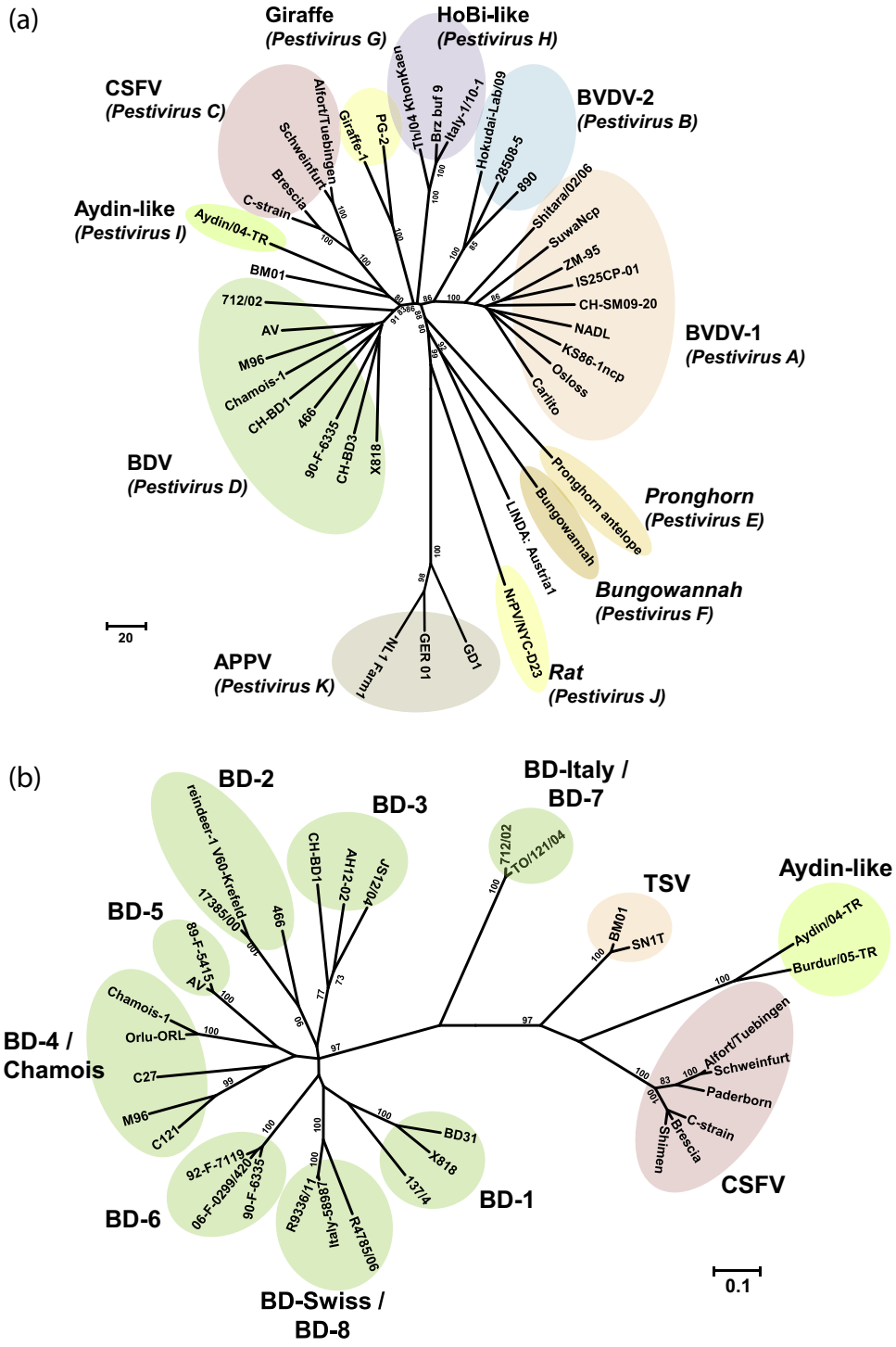

Fig. 1. (a) Phylogenetic analysis and classification of pestiviruses based on the entire nucleotide sequence of N^{pro}. The classification into species was done according to the most recent proposal of the *Flaviviridae* Study Group of the International Committee for the Taxonomy of Viruses (ICTV; Smith et al., 2017). The evolutionary history was inferred using the neighbor-joining method. The genetic analysis was calculated, and the figure prepared as described in Supplementary Table 1. The numbers close to the branches represent the values (%) of 1000 bootstrap replicates, and only values greater than 80% are indicated. Line lengths are proportional to genetic distance and are in the units of the number of base differences per sequence, as indicated by the scale bar. (b) Phylogenetic analysis of Border disease viruses (BDV) based on the entire nucleotide sequence of N^{pro}. The evolutionary history was inferred by using the Maximum Likelihood method with classical swine fever virus (CSFV), Tunisian sheep pestiviruses (TSV) and Aydin-like viruses included as the most closely related pestiviruses. The classification into subgenotypes was done according to the most recent proposals published (Luzzago et al., 2016; Mishra et al., 2016; Peletto et al., 2016). The genetic analysis was calculated, and the figure prepared as described in Supplementary Table 2. The numbers close to the branches represent the values in percent of 1000 bootstrap replicates, and only values greater than 70% are indicated. The tree is drawn to scale, with branch lengths measured in the number of substitutions per site as indicated by the scale bar.

Eight sheep (0.68%) were positive for BDV and ten cattle (1.08%) seroconverted; the high SNT titres detected at the end of the grazing season suggested BDV infection. Taken together these observations strongly suggest that commingling sheep persistently infected with BDV and pestivirus-naive cattle poses a risk of BDV transmission from the sheep to the cattle.

The seroprevalence of BDV in cattle was investigated by SNT in the context of the BVDV eradication program in Switzerland

(Kaiser et al., 2017). Of 1555 blood samples that tested positive by enzyme-linked immunosorbent assay (ELISA) in cattle, 104 (6.7%) had significantly higher titres against BDV than BVDV. These samples originated from 65 herds, three of which had a calf persistently infected with BDV. All herds with persistently infected calves and most herds with seropositive cattle to BDV included small ruminants, more often sheep than goats. Housing sheep and cattle together, particularly during lambing when the risk of infection is greatest, was identified as the most important risk factor for BDV infection in cattle.

Border disease virus transmission from persistently infected cattle to naive cattle is also possible. The first case of BDV infection in cattle in New Zealand involved a Belted Galloway bull that was persistently infected with BDV. The bull had an unknown infection status (McFadden et al., 2012) at the time he was turned out with 62 dairy heifers. However, conception rates were poor, and further laboratory testing showed that of the 40 heifers tested, all were seropositive for BDV antibody. The bull had been sourced from a mixed sheep and beef farm with persistently infected sheep.

Wildlife populations are thought to play a role in the spread of BDV, similar to the spread of BVDV and CSFV (Ridpath and Passler, 2016). It has been shown that wild rabbits (*Oryctolagus cuniculus*) constitute a reservoir for BVDV (Frölich and Streich, 1998; Grant et al., 2015), and antibodies against BDV-4 (and BVDV) were recently detected in the European hare (*Lepus europaeus*; Colom-Cadena et al., 2016). It is suspected that the European hare also plays a role in the spread of BDV in the Pyrenean chamois (*Rupicapra pyrenaica pyrenaica*) population. Another mode of transmission of pestiviruses to cattle, small ruminants and pigs is contaminated vaccines (Nettleton, 1990, and references therein). This occurred in goats vaccinated with contaminated orf vaccine (Løken et al., 1991; Thabti et al., 2002) and pigs vaccinated against Aujeszky disease (Vannier et al., 1988). However, in none of these reports was the species of pestivirus (e.g. BVDV or BDV) unequivocally identified.

Experimental transmission of BDV from sheep to cattle

Seroconversion in cattle after exposure to infected sheep has been the subject of several reports (Krametter-Frötscher et al., 2008b, 2010b; Reichle, 2009; Braun et al., 2014). Four calves co-housed with six sheep persistently infected with BDV seroconverted within 28 to 51 days after the start of exposure, which showed that the calves had become infected with BDV (Krametter-Frötscher et al., 2008b). A similar experiment was conducted with nine calves that were co-housed with two sheep persistently infected with BDV (Reichle, 2009; Braun et al., 2014). Six of the nine calves seroconverted within 36–72 days, and the SNT titre confirmed that the antibody was directed against BDV. Another study examined the impact of nine persistently infected sheep on nine co-housed pestivirus-naive heifers that were between 47 and 73 days pregnant (Krametter-Frötscher et al., 2010a). All heifers seroconverted 23–38 days after the start of exposure to the sheep and five aborted after 54–202 days. A mild fever was the only clinical sign in the heifers. Border disease virus was detected in four aborted fetuses and in the placenta of the remaining fetus, which was not available for virological examination. Three heifers gave birth to clinically healthy calves; two were pestivirus-negative and one was positive, and when the latter was retested at 7 months, it was virus-negative but seropositive. Even though calves (Reichle, 2009; Krametter-Frötscher et al., 2008a; Braun et al., 2014) and heifers in early pregnancy (Krametter-Frötscher et al., 2010) co-housed with sheep persistently infected with BDV seroconverted, viraemia was not detected.

Experimental transmission of BDV among cattle

Seroconversion in cattle as a result of transmission of BDV from other cattle has been described in several reports (Reichle, 2009; Braun et al., 2014; Frei, 2014; Braun et al., 2015a,b). Border disease virus was transmitted from a persistently infected bull calf to six pregnant seronegative heifers co-housed with the calf in a free stall operation. The heifers were exposed to the calf for 60 days starting on day 50 of gestation (Frei, 2014; Braun et al., 2015a). Three of six heifers had mild viraemia as analysed by real-time PT-PCR with weakly positive cycle threshold (Ct) values of 37.8–42.5 from day 8 to day 14 after exposure. Nonetheless, all heifers seroconverted within 20–40 days of exposure (Frei, 2014; Braun et al., 2015a). On day 60, all heifers had pestivirus antibodies as tested by ELISA that were identified as antibodies to BDV with high titres (152 to >512) in the SNT whereas anti-BVDV titres were negative or very low, indicating that antibodies were indeed produced in response to an infection with BDV. The heifers were slaughtered 60 days after exposure, and the fetuses and placentae underwent postmortem and virological examination. The placentomes from the three viraemic heifers were macroscopically normal but had histological evidence of chronic inflammation that varied in severity (Fernández et al., 2018) and resembled the lesions seen in pregnant BDV-infected ewes and in pregnant BVDV-infected cattle (Osburn and Castrucci, 1991). Fetal organs and placentomes from the three heifers that had mild viraemia were positive in immunohistochemistry (IHC) using pestivirus-specific antibodies (C16, 15C5; Hilbe et al., 2007) but were consistently negative with BVDV-specific antibodies. Notably, pestivirus-specific staining was mainly located in the fetal cells of the placentomes, whereas staining of maternal cells was sparse. Real-time PCR detected pestiviral RNA in the fetal organs and placentomes, which were upon sequencing (approx. 300 bp in the 5′-UTR) identical to the sequence isolated from the persistently infected calf in two heifers or contained only one single point mutation in the third heifer. Based on the unequivocally positive results of the immunohistochemical and virologic examinations of all fetal organs, the fetuses of the three viraemic heifers were diagnosed as persistently infected with BDV. Interestingly, heifers that carried a persistently infected fetus had significantly higher percentage of optical density (OD) in the antibody ELISA after day 40 compared with the other heifers, and the values of the relative optical density in ELISA increased significantly with increasing duration of infection. This phenomenon had not been previously described for BDV infection but was known for BVDV infection; cows at 180 days of pregnancy and with a fetus persistently infected with BVDV had titres ten times those of cows with a non-infected fetus (Brownlie et al., 1998). Comparison of cows with and without a fetus persistently infected with BVDV showed that OD values were significantly related to duration of pregnancy, time of sampling and fetal infection status (Lindberg et al., 2001; Stokstad et al., 2003). Compared with cows carrying a non-infected fetus, cows that were pregnant with a persistently infected fetus had titres that rose faster and were significantly higher after day 135 of pregnancy (Stokstad et al., 2003).

Attempts to generate persistently infected fetuses using BDV-infected semen were unsuccessful in two experiments (Frei et al., 2014; Braun et al., 2015b; Züblin, 2016; Braun et al., 2018). In the first experiment, five heifers were inseminated with BDV-infected semen from a persistently infected bull (Frei et al., 2014; Braun et al., 2015b). All inseminated heifers seroconverted but failed to conceive, most likely because of poor semen quality. The experiment was repeated, but the design was modified and fertile semen from an Eringer bull was added to the BDV-infected semen (Züblin, 2016; Braun et al., 2018). All five inseminated cows seroconverted and four conceived. The cows were slaughtered

56 days after insemination and examination of the uteri, placentae and fetuses revealed no macroscopic or histological lesions, and immunohistochemical and molecular examinations for pestiviruses were negative. Genotyping of fetal tissue identified the Eringer bull as the sire of all fetuses. It was concluded that insemination using BDV-infected semen causes seroconversion in cows but does not produce persistently infected fetuses. Thus, it appears that insemination of cows with BDV-infected semen plays a minor role in the transmission of BDV. This is supported by the observation that of 61 calves born to cows inseminated with BVDV-infected semen, only two (3.3%) were persistently infected (Kirkland et al., 1994). Assuming a similar infection rate for BDV-infected semen, a minimum of 30 cows would have to be inseminated to obtain one persistently infected calf. Furthermore, acute BVDV infection only generates persistently infected offspring when it occurs between approximately 30–120 days of gestation (Brownlie, 1990). Infection in the first month of gestation usually results in loss of pregnancy and return to estrus, or possibly the birth of a normal non-infected calf.

Transmission of BDV from cattle to sheep

To our knowledge, the natural transmission of BDV from persistently infected cattle to co-housed pestivirus-naive sheep has not been documented. However, there are close similarities in the clinical pictures of BDV and BVDV infections in sheep and cattle (Carlsson, 1991), and therefore the true source of the infection may not have been investigated in all reports. In regions where BVDV is endemic, cattle have a relatively high seroprevalence, which is accompanied by a relatively low prevalence of persistently infected animals in the population. Based on the considerable cross-reactivity of antibodies to BVDV and BDV, cattle seropositive for BVDV are protected against BDV, which may explain why BDV has not become established in the bovine population (Peterhans et al., 2010). Accordingly, of almost 7500 cattle identified as persistently infected in the context of the mandatory BVDV eradication program in Switzerland during the first three phases (2008–2011), only eight were infected with BDV (Stalder et al., 2016). Similarly, in an epidemiological study relating to the BVDV control program in Western Austria, only 13 of 232 cattle persistently infected with pestivirus were infected with BDV (Schoepf et al., 2016). Thus, although cattle are generally more prolific in shedding pestiviruses and have a higher prevalence of persistent infection than small ruminants, both of which theoretically increase the infection pressure, transmission of BDV from cattle to sheep appears to be of minor significance (Løken, 1992[1] ; Barrett et al., 2011). It should be remembered however that BVDV may be transmitted from cattle to sheep and generates a clinical picture indistinguishable from that of true Border disease (Carlsson, 1991). For instance, of 14 sheep seropositive for pestiviruses in Northern Ireland, neutralisation studies with BVDV and BDV showed significantly higher titres against BVDV in all cases (Graham et al., 2001). For these reasons, small ruminants should not be ignored as a source of BVDV in eradication programs for cattle (Preyler-Theiner et al., 2009; Kaiser et al., 2017).

Clinical and haematological findings in cattle after transient BDV infection

Mild fever and abortion were the only clinical signs in eight heifers that were 47–73 days pregnant and kept in close confinement with nine sheep persistently infected with BDV (Krametter-Frötscher et al., 2010a). Nine calves co-housed with two sheep persistently infected with BDV developed mild to moderate mucosal lesions on the palate, corners of the mouth, lips and gingiva of the incisors. However, those lesions were in all likelihood not attributable to BDV infection because analogous lesions were also seen in calves that did not seroconvert after oral challenge with BDV (Reichle, 2009; Braun et al., 2014).

Pestivirus-naive heifers kept in close confinement with a calf persistently infected with BDV did not have clinical signs that could be linked to BDV infection (Frei, 2014; Braun et al., 2015a). The same was true for two studies in which heifers were inseminated with BDV-infected semen (Frei, 2014; Braun et al., 2015b; Von Büren, 2016; Braun et al., 2018). Even though seroconversion strongly suggested infection of the cattle used in these experiments, general health was not affected. To obtain a more objective view of the general health condition of cows inseminated with BDV-infected semen, eating and rumination variables of the cows were recorded using a custom-made halter equipped with a pressure sensor in the noseband, and intraruminal temperature was recorded using an intraruminal temperature bolus (Braun et al., 2018). Duration of eating and rumination, number of regurgitated cuds per day, the number of chewing cycles per cud and the intraruminal temperature were not affected. By contrast, insemination with BDV-infected semen caused significant transient leukopenia attributable to lymphopenia, which was most pronounced on day 6 after insemination (Von Büren, 2016; Braun et al., 2018). Significant transient leukopenia was also seen in lambs (Thabti et al., 2002) and pregnant ewes (García-Pérez et al., 2009) that were experimentally infected with BDV, and leukopenia and lymphopenia occurred in calves that were experimentally infected with BVDV strains of varying virulence (Chase et al., 2015, and references therein).

Clinical findings in cattle persistently infected with BDV

To date, there are few descriptions of the clinical findings in cattle persistently infected with BDV (Cranwell et al., 2007; McFadden et al., 2012; Frei et al., 2014; Braun et al., 2015a). The range of clinical signs seen in three cases from the United Kingdom were very similar if not identical to that of BVDV infection (Cranwell et al., 2007); a 13-month-old heifer had a history of wasting and diarrhoea, a two-and-a-half-year-old heifer had diarrhoea and other signs of mucosal disease and a small and weak new-born calf died soon after birth. All three cases were positive for BVDV by ELISA and confirmed as persistently infected with BDV using RT-PCR.

A case from New Zealand involved a three-year-old Belted Galloway bull that was examined because the pregnancy rate in a group of 62 dairy heifers was only 23% after a 57-day mating period (McFadden et al., 2012). The bull, which had been sourced from a farm with 2000 sheep, was small for his age and lacked typical masculine characteristics such as a thickened neck. Scrotal circumference was 22 cm compared with the minimum acceptable threshold of 34 cm. BVDV antigen ELISA was done twice and was positive both times, and subsequent PCR identified the virus as BDV. The bull was slaughtered and BDV was detected in splenic, testicular and lymphatic tissues. The histological diagnosis was severe chronic testicular degeneration and atrophy. Border disease virus was also detected in sheep from the farm where the bull originated.

Three bull calves that tested pestivirus positive in the mandatory BVDV eradication program in Switzerland and were confirmed to be persistently infected with BDV using genotyping underwent further study (Frei et al., 2014). There were two Swiss Braunvieh and one Swiss Braunvieh × Limousin calves, which

[1] See: Løken, T., 2000. Border disease in goats. In: Tempesta, M. (Ed.). Recent advances in goat diseases. International Veterinary Information Service, Ithaca NY. www.ivis.org (Accessed 22 January 2019).

originated from three mixed farms with cattle and sheep. One calf was slightly underweight, had a stocky body type and suffered from enteritis, bronchopneumonia and omphalitis. The calf did not respond to treatment, deteriorated, became recumbent and was euthanized (Fig. 2(a)). Although the other two calves were clinically healthy and had a good body condition and appetite, their growth was retarded. One of these calves was raised in quarantine and later used in experiments involving exposure of pestivirus-naive cattle to BDV (Frei, 2014; Braun et al., 2015a) and the insemination of pestivirus-naive heifers with BDV-infected semen (Frei et al., 2014; Braun et al., 2015b; Züblin, 2016; Braun et al., 2018). The bull was clinically healthy and afebrile during his entire life, but sexual maturity was delayed until the age of about 400 days. The bull had good libido but had incomplete erection resulting in *impotentia coeundi* and, therefore electroejaculation was required for semen collection. The semen had poor quality and a high viral load with a virus titre of 2.51×10^8 (50% tissue culture infective dose [$TCID_{50}$]/ml) and 1.44×10^6 ($TCID_{50}/10^6$ sperm cells). When the bull was slaughtered at the age of 14 months (Fig. 2(b)), BDV was detected in the testes, and histological examination showed severe testicular degeneration. Lesions seen in the bones of the extremities of all three bulls are described in the following section.

Morphological findings in cattle persistently infected with BDV

A number of organ systems are affected in cattle persistently infected with BDV, and the lesions described vary and are considered 'BDV-induced' or 'highly likely BDV-induced' (Monies et al., 2004; Hilbe et al., 2009). Examples are testicular degeneration and atrophy, which occurred in a bull that had only a few remaining seminiferous tubules, a small number of spermatids and no active spermatogenesis (McFadden et al., 2012).

Skeletal lesions consisting of osteopetrosis-like or osteoporosis-like changes as well as so-called growth arrest lines have been described in the bones of calves persistently infected with BDV. Affected bones had a marbled appearance and were unstable and susceptible to fracture (Hilbe et al., 2000; Frei et al., 2014).

Radiographic and computed tomographic examination of a calf with lameness in the right hind limb and swelling of the lateral aspect of the right stifle revealed characteristic lesions of the femur and tibia, and this prompted the same examination in two other persistently infected calves (Frei et al., 2014). All three calves had different stages of bone lesions that corresponded to lesions described in calves persistently infected with BVDV (O'Connor and Doige, 1993; Scruggs et al., 1995; Hilbe et al., 2000; Nuss et al., 2005; Webb et al., 2012) including focal metaphyseal radiopacities and radiolucencies, cortical thickening of the diaphysis and concentric zones of sclerosis ('bone in bone', 'growth arrest lines'). Histological examination showed that the growth arrest lines reflected plump and interwoven retained primary trabeculae (osteopetrosis).

Placental changes in cows with persistently infected offspring were described in a previous section (Experimental transmission of BDV from sheep to cattle).

Diagnosis of BDV infection in cattle

Techniques for the detection of ruminant pestiviruses, pestivirus antigens and pestivirus antibodies include virus isolation, ELISA (enzyme-linked immunosorbent assay), AGID (agarose gel immunodiffusion), SNT (serum neutralisation), IHC (immunohistochemistry), *in situ* hybridization and RT-PCR (reverse transcriptase polymerase chain reaction). These techniques and their advantages and limitations have been summarised (Saliki and Dubovi, 2004; Goyal, 2005; Hilbe et al., 2007; Dubovi, 2013; Lanyon et al., 2014a). Even though virus isolation is still considered the gold standard, this technique is cumbersome, time consuming and expensive. Therefore, antigen and antibody detection are used routinely to detect pestivirus infections at the herd level and in individual animals. However, these techniques cannot reliably differentiate BVDV and BDV infections and the diagnostic sensitivities and specificities are low (Kirkland, 2017). In contrast to BVDV, there is no antibody available for the reliable detection of BDV in IHC. Therefore, a different approach, involving two antibodies is used, with one antibody that is broadly reactive to pestiviruses and one that is BVDV-specific. Thus, tissues from BDV-infected animals react positively with the former and negatively with the latter antibody (Hilbe et al., 2007; Braun et al., 2015a). As the pestivirus antibody used (Braun et al., 2015a) is cross-reactive with many pestivirus species, a negative staining with the BVDV-specific antibody might originate from an infection with various pestiviruses, and further analyses are required to finally identify the pestivirus species. Likewise, different classical and real-time RT-PCR protocols are available for the detection of BDV and BVDV, but a broadly reactive (referred to as pan-pestivirus reactive) PCR method that has high sensitivity to the different pestivirus species is required for diagnostic purposes. Genotyping of the pestivirus is then achieved in positive samples by nucleotide sequencing (Ridpath, 2003; Stalder et al., 2016). Similarly, an ELISA that differentiates BDV and BVDV antibodies is not available, and one must be aware that commercial tests marketed for the detection of 'BDV antibodies in sheep' or 'BVDV antibodies in cattle' simply detect antibodies against ruminant pestiviruses including BDV and BVDV. However, cross-neutralisation (cross-SNT) using different BVDV and BDV strains can determine the specificity of the antibodies, provided that the virus strains used as challenge

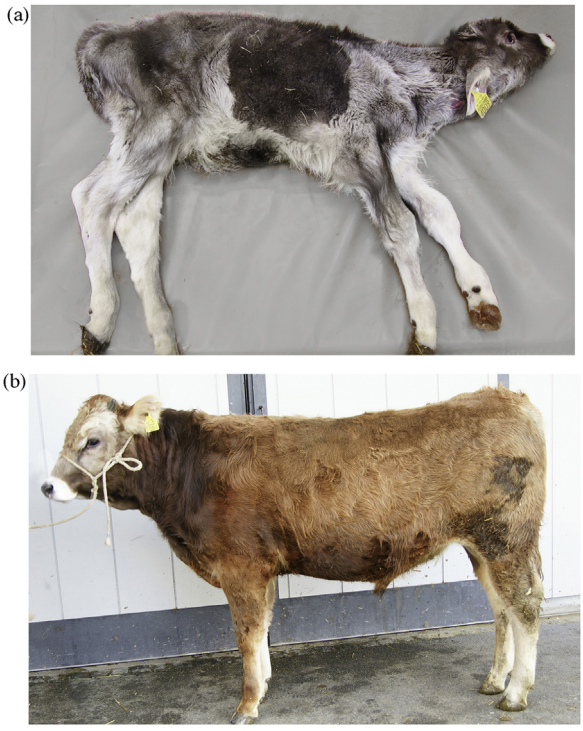

Fig. 2. (a) Swiss Braunvieh calf from a mixed cattle and sheep farm that is persistently infected with Border disease viruses (BDV). The calf was 115 days of age, weighed 41 kg and was terminally ill. Postmortem examination showed severe apostematous bronchopneumonia, severe purulonecrotic omphalitis and osteopenia and osteopetrosis of the humerus and femur. (b) Fourteen-month-old Swiss Braunvieh bull persistently infected with Border disease viruses (BDV). The bull had a normal body condition but was small for his age.

viruses are adapted to the current local epidemiological situation (Kaiser et al., 2017). Selecting the appropriate virus strains is essential, because pestiviruses are highly diverse. For example, BVDV-1 contains at least 21 different subgenotypes (Yeşilbağ et al., 2017) and knowledge of the diversity of BDV (Fig. 1B and Supplementary Table 2) is likely to increase in the future. Finally, in addition to the selection of the appropriate material for the various diagnostic methods, the time point of sample collection is critical. Maternal antibodies can interfere with antigen and antibody detection in young animals (Lanyon et al., 2014b), and an ELISA done in periparturient cows might produce a false-negative result because of a possible drop in serum immunoglobulin concentrations in the dam over that period (Bachofen et al., 2013a).

Recommendations for the prevention of BDV infection in cattle

Commingling of sheep and cattle is the biggest risk factor for BDV infection in cattle (Krametter-Frötscher et al., 2010a; Braun et al., 2013a, 2014; Kaiser et al., 2017), whereas the transmission of BDV from wildlife species, even though theoretically possible, is of minor importance (Casaubon et al., 2012; Martin et al., 2015; Fernández-Aguilar et al., 2016; Paniagua et al., 2016; Rodríguez-Prieto et al., 2016). For effective prevention of transmission of BDV from sheep to cattle, commingling of sheep and cattle in barns or on pasture should be avoided, particularly in the lambing season, when infection pressure is greatest (Kaiser et al., 2017). An added benefit of keeping sheep, goats and cattle separate is the lower risk of malignant catarrhal fever, a fatal disease of cattle caused by ovine herpes virus 2 (Russell et al., 2009). When separate housing or pasturing of sheep and cattle is not an option, examination of the sheep for pestiviruses should be considered (Kaiser et al., 2017). Although BDV has been isolated from goats (De Mia et al., 2005; Oguzoglu et al., 2009; Toplu et al., 2011; Li et al., 2013; Rosamilia et al., 2014; Giammarioli et al., 2015) the authors of these papers have found no reports of transmission of BDV from goats to cattle. The explanation lies probably in the fact that the prevalence of BDV is very low in goats in comparison to sheep and that the survival rate of the conceptus is mostly very low when infection occurs early in gestation (Krametter-Froetscher et al., 2010a), similar to pregnant goats infected with BVDV (Bachofen et al., 2013b).

In addition to sheep, cattle persistently infected with BDV pose a risk to other commingled cattle, particularly those in early pregnancy because of the potential of persistent infection of the fetus. Although in the context of mandatory BVDV eradication programs, cattle persistently infected with BDV are identified as pestivirus-infected, special laboratory techniques are required to confirm BDV infection. It is anticipated that national programs for the eradication of BVDV will result in eradication of BVDV in the bovine population. However, to guarantee timely detection of potential BDV or BVDV transmission from sheep to cattle, surveillance of pestivirus infections should continue in mixed sheep and cattle farms where the infection status of the sheep is unknown. While the pressure of infection in the era before eradication of BVDV might have been rather from cattle to sheep (Barrett et al., 2011), the situation changes or has changed dramatically in countries with eradication (Sandvik, 2014). As herd and population immunity wane after eradication of BVDV, at least in countries where vaccination is prohibited, there is also a greater risk of BDV transmission from sheep to cattle. However, management of the bovine population and biosecurity measures might strongly influence the likelihood of transmission, as, for example, despite having a largely pestivirus-naive bovine population 10 years after start of the eradication program in Switzerland, transmission of BDV from sheep to cattle did not markedly increase (Kaiser et al., 2017).

Conclusions

Border disease was not previously considered a bovine disease because the virological and clinical features of BD and BVD are similar and thus the two diseases were difficult to differentiate. Border disease virus infection is of importance in countries with mandatory BVD virus eradication programs because BD virus is transmissible from sheep to cattle, from cattle to cattle and from cattle to sheep. This complicates BVDV eradication programs and may make complete eradication impossible. Thus, to effectively eradicate BVDV from the bovine population, infection of cattle with BDV must be prevented. To achieve this, separate housing and pasturing of sheep and cattle are recommended.

Conflict of interest

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tvjl.2019.01.006.

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