ISSN 1466-2523

Animal Health Research Reviews **11**(2); 191–205
doi:10.1017/S1466252309990065

Bovine viral diarrhea virus infections in heterologous species

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Received 10 June 2009; Accepted 20 September 2009; First published online 3 November 2009

Abstract

Infections with Bovine viral diarrhea virus (BVDV) are not limited to cattle, but may be detected in various species in the mammalian order Artiodactyla. Despite epidemiological evidence of BVDV infections in species other than cattle, current knowledge regarding the impact of BVDV on heterologous species is incomplete. In heterologous hosts, BVDV infections with clinical signs analogous to those in cattle have been described and include disease of multiple organ systems, most notably the reproductive tract and immune system. Clinical infections may negatively impact the health and well-being of heterologous species, including camelids and captive and free-ranging wildlife. Of additional importance are BVDV infections in small ruminants and swine where difficulties arise in laboratory testing for Border disease virus (BDV) and Classical swine fever virus (CSFV), respectively. Pestiviruses are antigenically closely related and their cross-reactivity requires additional efforts in virological testing. In cattle populations, persistently infected animals are considered the main source of BVDV transmission. This phenomenon has also been detected in heterologous species, which could facilitate reservoirs for BVDV that may be of great importance where control programs are in progress. This review summarizes the current epidemiological and clinical knowledge on heterologous BVDV infections and discusses their implications.

Keywords: Bovine viral diarrhea virus, Pestivirus, cross-species infection, epidemiology, host range

Introduction

Pestiviruses of the family Flaviviridae are small enveloped RNA viruses that have substantial impact on the livestock industries. Pestivirus isolates are genetically and antigenically related, which in the past has provided difficulties with classification. Traditional classification of viral isolates according to mammalian host of origin may not always be accurate, as pestiviruses do not demonstrate strict host specificity (Nettleton, 1990). More recent molecular techniques have allowed classification of Pestivirus species according to genotypic diversity rather than animal host (Giangaspero and Harasawa, 2007). Currently, the genus Pestivirus is comprised of Bovine viral diarrhea virus (BVDV) 1, BVDV 2, Border disease virus (BDV) and Classical swine fever virus (CSFV). Recent description of genetically distinct pestiviruses such as the genotypes Pronghorn pestivirus, Giraffe pestivirus, strain V60 (Reindeer-1), Ho_Bi strain and others may lead to further rearrangements of classification (Dekker *et al.*, 1995; Fischer *et al.*, 1998; Avalos-Ramirez *et al.*, 2001; Becher *et al.*, 2003; Schirrmeier *et al.*, 2004; Vilcek *et al.*, 2005).

Pestiviruses employ various strategies that ensure their survival and successful propagation in mammalian hosts, including suppression of the host's immune system, transmission by various direct and indirect routes, and, perhaps most importantly, induction of persistently infected (P1) hosts that shed and transmit BVDV more efficiently than other sources. Accumulating evidence suggests that pestiviruses are able to infect various mammalian host species in the order Artiodactyla, which may play an important role in the viral survival strategy

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Table 1. Reported prevalence rates for antibodies directed against BVDV in domestic small ruminants

Percent seropositive			
Sheep	Goats	Country	Reference
34.9, 29.4	11.5	Austria	Krametter-Froetscher *et al.* (2006), Schiefer *et al.* (2006), Krametter-Frotscher *et al.* (2007)
27.5	31.4	Egypt	Zaghawa (1998)
6.7	–	Germany	Bechmann (1997)
23.4	16.9	India	Mishra *et al.* (2009)
14.0	4.6	Namibia	Depner *et al.* (1991)
12.7	4.5	Nigeria	Taylor *et al.* (1977b)
–	3.6	Norway	Loken (1990)
16.1	25.4	Switzerland	Danuser *et al.* (2009)
32.1	24.9	Tanzania	Hyera *et al.* (1991)
32.1	–	Turkey	Yesilbag and Gungor (2009)

–, no data available.

(Vilcek and Nettleton, 2006). The implications of heterologous pestivirus infections are two-fold. First, infection of hosts other than cattle may drastically handicap the successful implementation of BVDV control strategies if these hosts become reservoirs; and second, clinical disease in other mammalian hosts such as zoo animal and wildlife species may be observed.

Among pestiviruses, BVDV has been the species most intensely studied as an infectious agent of heterologous hosts. BVDV infection in species other than cattle has been detected mainly by seropositivity, especially in wildlife species. Although the presence of antibodies may provide only limited information as to the role of a species in the ecology of BVDV, high seroprevalence rates within populations suggest the existence of endemic cycles (Van Campen *et al.*, 2001). BVDV infections have been documented in domestic small ruminants and swine, free-ranging and captive wildlife, and in camelids, and the epidemiology of BVDV infection may revolve around these proposed host clusters (Evermann, 2006). Within these proposed host clusters, intra-host maintenance of BVDV occurs but the inter-cluster transmission requires optimal conditions or may be negligible (Evermann, 2006). This review will summarize BVDV infections in each host cluster as well as swine and discuss their implications.

BVDV in domestic small ruminants and swine

Goats and sheep

Among Artiodactyla, sheep and goats may have a unique role in the ecology of BVDV. Sheep and goats are phylogenetically more closely related to cattle than most other species considered in this review; therefore, the chance to establish permissive infections is high (DeFillipis and Villareal, 2000). Furthermore, sheep and goats may have close contact with cattle under certain management conditions, such as subsistence agriculture, alpine farming, or hobby farming, thus contributing to BVDV infections in small ruminants. Although one report did not identify a positive correlation between seropositivity of sheep flocks and presence of cattle (Graham *et al.*, 2001), other studies reported significantly higher seroprevalence rates in sheep on farms with cattle (Tegtmeier *et al.*, 2000; Krametter-Frotscher *et al.*, 2007), especially where communal alpine pasturing of sheep, goats and cattle was practiced (Krametter-Frotscher *et al.*, 2007).

Several serological surveys have demonstrated the occurrence of BVDV in small ruminants (Table 1); however, cross-reactivity of pestivirus antibodies warrants caution when evaluating the results of such surveys. Surprisingly, in recent reports on pestiviral seroprevalence in sheep, cross-neutralization assays identified highest reactivity against BVDV 1 rather than BDV (Graham *et al.*, 2001; Schleiner *et al.*, 2006; Krametter-Frotscher *et al.*, 2007; Mishra *et al.*, 2009). In Argentina, which is considered free from BDV, 79.7% (43/54 sheep) of samples were seropositive to BVDV 1 or BVDV 2, indicating BVDV circulation in Patagonian populations (Julia *et al.*, 2009). This is contrasted with another recent report where the majority of seropositive sheep resulted from BDV infection, while the infecting pestivirus in goats remained largely unresolved, as indicated by cross-neutralization assays (Danuser *et al.*, 2009). When antibodies against pestivirus are detected in small ruminants, the distinction of pestivirus species may hold critical information on epidemiology, prevention and control (Konig *et al.*, 2003).

From reports on pestiviral infections in small ruminants prior to the 1990s, determination of whether BDV or BVDV was the infecting species may be difficult. Of 53 viral strains designated as BDV in the nucleotide sequence databases, 22 were revealed to be BVDV by genotyping based on palindromic nucleotide substitutions (Giangaspero and Harasawa, 1999). Infections with both species of BVDV have been reported in domestic small ruminants worldwide (Paton *et al.*, 1995; Pratelli *et al.*, 2001; Yadav *et al.*, 2004; Kim *et al.*, 2006; Willoughby *et al.*, 2006; Krametter-Frotscher *et al.*, 2007;

https://doi.org/10.1017/S1466252309990065 Published online by Cambridge University Press

Mishra *et al.*, 2007, 2008). The inverse, infection and clinical signs of pestivirus infection in cattle associated with BDV appear to be rare (Schirrmeier *et al.*, 2008). Therefore, determination of which pestivirus is the cause of infection in small ruminants is especially important where BVDV control programs in cattle are in progress.

Infections with BVDV in domestic small ruminants result in clinical signs of Border disease. Postnatal infections commonly cause mild clinical signs, including pyrexia and leucopenia (Taylor *et al.*, 1977a). Experimental inoculation of juvenile sheep by the intranasal, intratracheal and intrabronchial routes resulted in anorexia, tachycardia, pyrexia and lung lesions especially associated with the pulmonary vasculature (Meehan *et al.*, 1998). Strain-dependent severity of BVDV-associated pathology was observed in 62 gnotobiotic lambs infected with 1 of 10 BVDV strains, and pyrexia, pneumonia, myocarditis and encephalitis were observed (Jewett *et al.*, 1990). Infections with BVDV in pregnant small ruminants may result in *uteroplacental* pathology and pregnancy loss by fetal resorption or abortions (Loken and Bjerkas, 1991). The outcome of transplacental infection depends on the length of gestation and biotype of infecting BVDV strain. Fetal mummification, stillbirth, premature birth and birth of offspring with congenital disorders may result from *in utero* BVDV infection. Congenital disorders of affected fetuses commonly involve the central nervous system, and neuropathogenicity may be more severe with cytopathic biotypes (Gruber *et al.*, 1995; Hewicker-Trautwein *et al.*, 1995). Although fetal death and nonviability of lambs are common sequelae of transplacental BVDV in sheep, reports of viable PI offspring exist (Carlsson and Belak, 1994; Scherer *et al.*, 2001). In contrast to cattle and sheep, viable PI kids appear to be a rare result of *in utero* BVDV infection in goats and reproductive failure or severe gross and histological pathology of affected fetuses are the likely result of infection (Loken and Bjerkas, 1991; Kim *et al.*, 2006; Broaddus *et al.*, 2009).

Swine

The close antigenic relationship between ruminant pestiviruses and CSFV has important implications for diagnostic testing and control of CSFV. Currently, examination of blood samples for CSFV antibodies relies on a combination of enzyme linked immunosorbent assay (ELISA) and virus neutralization techniques, and considerable efforts are required to establish a CSFV-specific diagnosis (de Smit *et al.*, 1999). During the CSFV outbreak in the Netherlands in 1997/1998, 26.5% of CSFV ELISA positive samples were demonstrated to be caused by the presence of antibodies to ruminant pestiviruses (de Smit *et al.*, 1999). The presence of antibodies against ruminant pestivirus in swine resulting in suspicion of CSFV infection has prompted the unnecessary depopulation of herds, further emphasizing the impact of porcine infections with ruminant pestiviruses (Snowdon and French, 1968; Oguzoglu *et al.*, 2001).

Comparative cross-neutralization experiments or monoclonal antibodies have been commonly used to differentiate the causative viral species in seropositive samples (Liess and Moennig, 1990). However, CSFV challenge in swine with prior BVDV infection resulted in higher titers against BVDV than CSFV according to the neutralization peroxidase linked assay, indicating that prior BVDV infection could result in false-negative CSFV diagnosis (Wieringa-Jelsma *et al.*, 2006). Furthermore, a recently developed E2 subunit CSFV marker has been used in combination with an antibody-ELISA against the E^{RNS} to differentiate vaccinated pigs from pigs exposed naturally to CSFV; however, BVDV infection and subsequent seroconversion may result in false-positive CSFV serologic tests, complicating the use of this vaccination and testing strategy in a control scenario (Blome *et al.*, 2006; Loeffen *et al.*, 2009).

Since the first description of an antigenic relationship between CSFV and BVDV in 1960 (Darbyshire, 1960), scientific interest has revolved around the use of BVDV to immunize swine against CSFV (Beckenhauer *et al.*, 1961; Simonyi and Biro, 1967; Baker *et al.*, 1969; Liou *et al.*, 1975). Difficulties arise when comparing these studies, as various BVDV isolates or vaccine titers were used for immunization, which may explain some of the discordant results. In extensive studies using strain Oregon C24V BVDV vaccine prior to challenge with various CSFV laboratory and field isolates, Baker *et al.* (1969) demonstrated protection rates of up to 95% in challenged vaccinates. Furthermore, BVDV vaccination was safe, provided protection from clinical CSFV infection for over 2 years, and BVDV was not spread to in-contact pigs or cattle (Baker *et al.*, 1969). In contrast, all but one pig immunized with BVDV C24V died after challenge with CSFV (Simonyi and Biro, 1967). When immunizing swine with one of four strains of BVDV and subsequent challenge with CSFV, no clinical signs were observed after immunization with BVDV strain Tobias, while mild clinical signs of disease were observed in swine immunized with BVDV strains NY-1 or VJGM, and typical signs of classical swine fever were observed in swine immunized with BVDV strain Egan (Liou *et al.*, 1975). In a comparison of vaccination efficacy of a BVDV strain NY-1 vaccine with a modified live CSFV vaccine, BVDV vaccinated swine were not as well protected as CSFV vaccinates when challenged with 1 of 10 CSFV isolates (Tamoglia *et al.*, 1965). In that study, transmission of vaccine virus was observed in CSFV vaccinates, but not in BVDV vaccinates (Tamoglia *et al.*, 1965). Recovery of BVDV was possible from the respiratory tract of swine vaccinated with strain CL10, indicating that BVDV may be transmitted by vaccinates (Phillip and Darbyshire, 1972). More recently, the BVDV strain St. Oedenrode, which had been isolated from a naturally infected pig, was used to

https://doi.org/10.1017/S1466252309990065 Published online by Cambridge University Press

immunize swine prior to CSFV challenge (Wieringa-Jelsma *et al.*, 2006). Immunization with this strain resulted in a self-limiting BVDV infection (R=0.2) and protected vaccinates from clinical disease and CSFV transmission upon challenge (Wieringa-Jelsma *et al.*, 2006).

Only a limited number of serosurveys have been performed in domestic swine and reported seroprevalence rates are relatively low when compared to other domestic livestock. Risk factors associated with seropositivity of domestic swine include the presence of cattle on the same farm, high density of small ruminants near swine populations, vaccination with BVDV contaminated vaccines, and age of tested swine (Lenihan and Collery, 1977; Vannier *et al.*, 1988; Liess and Moennig, 1990; Loeffen *et al.*, 2009). In an Irish serosurvey, 27.8% of swine in contact with cattle possessed neutralizing antibodies to BVDV, as compared to 4.0% in swine without contact with cattle (Lenihan and Collery, 1977). The feeding of bovine offal was also described as a source of BVDV infection in swine (Stewart *et al.*, 1971). Increasing specialization of farms resulting in decreased chances for interspecific contacts and improved quality control in vaccine production were suggested to be reasons for a decrease in seroprevalence rates in Dutch swine, where 20.0% of slaughterhouse samples from sows and boars were positive in 1991 (Terpstra and Wensvoort, 1991), as compared to 2.5% in sows and 0.42% in finishing pigs, and 11.0 and 3.2% at the respective herd level in 2009 (Loeffen *et al.*, 2009). Only one of 660 serum samples was determined to be positive for BVDV antibodies in a study in Northern Ireland, and the authors suggested that use of a BDV ELISA rather than BVDV ELISA for initial serosurveillance may have confounded this comparatively low result (Graham *et al.*, 2001). Other reports found seroprevalence rates of 3.01% in Canada, 6.4% in Denmark, 3.2% in Ireland and 2.2% in Norway (Jensen, 1985; Afshar *et al.*, 1989; Loken *et al.*, 1991; O'Connor *et al.*, 1991).

Studies on postnatal BVDV infections in non-pregnant swine have rarely described the occurrence of clinical signs based on observation of infected animals (Beckenhauer *et al.*, 1961; Carbrey *et al.*, 1976; Liess and Moennig, 1990; Dahle *et al.*, 1993; Walz *et al.*, 1999; Woods *et al.*, 1999; Makoschey *et al.*, 2002). When evaluated, an elevation of the rectal temperature after BVDV inoculation was not detected in most studies despite evidence of viremia and seroconversion (Beckenhauer *et al.*, 1961; Carbrey *et al.*, 1976; Walz *et al.*, 1999). Experimental infection of six- to ten-week-old pigs with a BVDV 2 inoculum containing non-cytopathic and cytopathic biotypes, resulted in slight pyrexia, leucopenia and thrombocytopenia (Makoschey *et al.*, 2002), which were less pronounced than had been reported in cattle experimentally inoculated using a very similar protocol (Makoschey *et al.*, 2001). Significant, but less severe than observed with homologous pestivirus infections, decreases in lymphocyte populations were detected in intranasally inoculated pigs and a more marked decrease in CD8+ lymphocytes was noticed (Rypula, 2003). Experimental infection of eight-week-old pigs with either BVDV 1 or BVDV 2 did not result in clinical signs or increases in body temperature in any group, despite the use of a BVDV 2 isolate that was demonstrated to be virulent for cattle (Walz *et al.*, 1999). In contrast, inoculation of three-day-old piglets with either BVDV strain NY-1 or a cell-culture contaminant, BVDV-C, resulted in loss of appetite, diarrhea and intestinal pathology for 1–4 days (Woods *et al.*, 1999). Importantly, the co-infection of either BVDV NY-1 or BVDV-C with attenuated transmissible gastroenteritis virus resulted in severe clinical signs that were worse with the cell-culture contaminant BVDV-C (Woods *et al.*, 1999). That report underscored the potential impact of cell culture contamination with BVDV, which may result in enhanced pathogenicity of attenuated vaccines (Woods *et al.*, 1999).

Carbrey *et al.* (1976) suspected BVDV infection as the cause of reproductive failure, including poor conception, small litter size and abortions after antibody titers against BVDV were determined to be higher than against CSFV in breeding sows. Experimental infection of pregnant gilts with one of four BVDV isolates resulted in reproductive disease including intrauterine infection, pregnancy loss and reduction in litter size (Stewart *et al.*, 1980). In that study, fetal infection was established in 1 of 20 infected gilts (Stewart *et al.*, 1980). Similarly, experimental transplacental infection was documented in only one of 43 fetuses after intranasal inoculation of four pregnant gilts, indicating an inconsistent ability of BVDV to cross the blood-placental barrier in swine (Walz *et al.*, 2004). Seroconversion, failure to thrive and premature death have been reported in transplacentally infected swine (Carbrey *et al.*, 1976; Paton *et al.*, 1992). Petechiation and hemorrhages, enlarged lymph nodes, meningitis, myocarditis, nephritis and hepatic necrosis were observed in piglets born to a pregnant sow that was exposed to a persistently infected calf (Paton *et al.*, 1992). Contamination of a CSFV vaccine with BVDV resulted in dead or mummified fetuses, and many living fetuses from vaccinated sows were BVDV positive and showed alopecia, congenital tremors, lymphadenopathy, multifocal petechiation and ascites. Experimental infection with one of four strains of BVDV between 28 and 55 days of gestation resulted in fetal infection in only one of 20 gilts (Stewart *et al.*, 1980). The authors suggest that passages in porcine PK-15 cells may have resulted in a loss of virulence and the inability to cause transplacental infection in the other BVDV strains evaluated in the experiment (Stewart *et al.*, 1980). In the transplacentally infected 13 fetuses, low antibody titers (<1 : 4–1 : 16) and histopathological lesions within leptomeninges and choroid plexus were detected (Stewart *et al.*, 1980). In contrast, antibodies against BVDV did not develop in a persistently viremic pig until slaughter at 26 months and in a littermate, seroconversion was not detected until six

to eight months of age (Terpstra and Wensvoort, 1997). In the affected litter of 13, 10 piglets died or were euthanized within weeks after birth and multiple clinical signs, including thymic atrophy, were detected. Consistent shedding of BVDV until slaughter was detected only in the seronegative PI pig and ceased in its littermates upon seroconversion (Terpstra and Wensvoort, 1997).

BVDV in New and Old World Camelids (NWC and OWC)

BVDV infections were identified through detection of antibodies as early as 1975 in OWC and 1983 in NWC (Burgemeister *et al.*, 1975; Doyle and Heuschele, 1983). In different countries, seroepidemiologic studies identified BVDV antibodies in 0–19.7% of tested OWC (Burgemeister *et al.*, 1975; Hedger *et al.*, 1980; Bornstein and Musa, 1987; Bohrmann *et al.*, 1988; Wernery and Wernery, 1990; Raoofi *et al.*, 2009), but a much higher seroprevalence (52.5%) was reported from two regions in Egypt (Zaghawa, 1998). Wernery and Wernery (1990) explained a higher seroprevalence rate in breeding camels of 9.2% as compared to 3.6% in racing camels by close contact with cattle herds, more intensive management and large herd sizes in breeding camels. While the seroprevalence was not different between male and female dromedary camels, higher age was associated with an increased rate of seropositivity (Raoofi *et al.*, 2009).

In an outbreak of reproductive disease among nine pregnant dromedary camels, abortion, still births, weak calves, early neonatal death and neonatal hemorrhagic disease were observed (Hegazy *et al.*, 1996). Gross and histopathological lesions included congenital cataracts, mild cerebellar hypoplasia, lymphoid depletion, vasculitis, optic neuritis and underpopulated cerebellar molecular layer. Cytopathic BVDV was isolated from two stillborn and one live-born camel calves (Hegazy *et al.*, 1996). Viral isolates were further characterized later by the same laboratory and were typed as BVDV 1 and BVDV 2 (Yousif *et al.*, 2004). Non-cytopathic BVDV has also been isolated from tissues of camels in which histopathological changes were consistent with a BVDV infection (Wahab *et al.*, 2005).

In the past, seroepidemiologic and experimental infection studies suggested that BVDV may cause infections without presenting a serious risk to NWC. Low seroprevalence rates, infections with mild or no clinical signs, and limited viral replication within buffy coat cells supported the conclusion that BVDV may not be a significant pathogen in NWC (Mattson, 1994; Evermann, 2006). Experimental inoculation of four pregnant llamas with a non-cytopathic isolate from an aborted llama fetus did not result in clinical signs or fetal infection (Wentz *et al.*, 2003). Reported seroprevalence rates in South American domestic NWC are 11.1% in Peruvian alpacas, 2.05% in Argentinean llamas and 10.8 and 14% in Chilean alpacas and llamas, respectively (Rivera *et al.*, 1987; Puntel *et al.*, 1999; Celedon *et al.*, 2001). Seropositivity was associated with the presence of other domestic livestock and domestic NWC without exposure to other livestock or free-ranging NWC were seronegative (Karesh *et al.*, 1998; Celedon *et al.*, 2001). In North America, a seroprevalence rate of 4.4% was reported for llamas in Oregon (Mattson, 1994). In southern California, 18.6% of tested alpacas were seropositive and antibody titers were higher against BVDV 1 than BVDV 2 in most cases (Shimeld, 2009). The highest titers were detected on farms on which PI crias were present (Shimeld, 2009). Antibodies against BVDV were detected in crias from 16 of 63 (25.4%) herds in the United States (Topliff *et al.*, 2009).

Reports of BVDV isolation and identification of persistent infections in alpacas have prompted increasing attention by industry and the scientific community and the virus is now considered an emerging pathogen of NWC (Byers *et al.*, 2009). Preceding the descriptions of persistent infections in alpacas, a cytopathic BVDV isolate was identified in kidney, liver, lung and spleen samples from a stillborn llama (Belknap *et al.*, 2000). In the same report, BVDV was detected in tissues of a late pregnant adult llama and an emaciated juvenile llama. Non-cytopathic BVDV 1b isolates were detected in tissues of a stillborn alpaca (lung, liver, kidney and spleen) and tissues from a seven-month-old alpaca (lung, liver and kidney) with ill-thrift, respectively (Goyal *et al.*, 2002; Foster *et al.*, 2005). The first description of a persistent infection in alpacas was made in Canada following natural exposure of a pregnant alpaca to a chronically ill cria (Carman *et al.*, 2005). From the persistently infected cria, a BVDV 1b strain was isolated from buffy coat cells on different occasions before euthanasia of this animal. Several cases of PI alpacas have since been reported in North America and Great Britain (Mattson *et al.*, 2006; Foster *et al.*, 2007; Barnett *et al.*, 2008; Byers *et al.*, 2009; Kim *et al.*, 2009). Persistently infected alpacas may survive for several months but are affected by low birth weight, failure to thrive, inappetence, lethargy, chronic diarrhea and chronic recurrent infections especially of the respiratory tract. In PI alpacas, BVDV antigen may be detected in epithelial and immune cells of many tissues, including skin, brain, thyroid gland, parotid salivary gland, testis, prostate, esophagus, gastric compartments, kidneys, bone marrow, liver, lung, thymus and lymph nodes, and skin staining patterns are consistent with those in cattle (Carman *et al.*, 2005; Foster *et al.*, 2007; Byers *et al.*, 2009).

From NWC in Chile, both BVDV 1 and BVDV 2 have been isolated (Celedon *et al.*, 2006). In contrast, in reports on BVDV isolations from alpacas in North America and the United Kingdom in which the subgenotype of the infecting isolate was determined, all isolates belonged to BVDV 1b (Carman *et al.*, 2005; Foster *et al.*, 2005, 2007; Byers *et al.*, 2009). A recent study analyzed 46 BVDV

https://doi.org/10.1017/S1466252309990065 Published online by Cambridge University Press

Table 2. Reported prevalence rates for antibodies directed against BVDV in free-ranging wildlife

Species	Rate of seropositives (percent)	Reference
Five species in Germany, hunter-harvested[a]	5.9–6.6	Weber *et al.* (1978)
Five species of deer in Great Britain, random sampling between 1961 and 1973[b]	0–16	Lawman *et al.* (1978)
Two species of exotic deer at Point Reyes National Seashore, hunter-harvested[c]	0–4	Riemann *et al.* (1979)
Fifteen species in nine African countries/regions, collected between 1963 and 1977[d]	6.8–100	Hamblin and Hedger (1979)
Four species in Alaska, captured animals at various sites[e]	0–3	Zarnke (1983)
Two species of deer, harvested at two locations in Maryland and Virginia, US[f]	0/5–2/5	Davidson and Crow (1983)
Four species in Germany, hunter-harvested[g]	0–1.3	Dedek *et al.* (1987)
Ten species in Namibia, hunter-harvested[h]	0–57	Depner *et al.* (1991)
Three species in Northern Tanzania, various locations in two national parks[i]	33–49	Hyera *et al.* (1992)
Two species of deer from eight National Parks in Western US, convenience sampling[j]	55–59	Aguirre *et al.* (1995)
Three species of deer from Germany, also includes other species of captive deer, convenience sampling[k]	7.7 (14 of 180)	Frolich (1995)
Sixteen species in Zimbabwe, convenience sampling at various sites[l]	<1.0–75	Anderson Rowe (1998)
Four species of deer in Denmark, hunter-harvested in eight districts[m]	0.6	Nielsen *et al.* (2000)
Four species of deer in Norway, hunter-harvested at various sites[n]	1.1–12.3	Lillehaug *et al.* (2003)
Four species in southern Austria, hunter-harvested[o]	0.7% (1/145)	Krametter *et al.* (2004)
Four species in High Valley of Susa, northwest Italy[p]	0–25.5	Olde Riekerink *et al.* (2005)
Three species of deer in six German National Parks[q]	0 (0/164)	Frolich *et al.* (2006)
Caribou (*Rangifer tarandus caribou*), hunter-harvested in Georges River area, Northern Quebec, Canada	60.7–69.3	ElAzhary *et al.* (1979), ElAzhary *et al.* (1981)
Caribou in Saskatchewan, Canada	0	Jordan *et al.* (2003)
European bison (*Bison bonasus*), hunter-harvested diseased bison in Bialowieza Primeval Forest	29.5	Salwa *et al.* (2007)
European rabbit (*Oryctolagus cuniculus*), hunter-harvested in North-western Germany	40 (40/100)	Frolich and Streich (1998)
Fallow deer (*Dama dama*), hunter-harvested or trapped in Tasmania, Australia	14.5 (11/76)	Munday (1972)
Fallow deer, captured in south-eastern New South Wales, Australia	1.2 (1/86)	English (1982)
Fallow deer, from San Rossore Preserve, Tuscany, Italy, hunter-harvested	58 (25/43)	Giovannini *et al.* (1988)
Grey brocket deer (*Mazama gouazoubira*), hunter-harvested in the Gran Chaco, Bolivia	0 (0/17)	Deem *et al.* (2004)
Guanaco (*Lama guanicoe*), captured in Cabo Dos Bahias Provincial Reserve, Argentina	0%, 0/20	Karesh *et al.* (1998)
Guanaco and Vicuña (*Vicugna vicugna*) several regions in Chile	0, 0/82	Celedon *et al.* (2001)
Moose (*Alces alces*), hunter-harvested in Cypress Hills Park, Southeastern Alberta	13.6 (3/22)	Thorsen and Henderson (1971)
Moose, seven areas in Alaska	13/110 (12%)	Kocan *et al.* (1986)
Mule deer (*Odocoileus hemionus*), trapped in south-central Idaho, US	68 (adults), 12 (fawns)	Stauber *et al.* (1977)
Mule deer, hunter-harvested in south-central New Mexico, US	34 (26/76)	Couvillion *et al.* (1980)
Mule deer, captured at Pinedale, WY, USA	60% (74/124)	Van Campen *et al.* (2001)
Pampas deer (*Ozotoceros bezoarticus celer*), captured in Campos del Tuyu Reserve, Argentina	0 (0/14)	Uhart *et al.* (2003)
Pronghorn (*Antilocapra americana*), live-trapped at four locations in Alberta and Saskatchewan, Canada	3.6 (3/84)	Barrett and Chalmers (1975)
Pronghorn, live-trapped at three locations in southeastern Idaho, US	2 (adults), 0 (fawns)	Stauber *et al.* (1980)
Pronghorn, hunter-harvested in four areas of Arizona, US	5.0, 7/128	Dubay *et al.* (2006)
Red deer (*Cervus elaphus*), hunter-harvested, stratified sampling	1.7 (4/234)	Koppel *et al.* (2007)
Reindeer (*Rangifer tarandus*), from Northern Norway and Svalbard	41 (adults) 6 (calves)	Stuen *et al.* (1993)
Wapiti (*Cervus elaphus),* hunter-harvested in southwestern Alberta, Canada	52	Kingscote *et al.* (1987)
White-tailed deer (*Odocoileus virginianus*); random sampling in New York state	3	Kahrs *et al.* (1964)
White-tailed deer, hunter-harvested from two herds	5.75	Friend and Halterman (1967)

https://doi.org/10.1017/S1466252309990065 Published online by Cambridge University Press

Table 2. (Continued)

Species	Rate of seropositives (percent)	Reference
White-tailed deer, hunter-harvested on Anticosti Island, Quebec, Canada	0	Sadi *et al.* (1991)
White-tailed deer, captured, on 15 ranches in northeastern Mexico	63.5 (331/521)	Cantu *et al.* (2008)
White-tailed deer, convenience sampling, from 23 facilities across Alabama, US	1.2% (2/165)	Passler *et al.* (2008)
White-tailed deer, captured at multiple locations in Southern Minnesota, US	25 (SE) 41 (SW)	Wolf *et al.* (2008)

[a]Seropositive: roe deer and red deer; seronegative: fallow deer, wild boar and European mouflon.
[b]Seropositive: fallow deer, red deer, Chinese water deer and sika deer; seronegative: roe deer.
[c]Seropositive: axis deer; seronegative: fallow deer.
[d]Seropositive: African buffalo, nyala, kudu, eland, waterbuck, defassa waterbuck, lechwe, reedbuck, sable antelope, oryx, tsessebe, hartebeest, wildebeest, impala, springbok, duiker, giraffe and wart hog; seronegative: bush buck, puku, kob, roan antelope, topi, blesbok, Grant's gazelle, klipspringer, oribi, steinbok, grysbok, hippopotamus, elephant, bush pig and zebra.
[e]Seropositive: caribou; seronegative: dall sheep, moose and American bison.
[f]Seropositive: sika deer and white-tail deer.
[g]Seropositive: roe deer and red deer; seronegative: fallow deer and European mouflon.
[h]Seropositive: giraffe, gemsbok, roan antelope, blue wildebeest, eland, kudu and sable antelope; seronegative: red hartebeest, black wildebeest and springbok.
[i]Seropositive: African buffalo, wildebeest and topi.
[j]Seropositive: mule deer and wapiti.
[k]Seropositive: fallow deer, roe deer and red deer.
[l]Seropositive: nyala, eland, bushbuck, Lichtenstein's hartebeest, kudu, reedbuck, African buffalo, sable antelope, impala, wildebeest, waterbuck, tsessebe and giraffe; seronegative: warthog and white rhinoceros.
[m]Seropositive: red deer; seronegative: roe deer, fallow deer and sika deer.
[n]Seropositive: roe deer, reindeer, moose and red deer.
[o]Seropositive: red deer; seronegative: roe deer, fallow deer and chamois.
[p]Seropositive: red deer, wild boar and chamois; seronegative: roe deer.
[q]Seronegative: red deer, roe deer and fallow deer.

isolates from over 12,000 North American alpacas and classified all isolates as non-cytopathic strains of subgenotype 1b. Nucleotide identity of ≥99% was demonstrated in 45 of 46 isolates using the highly conserved 5′-UTR, indicating an unusual association of the 1b genotype with BVDV infections in North American alpacas (Kim *et al.*, 2009). Kim *et al.* (2009) offer two explanations for this peculiarity, firstly that exposures of alpacas to BVDV are rare and spread of the existing BVDV 1b strain is by extensive movement of a few PI animals or secondly, only unique 1b subgenotypes are able to establish transplacental infections in alpacas. Interestingly, the simultaneous inoculation of pregnant alpacas with two BVDV 1b isolates of cattle or alpaca origin, respectively, and a BVDV 2 strain of cattle origin, resulted in birth of crias PI with 1b of cattle or alpaca origin, but not BVDV 2 (Edmonson *et al.*, 2009). This may further support a unique role of BVDV 1b in alpacas; however, viremia, nasal shedding and seroconversion were observed when alpacas were inoculated with BVDV 1b or BVDV 2 strains (Johnson *et al.*, 2009). Movement of alpacas (including dams with cria by foot) between farms, mainly for breeding purposes, are common practice and were described in reports of reproductive disease and birth of PI offspring, highlighting the importance of sound biosecurity practices (Carman *et al.*, 2005; Foster *et al.*, 2007; Barnett *et al.*, 2008; Topliff *et al.*, 2009).

BVDV in wildlife

In addition to the ability to induce persistent infections, the large number of wildlife species in which infections with BVDV have been demonstrated, emphasizes the potential for another important survival strategy of BVDV, the ability to cross species barriers. With few exceptions, infections with BVDV appear to be limited to species in the order Artiodactyla. Antibodies were detected in 2 of 44 Bennett's wallaby (*Macropus rufogriseus*); however, the titers against BVDV C24V were at dilutions of less than 1:3 (Munday, 1972). Antibodies against BVDV were also detected in free-ranging rabbits (*Oryctolagus cuniculus*), but virus isolation or detection of viral genome from spleen samples were not successful (Frolich and Streich, 1998).

The mammalian order Artiodactyla is comprised of 10 families and 240 species (Grubb, 2005), and evidence of BVDV infection exists in the seven families Antilocapridae, Bovidae, Camelidae, Cervidae, Giraffidae, Suidae and Tragulidae, including over 50 species (Nettleton, 1990; Van Campen *et al.*, 2001; Grondahl *et al.*, 2003). In most species, evidence of BVDV infection mainly has been by the identification of antibodies, therefore it may be difficult to estimate the implications on health of affected species or on BVDV control programs; however, identification of high seroprevalence rates may suggest

https://doi.org/10.1017/S1466252309990065 Published online by Cambridge University Press

the presence of endemic cycles (Van Campen *et al.*, 2001). Several seroepidemiological studies in free-ranging wildlife have been performed globally and large variations of seroprevalence status exist among the studied populations (Table 2). The scale, both of the number of samples collected and the size of the sampled habitat, and the employed sampling strategies vary tremendously among serosurveys, perhaps partially explaining the observed variations in seroprevalence.

Although sources of BVDV infections in free-ranging wildlife are unknown, a likely source is contact with cattle, as has been suggested by various authors (Riemann *et al.*, 1979; Stauber *et al.*, 1980; Kocan *et al.*, 1986; Nielsen *et al.*, 2000). This is further supported by the absence of antibodies in deer that were without contact with cattle for over 50 years (Sadi *et al.*, 1991). Significantly higher seroprevalence rates were found in white-tailed deer on ranches where cattle were present as compared to ranches without cattle (Cantu *et al.*, 2008). In contrast, an association between BVDV seroprevalence and cattle density was not found in another study (Frolich, 1995). Similar findings were described in a recent report from Minnesota where a greater percentage of deer were seropositive in a region with lower cattle density (Wolf *et al.*, 2008). The authors of that report concluded that cattle use and management (i.e. dairy or beef) may have an important impact on interspecific BVDV transmission, as there is likely less wildlife contact with housed dairy cattle as compared to pastured beef cattle (Wolf *et al.*, 2008). This factor was not evaluated in the earlier publication from Germany where the majority of cattle operations are dairies (Statistisches Bundesamt, 2007). Various factors likely influence the transmission of BVDV between cattle and wildlife as has been described for other disease such as bovine tuberculosis (Schmitt *et al.*, 2002). With the presence of suitable environmental and management factors, transmission of BVDV from cattle to deer is possible as has been demonstrated recently in a cohabitation experiment (Passler *et al.*, 2009a). In that study, BVDV was efficiently transmitted from PI cattle to white-tailed deer and resulted in seroconversion in all adult deer and PI offspring in four of seven pregnancies (Passler *et al.*, 2009a).

Maintenance of BVDV within a cervid population without the presence of cattle was suggested by the presence of antibodies in over 60% of caribou that had not been in contact with domestic ruminants for over 25 years (ElAzhary *et al.*, 1981). The presence of endemic infections with BVDV as indicated by high seroprevalence rates was also suggested in reindeer in Norway and US cervid populations (Stuen *et al.*, 1993; Aguirre *et al.*, 1995; Van Campen *et al.*, 2001; Lillehaug *et al.*, 2003). This view is further supported by identification of high seroprevalence rates in eland populations of Zimbabwe, in which a PI and a virus-isolation-positive eland were identified (Anderson and Rowe, 1998). In a follow-up study, the non-cytopathic strains isolated from elands were further characterized with monoclonal antibodies and partial genetic sequencing and were demonstrated to be very similar to the BVDV 1a strains NADL and SD1, indicating that cattle had originally introduced BVDV into the eland population (Vilcek *et al.*, 2000).

Only a limited number of studies have surveyed free-ranging wildlife populations for the presence of BVDV or BVDV antigen. Anderson and Rowe (1998) utilized an antigen capture ELISA to detect BVDV in a subset of 303 seronegative animals during their serosurvey in Zimbabwe and detected two virus positive eland. In Germany, cytopathic BVDV was detected in spleen samples from two of 203 deer and both animals were seronegative roe deer (Frolich and Hofmann, 1995). These isolates were further characterized by monoclonal antibody typing and sequencing of the 5′-UTR, and results indicated that distinct BVDV strains may circulate within the sampled roe deer population (Fischer *et al.*, 1998). Recently, three surveys utilizing the immunohistochemistry (IHC) or ELISA technique, investigated the occurrence of BVDV in free-ranging cervids in the US and results suggest that PI cervids exist in wildlife populations (Duncan *et al.*, 2008b; Passler *et al.*, 2008; Pogranichniy *et al.*, 2008). In Alabama, 1 of 406 skin samples from white-tailed deer was positive on IHC and the antigen distribution resembled that of PI cattle (Passler *et al.*, 2008). Similarly, the skin sample of 1 of 5597 deer in Colorado was positive on IHC and this result was confirmed by the detection of viral RNA in skin and lymph node samples (Duncan *et al.*, 2008b). In Indiana, 2 of 745 white-tailed deer were positive for BVDV by antigen capture ELISA with subsequent isolation of cytopathic and non-cytopathic BVDV (Pogranichniy *et al.*, 2008). To date, the validation of BVDV assays for their use in wildlife has not been performed, and this may be critical as considerable variations were observed among the IHC and antigen capture ELISA on skin samples of white-tailed deer (Passler and Walz, unpublished observations). In addition to surveys, isolation of BVDV was successful in free-ranging roe deer in Hungary, a mule deer in Wyoming and two white-tailed deer in South Dakota (Romvary, 1965; Van Campen *et al.*, 2001; Chase *et al.*, 2008). In these reports, clinical illness including emaciation, weakness and death prompted further investigations leading to the isolation of BVDV from tissues.

In addition to free-ranging populations, BVDV has been identified in captive herds and zoo collections, and contact with other ruminant species was described in some reports (Nettleton *et al.*, 1980; Neumann *et al.*, 1980; Weber *et al.*, 1982; Doyle and Heuschele, 1983; Grondahl *et al.*, 2003; Nelson *et al.*, 2008). Although the role of BVDV as a pathogen of wildlife is largely unclear, isolation of BVDV from clinically ill wildlife emphasizes the potential for BVDV to induce disease in zoo collections. The isolation of BVDV from deceased captive deer submitted for necropsy was successful in different reports; however, whether clinical BVDV infection was

cause for the fatalities was mostly uncertain (Neumann *et al*., 1980; Weber *et al*., 1982; Diaz *et al*., 1988). Severe mucosal disease-like lesions were observed in a nilgai, an axis deer, and a barasingha deer that were co-infected with BVDV and the virus of malignant catarrhal fever, suggesting a possible immunosuppressive effect of BVDV in wildlife (Doyle and Heuschele, 1983). The close vicinity of ruminant species in zoo collections increases the potential for disease transmission and prompted the euthanasia of six PI mousedeer, emphasizing the threat of BVDV for captive endangered species (Grondahl *et al*., 2003; Uttenthal *et al*., 2006). In addition to the aforementioned species, the presence of persistent infection was recently demonstrated in a captive mountain goat (Nelson *et al*., 2008).

The BVDV antigen distribution in two PI white-tailed deer was similar to that of cattle with broad tissue distribution, most notably in epithelium and vascular endothelium (Duncan *et al*., 2008a). The role that PI wildlife may have in the epidemiology of BVDV, including the frequency of occurrence, transmission potential and survivability is largely unknown. Seroconversion and viral RNA were detected in a calf exposed to a PI Lesser Malayan mousedeer by indirect and direct routes; however, BVDV infection was not evident in a second calf exposed by the same routes (Uttenthal *et al*., 2006). The maternal line of PI mousedeer remained without clinical signs and were reproductively sound, giving birth to PI offspring (Uttenthal *et al*., 2006). Experimental inoculation of white-tailed deer fawns did not result in clinical signs, but BVDV was identified by reverse transcription-polymerase chain reaction (RT-PCR) on nasal and rectal swab samples, indicating a potential of transmission (Raizman *et al*., 2009). In a PI white-tailed deer, virus isolation titers from nasal swab samples were equivalent to those in PI cattle (Passler *et al*., 2007). The cohabitation of pregnant white-tailed deer with a PI white-tailed deer resulted in seroconversion of all exposed animals and birth of a PI fawn, indicating that maintenance of BVDV in cervid populations is possible when a PI animal is present (Passler *et al*., 2009b). Superinfection of a PI mousedeer with a cytopathic BVDV strain of partial antigenic homology did not result in clinical signs of mucosal disease (Semrau *et al*., 2008). In contrast to PI Lesser Malayan mousedeer, persistent infection may result in decreased survivability in white-tailed deer (Passler *et al*., 2009a). This may have implications on the risk of transmission, but would also affect the ability to detect PI white-tailed deer in hunter-harvested samples that are usually collected from adult deer.

Few reports on the clinical picture and outcome of BVDV infection in wildlife exist, but reported clinical signs are similar to BVDV infections in cattle. Experimental inoculation with BVDV NY-1 did not result in clinical signs in four mule deer and one white-tailed deer fawns, despite evidence of viremia and nasal shedding (Van Campen *et al*., 1997). Similar findings were made in yearling elk that were inoculated either with BVDV 1 Singer or BVDV 2 24515 (Tessaro *et al*., 1999). In two young reindeer, loose, bloody and mucoid feces, transient laminitis, or coronitis were observed after inoculation with BVDV Singer and mild lesions were detected at necropsy (Morton *et al*., 1990). Naïve white-tailed deer fawns developed moderate pyrexia and marked to moderate decreases in lymphocyte populations in response to either BVDV 1 or BVDV 2; and lethargy or coughing was observed in individual fawns (Mark *et al*., 2005; Ridpath *et al*., 2007). Similar to other species, BVDV infections in wildlife may have the most important implications on reproductive health. Experimental inoculation of pregnant white-tailed deer may result in reproductive failure, including fetal resorption, fetal mummification, stillbirth and abortion (Passler *et al*., 2007, 2008; Ridpath *et al*., 2008).

Summary

BVDV is one of the most important infectious agents affecting the cattle industry worldwide; however, BVDV is not host-specific to cattle as numerous wild and domestic species have been reported susceptible to BVDV infection. Infection with BVDV in heterologous species, with the potential for PI offspring, may have great implications for BVDV control in cattle populations, as these species may become reservoirs and sources of infection for cattle populations that are free from BVDV. In addition, BVDV disease and mortality in heterologous species, including rare and endangered livestock or zoo animal species, threaten natural resources and complicate laboratory testing strategies. Further research, including studies on interspecific interactions and BVDV transmission, are warranted to fully understand the importance of BVDV in heterologous species.

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