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Review article

Ruminant alphaherpesviruses related to bovine herpesvirus 1

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Abstract – Herpesviruses have mainly co-evolved with their hosts for millions of years. Consequently, different related host species may have been infected by various genetically related herpesviruses. Illustrating this concept, several ruminant alphaherpesviruses have been shown to form a cluster of viruses closely related to bovine herpesvirus 1 (BoHV-1): namely bovine herpesvirus 5, bubaline herpesvirus 1, caprine herpesvirus 1, cervid herpesviruses 1 and 2 and elk herpesvirus 1. These viruses share common antigenic properties and the serological relationships between them can be considered as a threat to BoHV-1 eradication programmes. BoHV-1 is a herpesvirus responsible for infectious bovine rhinotracheitis, which is a disease of major economic concern. In this article, the genetic properties of these ruminant alphaherpesviruses are reviewed on a comparative basis and the issue of interspecific recombination is assessed. The pathogenesis of these infections is described with emphasis on the host range and crossing of the host species barrier. Indeed, the non bovine ruminant species susceptible to these ruminant alphaherpesviruses may be potential BoHV-1 reservoirs. The differential diagnosis of these related infections is also discussed. In addition, available epidemiological data are used to assess the potential of cross-infection in ruminant populations. A better knowledge of these ruminant alphaherpesvirus infections is essential to successfully control infectious bovine rhinotracheitis.

alphaherpesvirus / bovine / goat / sheep / deer

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1. INTRODUCTION

Members of the Herpesviridae family are DNA viruses showing a spectacular evolutionary success. The name, derived from the Greek ερπειν (*herpein*), "to creep", refers to the characteristic lesions caused by two common human herpesviruses: fever blisters caused by herpes simplex virus (HSV), as well as varicella and shingles induced by varicella zoster virus (VZV). This virus family includes nearly two hundred viruses isolated from hosts as diverse as molluscs, fish, amphibians, reptiles, birds and mammals [102]. In nature, most herpesviruses are closely associated with a single host species, and almost all the animal hosts investigated to date support infections by at least one herpesvirus species. Host susceptibility to herpesviruses indicates that the viruses have mainly co-evolved with their hosts, leading to a close adaptation [24].

The Herpesviridae family is divided into three subfamilies, called Alpha-, Beta- and Gammaherpesvirinae. The Alphaherpesvirinae subfamily contains four genera: *Simplexvirus*, *Varicellovirus*, *Mardiviruses* and *Iltoviruses*[1]. This subfamily includes viruses characterised by a large host range, a short replication cycle and a capacity to induce latent infection mainly, but not exclusively, in neurons [102]. Among alphaherpesviruses infecting ruminants, the prototype is bovine herpesvirus 1 (BoHV-1), a pathogen of cattle associated with two major syndromes, called infectious bovine rhinotracheitis (IBR) and infectious pustular vulvovaginitis (IPV), and a variety of clinical signs, such as conjunctivitis, encephalitis and abortions [91]. IBR is a disease of major economic concern in many parts of the world and especially in Europe, both in countries where this infection has been eradicated and in those where the control of IBR is currently or will be undertaken [129].

Seroepidemiological surveys have been performed in other species of domestic or wild ruminants in order to investigate whether these animals could be potential BoHV-1 reservoirs. Antibodies against BoHV-1 have

[1] International Committee on Taxonomy of viruses, in: ICTVdB Index of Viruses, Appendix 00.031 herpesviridae [on line] (2002) http://www.ncbi.nlm.nih.gov/ICTVdb/Ictv/fs_herpe.htm [consulted 5 May 2005].

Table I. Ruminant alphaherpesviruses related to bovine herpesvirus 1.

Virus	Natural host	Disease	Geographic distribution
Bovine herpesvirus 1	Bovine	Infectious bovine rhinotracheitis Infectious pustular vulvovaginitis	Europe, America, Asia, Australia
Bovine herpesvirus 5	Bovine	Bovine encephalitis	Europe, America, Australia
Bubaline herpesvirus 1	Water buffalo	Subclinical genital infection	Europe, Australia
Caprine herpesvirus 1	Goat	Vulvovaginitis, abortion, neonatal systemic infection	Europe, America, Australia
Cervid herpesvirus 1	Red deer	Ocular syndrome	Europe
Cervid herpesvirus 2	Reindeer	Subclinical genital infection	Europe
Elk herpesvirus 1	Elk	Subclinical genital infection	North America

been detected in many ruminant species [127]. In addition, several ruminant alphaherpesviruses related to BoHV-1 have been isolated and characterised. Bovine herpesvirus 5 (BoHV-5) is responsible for meningoencephalitis in calves [57]. Caprine herpesvirus 1 (CpHV-1) causes systemic disease in young kids and abortion in adult goats [109]. Cervid herpesvirus 1 (CvHV-1) has been isolated from ocular disease in red deer (*Cervus elaphus*) in Scotland [56]. Cervid herpesvirus 2 (CvHV-2) has been isolated from reindeer (*Rangifer tarandus*) in Finland [34], and serological evidence of infection with a virus related to BoHV-1 has been reported in caribou (*Rangifer tarandus caribou*) in Canada [35]. Elk herpesvirus 1 (ElkHV-1) has been isolated from elk (*Cervus elaphus*) in North America [27] and bubaline herpesvirus 1 (BuHV-1) infection has been reported in water buffalo (*Bubalus bubalis*) in Australia [118] (Tab. I).

Successful control of IBR depends on the use of efficient, sensitive and specific diagnostic tests. However, since most of the diagnostic tests are based on the detection of antibody in polyclonal sera, their specificity is compromised by the existence of a serological cross-reactivity between BoHV-1 and these other closely related ruminant alphaherpesviruses. This can be illustrated by the original situation observed in Finland. In 1982, 23% of reindeer of this country had antibodies against BoHV-1, while all cattle were seronegative [33]. A superficial analysis of these data suggested a BoHV-1 infection of reindeer with an absence of transmission to cattle due to an apparent lack of contact between the two ruminant species. However, this simple hypothesis was rapidly rejected. Indeed, from a BoHV-1 seropositive reindeer, a new virus was isolated and further characterised as CvHV-2. This infection provided a likely explanation for the presence of anti-CvHV-2 antibodies cross-reacting with BoHV-1 in reindeer [34]. In spite of this epidemiological situation in reindeer, the Finnish cattle population maintained an IBR free status. This example reveals the importance of clarifying the cause of potential serological cross-relationships with BoHV-1.

This review focuses on ruminant alphaherpesviruses related to BoHV-1, with particular emphasis on molecular virology, pathogenesis, host range, diagnosis and prevention. Indeed, it is of major interest to obtain greater knowledge about the risks of acute and latent infections of cattle with other ruminant herpesviruses and about the potential presence of BoHV-1 reservoirs among ruminant species other than cattle.

2. MOLECULAR VIROLOGY

2.1. Morphology and genomic organisation

The inner part of the herpesvirus virion consists of a core containing the viral genome,

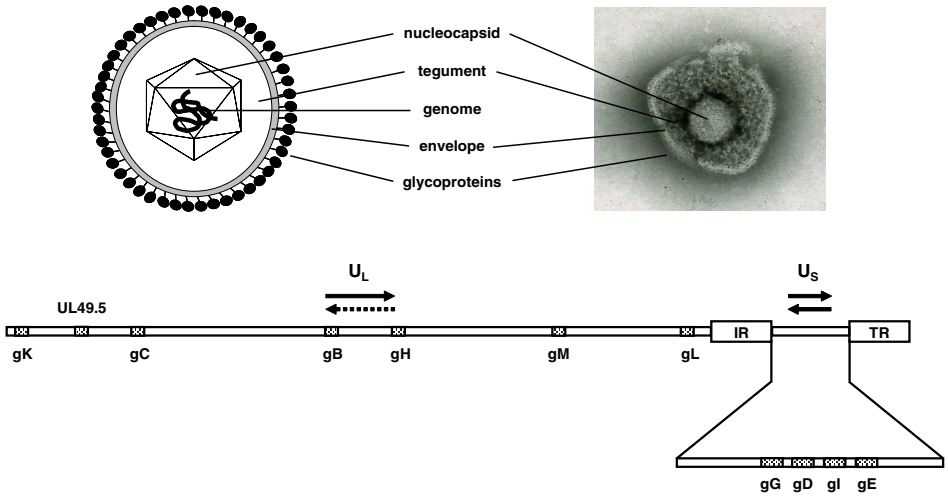

Figure 1. Morphology and genomic organisation of ruminant alphaherpesviruses. The genome consists of a double-stranded linear DNA. It contains an arrangement of one long unique unit (U_L) and one short unique unit (U_S) flanked by two inverted repeat sequences, named internal repeat (IR) and terminal repeat (TR). The genome includes ten genes encoding glycoproteins: six are located in the U_L segment and four in the U_S segment. The U_S segment can have two possible orientations (depicted by the arrows). The U_L segment is predominantly present in one orientation. The broken arrow illustrates that about 5% of the genomes show the U_L segment in this inverted orientation.

protected by an icosahedral nucleocapsid of 100 to 110 nm diameter made up of 150 hexamers and 12 pentamers. This structure is surrounded by a proteinaceous layer, defined as the tegument. The latter is surrounded by a lipid bilayer, the envelope, containing a large number of viral glycoproteins, among which glycoproteins gB, gC and gD are the most abundant. The mature virion particle ranges from 120 to 300 nm in diameter [102] (Fig. 1).

The genome of ruminant alphaherpesviruses consists of a double-stranded linear DNA. Like the other alphaherpesviruses belonging to the *Varicellovirus* genus, it contains an arrangement of one long unique unit (U_L) and one short unique unit (U_S) flanked by two inverted repeat sequences, named internal repeat (IR) and terminal repeat (TR) [112] (Fig. 1). These characteristics allow its classification in class D of herpesvirus genomes [101]. In this genomic class, the U_L segment is predominantly fixed in only one orientation, called the prototype orientation, so that equimolar amounts of the two isomers can be predicted in virion DNA due to the inversion of the U_S segment [102]. However, low levels (5%) of genomes having the U_L segment in an inverted orientation have been detected in BoHV-1 virion DNA [113].

Alphaherpesvirus genes are expressed in a cascade-like fashion. The first step occurs immediately after the release of the virion genome from the capsid to produce immediate-early proteins. The second step occurs after the synthesis of immediate-early proteins, leading to the production of early proteins. The third step, in which late proteins are produced, is delayed until after the synthesis of virion DNA. Finally, early-late protein expression starts before viral DNA replication but does not decrease during late protein expression [101].

2.2. Genomic comparison between ruminant alphaherpesviruses

The genomes of BoHV-1 and BoHV-5 have been sequenced [26, 79, 112]. The BoHV-5 genome is 138 390 bp long (72% G+C content), with 2 518 bp more than BoHV-1 (75% G+C content). It includes 72 genes, of which 68 are present as single copies within the unique regions and two are completely located within the repeat region (BICP4 and BICP22) [26]. The BoHV-1 genome comprises 67 unique genes and two genes, both duplicated, in the inverted repeats [112]. The highest BoHV-5 similarity to BoHV-1 products (95% amino acid identity) is found in proteins involved in viral DNA replication and processing (UL5, UL15, UL29 and UL39) and in virion proteins (UL14, UL19, UL48 and US6). Among the least conserved (≤ 75%) are the homologues of immediate-early proteins BICP0, BICP4 and BICP22, these proteins being longer in BoHV-5 than in BoHV-1 [26]. It can be hypothesised that the same range of homology is shared by the other related ruminant alphaherpesviruses.

The comparison between other ruminant alphaherpesviruses is based on limited sequence data. The genome sizes are estimated to be 137 kbp for CpHV-1, 141 kbp for CvHV-1 and 145 kbp for CvHV-2 [41, 137]. Based on the complete gB gene sequence, which is the most conserved between herpesviruses [48], the percentages of nucleotide sequence identity with BoHV-1 gB are 78.5% for CpHV-1, 84% for CvHV-2, 85.8% for CvHV-1, 87.4% for BoHV-5 and 87.7% for BuHV-1 [107]. The gC[2] and gD gene sequences are fully known for each ruminant alphaherpesviruses, except for BuHV-1 [26, 29, 64, 112]. On this basis, the percentages of amino acid sequence identity between BoHV-1 and ElkHV-1 are 71.7% (gC) or 72.9% (gD) [29]. The G+C contents of the gC (or gD) genes are 79.4% (77.2%) for CvHV-1, 79.2% (76%) for CvHV-2 and 78.7% (78.5%) for ElkHV-1 [29]. A comparison of the coding sequence of the CvHV-2 gC region with other ruminant alphaherpesviruses has revealed a conserved central part of the gC gene, while the N-terminal is highly variable with large deletions and insertions [106, 108]. These results have allowed the classification of these viruses into a consistent group, where BoHV-5 and BuHV-1 are most closely related to BoHV-1, followed by ElkHV-1, CvHV-1, CvHV-2 and, more distantly, by CpHV-1 [29, 107] (Fig. 2).

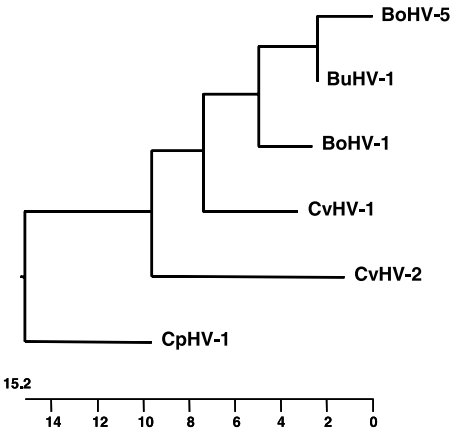

Figure 2. Phylogenetic tree inferred by amino acid sequences from the gB regions of ruminant alphaherpesviruses (reproduced from [107], with permission of Kluwer Academic Publishers). Based on the gC and gD sequences, ElkHV-1 clusters with CvHV-1 [29].

2.3. Viral glycoproteins

Viral glycoproteins of herpesviruses play an important role in the interactions between these viruses and their host-cells. They are involved in several steps of the viral cycle, such as the attachment, penetration, maturation and egress of the virus. Therefore, they constitute an important target for the

[2] Tempesta M., Tarsitano E., Camero M., et al., Short sequence repeats (SSR) in the glycoprotein C gene of caprine herpesvirus type 1 (CpHV.1), in: Proceedings of the 2nd European congress of virology, Madrid, 2004, pp. 11–14.

host immune response. Some glycoproteins also have immunogenic properties, allowing their use as a component of vaccines or diagnostic tests.

Most of the BoHV-1 glycoproteins have already been characterised [133]. The U_L segment includes genes coding for glycoproteins gB (UL27), gC (UL44), gH (UL22), gL (UL1), gK (UL53) and gM (UL10), while four genes corresponding to gG (US4), gD (US6), gI (US6) and gE (US8) are grouped in a tandem organisation in the U_S segment [112] (Fig. 1). Several constructions of mutant viruses have shown that gC, gI, gE, gG and gM are non essential glycoproteins [8, 65]. On the contrary, the deletion of the gene encoding either gB or gD or gH reduces the capacity of in vitro replication [44, 80]. Glycoproteins L and K are essential in HSV-1 and this is very likely to be the case in the other alphaherpesviruses [54, 104]. In the pseudorabies virus, an additional glycoprotein, designated gN (UL49.5), is a glycosylated 10 kDa transmembrane protein and is identified as an immune evasion molecule inhibiting the transporter associated with antigen processing (TAP) driven peptide import into the endoplasmic reticulum. The UL49.5 homologue encoded by BoHV-1 has the same immune evasion function, but is not classified as glycoprotein N [66].

Considering the lack of data on glycoproteins, we hypothesise by analogy that the main elements of structure and function of BoHV-1 glycoproteins are shared by the other ruminant alphaherpesviruses. Monoclonal antibody analysis allows the identification of antigenic differences between BoHV-1 and BoHV-5 [22, 32, 45, 76]. Glycoprotein C shows more divergence between BoHV-1 and BoHV-5 than gB and gD [22, 45]. BoHV-5 gC, although not essential, regulates neurotropism in some areas of the olfactory pathway and is important for BoHV-5 neurovirulence in rabbits [21]. This glycoprotein is also able to transfer the heparin binding phenotype of BoHV-5 to a recombinant BoHV-1 [71]. The BoHV-5 gE is involved in neural spread and neurovirulence within the central nervous system and cannot be substituted by BoHV-1 gE. However, BoHV-5 gE is not essential for the initial entry into the olfactory pathway [20]. Glycoprotein I is not required for the neurovirulence of gE in BoHV-5 [3], but a glycine-rich BoHV-5 gE-specific epitope is essential for expression of the full virulence potential of BoHV-5 [4]. Generally, gE and gI seem to be important for BoHV-5 neuropathogenicity and its ability to reactivate from latency [53]. Glycoprotein H is one of the most conserved glycoproteins in herpesviruses [46]. BoHV-1 and BoHV-5 gH are both expressed as early-late proteins. Glycoprotein H is essential for both penetration and cell-to-cell spread [7, 80, 81]. In CpHV-1, gD shows a relatively high homology to BoHV-1 gD amino acid sequences (similarity of 68.8%) and has a molecular mass similar to BoHV-1 gD. CpHV-1 gD contains complex *N*-linked oligosaccharides, but the presence of *O*-glycosylation has not been demonstrated. In contrast with BoHV-1 gD, CpHV-1 gD is seemingly expressed as a late protein [64].

2.4. Recombination between ruminant alphaherpesviruses

Recombination is thought to be an important source of genetic variation in herpesviruses. Several studies, performed in vitro and in vivo, have detected recombinant viruses after the co-inoculation of two distinguishable strains of the same herpesvirus species [130, 131]. After experimental co-inoculation of calves with two parental BoHV-1 mutants, recombination has been identified as a frequent event in vivo. Recombinant viruses have been detected both during primary infection and after reactivation from latency [114]. The mechanism involved is mainly homologous recombination. Its role in creating viral diversity needs to be evaluated in BoHV-1 control and eradication programmes. In order to assess the risk of recombination between BoHV-1 gE negative marker vaccine and field strains,

different factors influencing the onset of recombinant viruses have been investigated. In natural conditions, superinfection is a more likely event than co-infection. Superinfection with a time interval of 2 to 8 h between two successive infections allows the establishment of a barrier to prevent recombination between BoHV-1 strains [77]. Therefore, only co-infection or delayed infection over a very short interval of time might lead to the production of recombinant viruses.

The efficiency of interspecific recombination has been assessed between ruminant alphaherpesviruses. Indeed, successful homologous recombination requires two closely related parental viruses. Two recombinants between BoHV-1 and BoHV-5 have been isolated, but no recombinant has been detected between BoHV-1 and the less closely related CpHV-1 and CvHV-2 [78]. Nevertheless, even in the absence of mature recombinant viruses, these results do not exclude a recombination process occurring in the cell, because mixed concatemers between BoHV-1 and CvHV-2, and between CvHV-1 and CvHV-2, have been identified in co-infected cells[3]. The close genetic relatedness between ruminant alphaherpesviruses suggests a theoretical risk of recombination between these virus species. This risk must also be evaluated by considering the sites of alphaherpesvirus replication: two alphaherpesviruses are unlikely to recombine if they replicate in two distant sites, such as the genital and respiratory mucosae.

3. PATHOGENESIS AND CLINICAL SIGNS

The pathogenesis of BoHV-1 infection is well described [36, 58, 91]. After infection and virus replication in mucosa, BoHV-1 spreads both in the extracellular space and also from cell-to-cell. By this latter mechanism, it may enter axons of local nerve cells. Then, by intra-axonal transport, the viruses reach the sensitive neuronal bodies in the regional nervous ganglia, where latency can be established. This pathogenic mechanism is shared by the other ruminant alphaherpesviruses. Although infection can lead to lethal or systemic disease, especially in newborn animals, clinical signs are usually mild, but may vary according to the animal species and the virus species and strain concerned. Alphaherpesviruses, like other herpesviruses, are able to interfere with the host's innate and adaptative immune responses. A growing list of immune evasion mechanisms is described [139], such as, for example, inhibition of TAP proteins [66] or Fc receptor activity of viral glycoproteins [43].

3.1. Bovine herpesvirus 5

The pathogenesis of bovine herpesvirus encephalitis is not yet completely elucidated. Comparative experiments of inoculation with BoHV-1 and BoHV-5 have been carried out in cattle [5, 6, 11, 51, 83, 111]. After primary infection by intranasal inoculation, BoHV-1 and BoHV-5 replicate at the portal of entry in the respiratory mucosa [6]. Experimentally infected calves show similar profiles for the length of excretion (ten to sixteen days) and for the amount of excreted viruses. The rate of virus excretion is high, with a peak between the fourth and sixth days post infection [11, 83, 129]. After primary infection, BoHV-5 induces a transient viremia and virus is recovered in secondary organs [11].

The dissemination of BoHV-5 infection probably follows the same three routes as BoHV-1: blood, nervous system and cell-to-cell spread [6, 11, 51, 82, 91]. BoHV-5 induces a replication cycle in the cells of the respiratory epithelium and reaches the nervous system by a mechanism strongly associated with intra-axonal transport. Neurons of the peripheral nervous system are infected first of all, especially cells of the trigeminal

[3] Meurens F., Influence du délai de surinfection et de la parenté génétique sur la recombinaison de l'herpèsvirus bovin 1, Doctorate thesis, Liège, Belgium, 2004.

ganglia and olfactory cells of nasal mucosa. The virus invades all areas of the central nervous system by neuron-to-neuron spread, using the olfactory and trigeminal pathways [82]. In a rabbit model of infection, the olfactory pathway has indeed been shown to be the main route of infection of the central nervous system [68]. Cell-to-cell transmission without extracellular phase and in the absence of specific antibodies has been demonstrated for BoHV-1. It can be postulated that the same mechanism drives the local transfer of BoHV-5 to the central nervous system [82].

In calves, BoHV-5 has been shown to produce fatal meningo-encephalitis after intranasal inoculation or a meningitis-like disease after intravaginal infection because the virus involves the central nervous system [5, 83]. Inoculation of conjunctival, nasal and vaginal mucosae provokes conjunctivitis, rhinitis and vulvovaginitis, respectively. Clinical signs of BoHV-5 are characterised by serous nasal discharge and sneezing; apathy and anorexia are also observed. Neurological signs start with severe depression with anorexia, jaw champing and hypersalivation. In the next phase, calves are affected by muscle trembling, circling to one side, pushing their head against a wall and ataxia, followed by seizure-like episodes and opisthotonos [83]. Histological lesions in the brain consist of meningitis, mononuclear perivascular cuffing, neurophagia, satellitosis, gliosis, haemorrhage, necrosis and oedema [92].

After primary infection, BoHV-5 latency is established in surviving calves. The classical latency sites are the trigeminal ganglia, but BoHV-5 DNA could also be present throughout the central nervous system during latent infection and probably in nasal and tracheal mucosae, where viral DNA has been detected by PCR [83]. Virus reactivation may result in the establishment of latent infection in additional sites of the brain [138]. The establishment of latent infection has also been demonstrated in the rabbit model [16]. Reactivation of BoHV-5 can be provoked by the same glucocorticoid treatment as for BoHV-1: 0.1 mg of dexamethasone per kg body weight for five consecutive days [83].

3.2. Caprine herpesvirus 1

The pathogenesis of CpHV-1 infection in goats and BoHV-1 infection in calves is very similar [37]. Local respiratory or genital infection is followed by a mononuclear cell-associated viremia, which can lead to systemic infection and abortion. The main sources of infection are acutely and latently infected animals. During acute infection, the virus is excreted via ocular, nasal and genital routes. The genital route is thought to be the main entry site of the virus and is thought to be responsible for the maintenance of infection in a herd [123].

In kids, CpHV-1 causes a systemic disease characterised by high morbidity and mortality rates. Ulcerative and necrotic lesions are distributed throughout the enteric tract [75]. In adult goats, the infection leads to vulvovaginitis or balanoposthitis. Abortions associated with CpHV-1 occur during the second half of pregnancy and can be experimentally reproduced after intranasal or intravenous inoculation of pregnant goats [126, 136, 145]. The viral DNA is identified in both the placenta and several inner organs of the aborted foetus [61, 126, 141].

Natural reactivation from latent CpHV-1 infection can be induced by a physiological stress during the mating season. The hormonal status at oestrus could play a role in the induction of reactivation. Under experimental and natural conditions, the reactivation of a latent virus is difficult [15, 63, 125]. Experimental reactivation requires the use of high doses of dexamethasone: six consecutive daily injections at a dose rate of 4.4 mg per kg bodyweight [15]. Re-excretion after reactivation is observed in goats with relatively low antibody titres [120]. Viruses are isolated from nasal, genital, rectal and ocular swabs, suggesting several potential latency sites [15, 96], such as sacral ganglia where latent CpHV-1 has been

detected by PCR [121]. The site supporting CpHV-1 re-excretion may depend on the route of primary infection. After reactivation of a virus previously inoculated intranasally, the virus is shed from the nose and vagina [122]. In contrast, after a genital primary infection, reactivated CpHV-1 is only re-excreted from the vagina [123].

3.3. Cervid herpesvirus 1

Primary sites of CvHV-1 infection are the anterior respiratory and ocular mucosae [60]. Viruses can be recovered from between two and six days post-infection in nasal and ocular swabs [99]. However, a genital transmission cannot be excluded because CvHV-1 has been isolated from red deer sperm [134]. CvHV-1 is responsible for an ocular syndrome in red deer [56]. This syndrome is characterised by conjunctivitis and purulent ocular discharge, hypopyon, uniform corneal opacity without ulceration, mucopurulent nasal discharge and photophobia. Moderate swelling of the periorbital tissues and marked oedema of the upper eyelids are also observed [56].

Experimental infection induces hyperthermia, nasal ulceration and conjunctivitis. These clinical signs are mild in comparison with natural infection. CvHV-1 can also be isolated after intramuscular injection with 50 mg of a synthetic glucocorticoid for twelve consecutive days. This result suggests that this virus is able to establish a persistent infection and be reactivated [103].

3.4. Cervid herpesvirus 2

Reindeer infection by CvHV-2 is asymptomatic [86]. The first virus isolation was performed on vaginal swabs from reindeer identified as seropositive for BoHV-1. Reindeer were injected intramuscularly on four consecutive days with dexamethasone at a dose rate of 0.1 mg per kg bodyweight [34]. Therefore, CvHV-2 most likely establishes a latent infection and can be re-excreted in genital secretions. A serological investigation showing a high prevalence in adult reindeer suggests genital transmission [87].

3.5. Bubaline and elk herpesviruses 1

Recently, a field strain of BuHV-1 was isolated after a reactivation treatment. Water buffaloes were injected intramuscularly daily for five consecutive days with dexamethasone at a dosage of 4 mg per kg bodyweight. Only slight diarrhoea and serous nasal discharge were observed [25]. Concerning ElkHV-1 infection, pathogenesis and clinical signs remain to be investigated.

4. CROSS-SPECIES INFECTION

Cross-infection studies have been performed in order to gain greater knowledge about risks of acute and latent infections in cattle with other ruminant alphaherpesviruses and about potential BoHV-1 reservoirs among ruminant species other than cattle. The results of experimental infections of calves with BoHV-5, CpHV-1, CvHV-1, CvHV-2 and ElkHV-1, and infection of goats, sheep, red deer and reindeer with BoHV-1 are summarised in Tables II and III[4].

4.1. Bovine herpesvirus 1 infection of goats and sheep

Experimental infection of goats with BoHV-1 has clearly shown that this virus is able to infect the heterologous host. This infection leads to mild clinical signs, high levels of BoHV-1 excretion for several days during primary infection and a serological response. BoHV-1 is able to establish a latent infection in the trigeminal ganglia of goats and sheep [1, 42, 69, 95, 116, 140]. Reactivation of latent BoHV-1 is obtained

[4] Thiry E., Ackermann M., Banks M., et al., Risk evaluation of cross-infection of cattle with ruminant alphaherpesviruses related to bovine herpesvirus type 1, in: Körber R. (Ed.), 3. Internationales Symposium zur BHV-1-/BVD-Bekämpfung, Stendal, 2001, pp. 99–104.

Table II. Consequences of infection of calves with ruminant alphaherpesviruses related to bovine herpesvirus 1.

Virus	Primary infection	Serological response	Latency	Reactivation and reexcretion
BoHV-5	+	+	+	+
CpHV-1	+	+	+	–
CvHV-1	–	–	–	–
CvHV-2	+	+	–	–

Table III. Consequences of infection of ruminant species with bovine herpesvirus 1.

Host	Primary infection	Serological response	Latency	Reactivation and reexcretion
Goat	+	+	+	+
Sheep	+	+	+	+
Red deer	+	–	–	–
Reindeer	+	–	–	–

by a daily dexamethasone treatment on five consecutive days of 2.5 mg per kg bodyweight in goats [116] and 0.1 mg per kg bodyweight in sheep (Banks et al., personal communication). Field cases of BoHV-1 latent infections have also been recorded in goats [135]. Although they are usually subclinical in sheep, acute BoHV-1 infections can sometimes be associated with clinical signs, such as acute, fatal pneumonia, or with aborted foetuses [144]. However, sheep do not play a major role in BoHV-1 transmission to calves [50].

4.2. Bovine herpesvirus 1 infection of red deer and reindeer

Red deer could become infected following a profound BoHV-1 challenge, but titres of excreted virus are very low and almost certainly would not represent a source of contagious spread. Furthermore, there is no evidence that BoHV-1 establishes a latent infection in red deer. Seroconversions to BoHV-1 in red deer do not occur and are most likely the result of a CvHV-1 rather than BoHV-1 infection [86, 99]. Another deer species, the mule deer (*Odocoileus hemionus*), exhibits greater susceptibility to BoHV-1 because it actively excretes BoHV-1 and shows seroconversion after experimental inoculation [87].

In reindeer, experimental BoHV-1 infection is asymptomatic and does not usually give rise to neutralising antibodies. The titres of nasally excreted viruses are very low and the virus cannot be reactivated experimentally[4].

4.3. Bovine herpesvirus 5 infection of sheep

Sheep are susceptible to acute and latent infection with BoHV-5. Experimental inoculation of BoHV-5 shows that this virus is able to infect the heterologous host by invading the central nervous system. Resulting clinical signs are similar to those observed in cattle [10]. A dexamethasone treatment of 2 mg daily for five consecutive days results in reactivation of the latent infection and virus shedding in lambs [115]. No BoHV-5 natural infection has yet been reported in sheep.

4.4. Caprine herpesvirus 1 infection of calves and sheep

Bovine calves intranasally infected with CpHV-1 have been shown to excrete the

virus. CpHV-1 is able to establish a latent infection in trigeminal ganglia. However, reactivation of latent CpHV-1 from calves has not been successfully achieved [116]. In the same way, lambs are susceptible to CpHV-1 infection, but no virus has been isolated after clinical reactivation [90]. In natural conditions, CpHV-1 virulence is restricted to the natural host [42].

4.5. Cervid herpesvirus 1 infection of calves

Bovine calves are almost refractory to infection with CvHV-1 by intranasal challenge: neither clinical signs nor virus excretion are observed. Furthermore, when calves are challenged with BoHV-1 after a CvHV-1 infection, they develop pyrexia and the virus is recovered in nasal and ocular swabs, thereby showing that a prior infection with CvHV-1 does not induce any protective immune response [86, 99]. In addition, no infection has been noticed in cattle housed in close contact with infected deer [103].

4.6. Cervid herpesvirus 2 infection of calves

In experimental conditions, cattle can be successfully infected intranasally with CvHV-2 and mild rhinitis is observed. The virus is isolated for six to nine days from nasal and genital swabs [87]. Therefore, CvHV-2 replication can occur experimentally in bovines, but cattle housed in close contact with infected reindeer are not infected [34]. These results suggest that the risk of transmission between reindeer and cattle is low in natural conditions.

4.7. Elk herpesvirus 1 infection of cattle

Experimentally, cattle are susceptible to infection with ElkHV-1, but do not show any clinical signs. A cow inoculated intranasally has been shown to develop neutralising antibodies, while a genital inoculation failed to induce any serological response in another cow [27]. More recently, reactivation from latency was serologically demonstrated in cattle experimentally infected with ElkHV-1 after a daily dexamethasone treatment for five consecutive days of 0.1 mg per kg bodyweight [28]. Natural cross-infection has not yet been recorded.

5. EPIDEMIOLOGY

5.1. Bovine herpesvirus 5

Since 1962, several outbreaks of herpesvirus encephalitis have been described and were later on attributed to BoHV-5. In Australia and South America, this infection occurs in cattle not immunised against BoHV-1 and is inducing a major economic problem, mainly in central and southern Brazil and Argentina. Indeed, the morbidity rate may vary between 15 and 50% and the lethal rate is close to 100% [17, 57, 93, 110, 142]. In the USA, BoHV-5 has been associated with field cases of bovine encephalitis [31]. In Europe, BoHV-5 has been isolated only once in Hungary [9], but BoHV-5 infection is probably also present in Germany and eastern European countries [82].

5.2. Caprine herpesvirus 1

CpHV-1 was initially isolated in 1975 in California from the tissues of newborn kids affected with mild to severe enteritis [109]. In 1979, it was isolated from kids in a herd in the Bregaglia valley of Switzerland [75]. Distribution of CpHV-1 infection has not been systematically studied in goats but the virus has been identified in several countries in Europe including Greece, Italy, Spain and Switzerland, as well as in Australia, Canada, New Zealand and the USA [19, 47, 52, 63, 67, 75, 84, 96, 105, 109]. The apparent prevalences are variable. In many countries where goats play an economical role, a high seroprevalence is observed: between 30 and 40% in southern Italy and more than 50% in Greece [49, 67,

119]. CpHV-1 infection has not been identified in Belgium, France (Keuser and Thiry, unpublished results) or the United Kingdom.

5.3. Cervid herpesvirus 1

CvHV-1 was initially isolated in 1983 in farmed red deer. The outbreak occurred in a group of 80 red deer in the north of Scotland and 50 to 60 animals exhibited clinical signs [56]. More recently, CvHV-1 was identified in New Zealand where the virus was isolated during routine export examination of semen collected from red deer stags [134]. CvHV-1 infection is widespread in Great Britain. Indeed, 35% of the animals older than one year are seropositive for CvHV-1 [85]. Moreover, a Czech investigation showed that 71% of red deer imported from Scotland were seropositive [97]. The apparent prevalence of seropositive free ranging deer has been shown to be 11% in Belgium and 1% in France [128]. More recently, a further Belgian investigation has shown a seroprevalence of 30% in free ranging adults and 1.4% in calves (Gregoire and Linden, unpublished results). In 1988, 43% of deer in a Belgian farm were shown to be seropositive to CvHV-1 (Thiry, unpublished results). Although the serological analyses were performed with tests detecting anti-BoHV-1 antibodies, they are the most suggestive of CvHV-1 infection in wild populations of red deer.

5.4. Cervid herpesvirus 2

Serological evidence of exposure of reindeer to a virus related to BoHV-1 has formerly been reported in Canada [35] and in the USA [30]. More recently, evidence of alphaherpesvirus infection has been reported in isolated populations of the woodland caribou in western Canada [59]. In 1982, a prevalence of 23% reindeer seropositive to BoHV-1 was observed in the Finnish Lapland [33]. In Finland, 64% of adult reindeer and 1% of calves have been shown to be seropositive to CvHV-2 [87]. A Norwegian investigation showed similar results: 60% of reindeer and 15% of calves were shown to be seropositive [55]. In Norway, during the period 1993–2000, antibodies against BoHV-1 related alphaherpesviruses were found in 28.5% of reindeer [70]. These results indicate that alphaherpesvirus infections are endemic in reindeer and that CvHV-2 is most likely the herpesvirus responsible for the observed prevalences.

5.5. Bubaline and elk herpesviruses 1

BuHV-1 was isolated in 1971 from prepuces of water buffaloes [118]. More recently, a field strain of BuHV-1 has been isolated from buffaloes in Italy [25]. To date, only one case of ElkHV-1 infection has been reported. The virus was isolated from the semen of a North American elk [27].

6. DIAGNOSIS

The capacity of these related alphaherpesviruses to spread in ruminant populations is a threat to BoHV-1 eradication programmes. Indeed, infection with related viruses could lead to false positive diagnosis of BoHV-1. Moreover, heterologous ruminant species could serve as BoHV-1 reservoirs. Consequently, diagnostic tools able to distinguish between ruminant alphaherpesviruses related to BoHV-1 and BoHV-1 itself are of great interest.

6.1. Virological diagnosis

The use of tests based on virus isolation or viral DNA detection can avoid misinterpretation due to these cross-reactions. Restriction endonuclease analysis (REA) performed on viral isolates allows the identification and distinguishing of the related viruses [12, 14, 15, 23, 38–41, 94, 98, 100, 103, 137, 145] and could be used to detect interspecific recombinants [78]. However, this procedure is not convenient for general use in a diagnostic laboratory. Highly specific methods using viral DNA amplification have therefore been developed. Differential PCR assays use pairs of consensus primers selected for the detection of bovine,

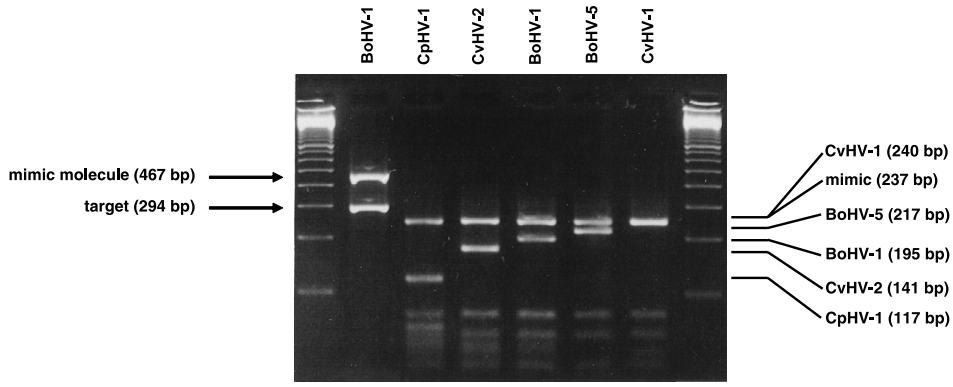

Figure 3. PCR amplification of ruminant alphaherpesvirus DNA. A mimic molecule is used for control. The final identification of the amplicon is performed by restriction enzyme analysis (reproduced from [106], with permission of the American Society for Microbiology).

caprine and cervid herpesviruses, and discrimination is achieved by subsequent REA of PCR products [73, 106] (Fig. 3). Another PCR system, using four primer pairs, specifically amplifies a part of the gC gene of each alphaherpesvirus [108]. A multiplex PCR is available for differentiation between BoHV-1 and BoHV-5 [2]. A quantitative real time PCR is available for the detection and quantitation of CpHV-1 DNA in goats[5]. There also exists monoclonal antibodies that can distinguish between BoHV-1 and BoHV-5 by immunofluorescence, immunoprecipitation or western blot [45, 76, 89]. More recently, an immunofluorescence assay able to differentiate the five related herpesviruses has been developed. This method is based on the use of four monoclonal antibodies directed against gC, and one against gD, of these related viruses [62] (Fig. 4).

6.2. Serological diagnosis

Serological analysis is very difficult due to the antigenic similarity of ruminant alphaherpesviruses related to BoHV-1. Indeed, these viruses cross-react in ELISA and seroneutralisation tests [72, 74, 88]. The current available serological tests are almost unable to discriminate the related alphaherpesviruses.

A method combining two blocking ELISA allows a distinction to be made between anti-BoHV-1 and anti-BoHV-5 antibodies in cattle. A serum positive to BoHV-1 in a blocking ELISA based on the recognition of BoHV-1 glycoprotein B is further analysed by a BoHV-1 gE blocking ELISA. Provided there is no vaccination of cattle with a gE negative BoHV-1 vaccine, a negative result in this second test will indicate an infection with BoHV-5. However, the sensitivity and the specificity of this test have been tested only on a very limited number of experimental sera [143].

An early study demonstrated a full agreement between seroneutralisation and indirect ELISA for the detection of anti-CpHV-1 antibodies in goats [96]. Commercially available BoHV-1 gB blocking ELISA has been tried in other animal species, namely goats and red deer. Compared to CpHV-1 seroneutralisation, this test, applied to the detection of anti-CpHV-1 antibodies in goats, exhibits a relative sensitivity of 95.8% ± 2.4% for experimental sera and

[5] Tempesta M., Decaro N., Elia G., et al., Development of a real time PCR for the detection and quantitation of caprine herpesirus type 1 DNA, in: Nauwynck H., Favoreel H. (Eds.), Proc. 2nd ESVV Veterinary Herpesvirus Symposium, Ghent, 2005.

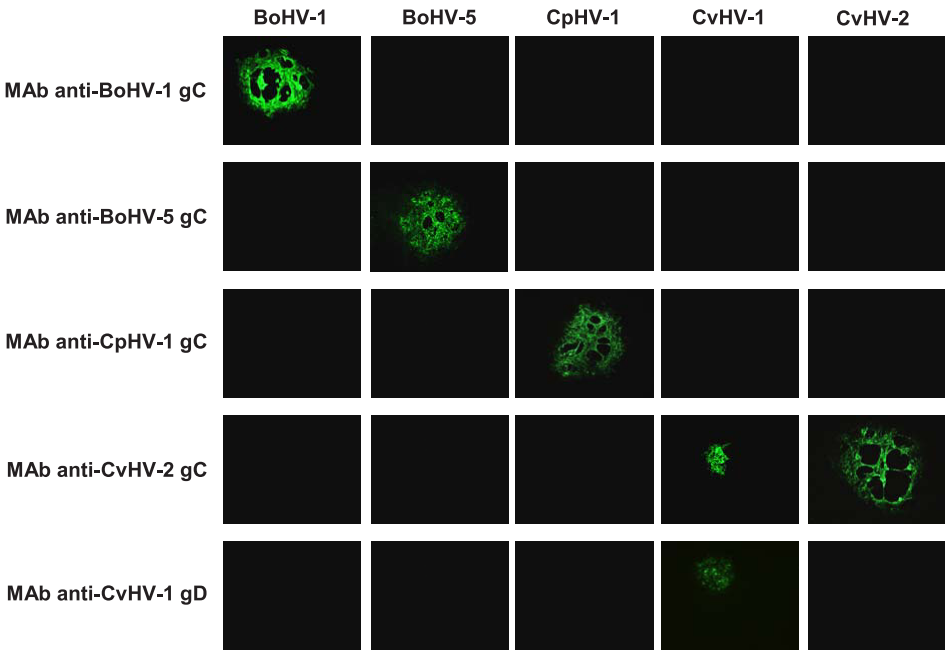

Figure 4. Indirect immunofluorescence staining of cells infected with ruminant alphaherpesviruses. The primary monoclonal antibodies directed against BoHV-1, BoHV-5, CpHV-1, CvHV-2 and CvHV-1 were detected by FITC-conjugated rabbit immunoglobulin anti-mouse IgG (reproduced from [62], with permission of the American Society for Microbiology). (A color version of this figure is available at www.edpsciences.org.)

98.7% ± 2.5% for field sera, as well as a relative specificity of 96.9% ± 2.5% for experimental sera and 91.4% ± 9.2% for field sera[6]. These good relative intrinsic values are enough to recommend their use at the herd level but not on an individual basis. It must be emphasised that this test cannot differentiate between anti-BoHV-1 and anti-CpHV-1 antibodies. The same BoHV-1 gB blocking ELISA has been successfully tested on deer sera to detect antibodies to CvHV-1 by cross-reaction with the same inability to distinguish between anti-BoHV-1 and anti-CvHV-1 antibodies (Reid, personal communication). Any further attempt to develop specific ELISA has failed to date. The challenge is therefore to develop a differentiating serological test that could be free from high antigenic cross-reactions.

Neutralising antibodies are raised after each alphaherpesvirus infection: for example, bovine field or experimental sera [82], sera from hyperimmunised rabbits [13] and monoclonal antibodies raised against gB, gC or gD [22, 45] exhibit neutralising properties against BoHV-5.

In several combinations, cross-neutralisation assays can differentiate antibodies between the related alphaherpesviruses. A one way cross-neutralisation can be demonstrated for each combination of BoHV-1 and related alphaherpesviruses. Therefore,

[6] Keuser V., Infection de la chèvre par l'herpèsvirus caprin 1 : diagnostic différentiel et caractérisation de la glycoprotéine D, Doctorate thesis, Liège, Belgium, 2003.

BoHV-1 specific antiserum neutralises the heterologous virus to a greater extent than anti-sera specific to related alphaherpesviruses that have been shown to neutralise BoHV-1 [29, 39, 83, 86].

7. PREVENTION

Although there is no commercially available vaccine against BoHV-5, it is possible to take advantage of a previous immunisation against BoHV-1. Indeed, a primary infection with BoHV-1 affords a cross-protection that protects cattle clinically against BoHV-5 superinfection [13, 18]. This feature can explain the epidemiology of BoHV-5 infection in several continents. Indeed, BoHV-5 can induce outbreaks of meningo-encephalitis in calves not vaccinated against BoHV-1. In North America, IBR vaccination is widely used and sporadic cases of BoHV-5 have only been seen to emerge in calves badly or not immunised against BoHV-1 [31]. A recombinant gE negative BoHV-1 vaccine has been shown to be unable to confer full protection against the challenge of BoHV-5 [117]. Therefore the efficacy of the cross-protection afforded by commercial BoHV-1 vaccines needs to be evaluated.

A classical inactivated vaccine confers protection against CpHV-1 infection in goats. This vaccine shows a high immunogenicity and good clinical protection [124]. However, this vaccine has very little chance of being marketed because the veterinary pharmaceutical industry has only a poor interest in the development of vaccines for minor species like goats. As goats are susceptible to BoHV-1, both live and inactivated BoHV-1 vaccines might be tested in goats for their efficacy in the face of a CpHV-1 infection. In this way, a recent preliminary experiment showed that a commercially available live attenuated gE negative BoHV-1 vaccine afforded only partial protection to intranasally challenged goats [132].

No vaccines are available to protect animals against CvHV-1, CvHV-2, ElkHV-1 or BuHV-1 infections. The main reasons are the low virulence of these viruses and the lack of interest by the industry in these animal species, which are seemingly of minor importance. Currently, no data indicate whether the BoHV-1 vaccine is able to protect ruminants infected by their own herpesviruses. However, the close antigenic relationship between these viruses may suggest a cross-protection, but this must, however, be evidenced in challenge experiments.

In the absence of commercialised vaccines, the control of these infections relies on hygienic prophylactic measures: isolation of infected animals and disinfection of farms. Serological diagnosis by a fast and inexpensive method, such as ELISA, is essential to control herds and to give and maintain a virus-free status. The removal of seropositive animals considered to be latent carriers, can lead to the forming of seronegative herds, which are likely to be free of virus infection. Such control measures are especially important in deer farming, which is becoming widespread in many countries.

In free-ranging ruminants, control of alphaherpesvirus infection seems extremely difficult to achieve. The only possibility of doing this relies upon the prevention of extensive contact between animals in order to reduce virus spread.

8. CONCLUSION

BoHV-1 is antigenically and genetically related to several ruminant alphaherpesviruses. The existence of antigenic cross-reactions between these viruses and their ability to cross, at least in some instances, the species barrier raise theoretical problems for differential diagnosis. Therefore, it is advisable to carefully evaluate the existence of any other alphaherpesvirus reservoir, both in regions and countries where BoHV-1 infection has been eradicated and in those where the control of IBR is currently or will

be undertaken. There must be a requirement to verify that BoHV-1 seropositive ruminants are not infected with BoHV-1 but are infected with their own specific virus. In order to avoid such misdiagnosis, new diagnostic tools are currently being developed. PCR and immunofluorescence tests, using monoclonal antibodies, allow unambiguous discrimination of each ruminant alphaherpesvirus related to BoHV-1. These advances in diagnostic methods must be completed by a better knowledge of the pathogenesis of ruminant alphaherpesvirus infections. The successful control of IBR depends on the parallel surveillance of putative reservoirs of BoHV-1.

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REFERENCES

[1] Ackermann M., Metzler A.E., McDonaugh H., Bruckner L., Muller H.K., Kihm U., Stellen nichtbovine paarhufer ein IBR-Virusreservoir dar? I. BHV-1 und CapHV-1 infektions und reaktivierungsversuche an ziegen, virustyp-spezifitat der humoralen antikorper und charakterisierung der viralen antigene, Schweiz. Arch. Tierheilkd. 128 (1986) 557–573.

[2] Alegre M., Nanni M., Fondevila N., Development of a multiplex polymerase chain reaction for the differentiation of bovine herpesvirus-1 and -5, J. Vet. Med. B Infect. Dis. Vet. Public Health 48 (2001) 613–621.

[3] Al-Mubarak A., Chowdhury S., In the absence of glycoprotein I (gI), gE determines bovine herpesvirus type 5 neuroinvasiveness and neurovirulence, J. Neurovirol. 10 (2004) 233–243.

[4] Al-Mubarak A., Zhou Y., Chowdhury S.I., A glycine-rich bovine herpesvirus 5 (BHV-5) gE-specific epitope within the ectodomain is important for BHV-5 neurovirulence, J. Virol. 78 (2004) 4806–4816.

[5] Bagust T.J., Comparison of the biological, biophysical and antigenic properties of four strains of infectious bovine rhinotracheitis herpesvirus, J. Comp. Pathol. 82 (1972) 365–374.

[6] Bagust T.J., Clark L., Pathogenesis of meningo-encephalitis produced in calves by infectious bovine rhinotracheitis herpesvirus, J. Comp. Pathol. 82 (1972) 375–383.

[7] Baranowski E., Dubuisson J., van Drunen Littel-van den Hurk S., Babiuk A.L., Michel A., Pastoret P.-P., Thiry E., Synthesis and processing of bovine herpesvirus-1 glycoprotein H, Virology 206 (1995) 651–654.

[8] Baranowski E., Keil G., Lyaku J., Rijsewijk F.A., van Oirschot J.T., Pastoret P.-P., Thiry E., Structural and functional analysis of bovine herpesvirus 1 minor glycoproteins, Vet. Microbiol. 53 (1996) 91–101.

[9] Bartha A., Hajdu G., Aldasy P., Paczolay G., Occurrence of encephalitis caused by infectious bovine rhinotracheitis virus in calves in Hungary, Acta Vet. Acad. Sci. Hung. 19 (1969) 145–151.

[10] Belak K., Kucsera L., Ros C., Kulcsar G., Makranszki L., Soos T., Belak S., Studies on the pathogenicity of bovine herpesvirus type 5 in sheep, Comp. Immunol. Microbiol. Infect. Dis. 22 (1999) 207–220.

[11] Belknap E.B., Collins J.K., Ayers V.K., Schultheiss P.C., Experimental infection of neonatal calves with neurovirulent bovine herpesvirus type 1.3, Vet. Pathol. 31 (1994) 358–365.

[12] Brake F., Studdert M.J., Molecular epidemiology and pathogenesis of ruminant herpesviruses including bovine, buffalo and caprine herpesviruses 1 and bovine encephalitis herpesvirus, Aust. Vet. J. 62 (1985) 331–334.

[13] Bratanich A.C., Sardi S.I., Smitsaart E.N., Schudel A.A., Comparative studies of BHV-1 variants by in vivo-in vitro tests, Zentralbl. Veterinarmed. B 38 (1991) 41–48.

[14] Bulach D.M., Studdert M.J., Comparative genome mapping of bovine encephalitis herpesvirus, bovine herpesvirus 1, and buffalo herpesvirus, Arch. Virol. 113 (1990) 17–34.

[15] Buonavoglia C., Tempesta M., Cavalli A., Voigt V., Buonavoglia D., Conserva A., Corrente M., Reactivation of caprine herpesvirus 1 in latently infected goats, Comp.

Immunol. Microbiol. Infect. Dis. 19 (1996) 275–281.

[16] Caron L., Flores E.F., Weiblen R., Scherer C.F., Irigoyen L.F., Roehe P.M., Odeon A., Sur J.H., Latent infection by bovine herpesvirus type-5 in experimentally infected rabbits: virus reactivation, shedding and recrudescence of neurological disease, Vet. Microbiol. 84 (2002) 285–295.

[17] Carrillo B.J., Ambrogi A., Schudel A.A., Vazquez M., Dahme E., Pospischil A., Meningoencephalitis caused by IBR virus in calves in Argentina, Zentralbl. Veterinarmed. B 30 (1983) 327–332.

[18] Cascio K.E., Belknap E.B., Schultheiss P.C., Ames A.D., Collins J.K., Encephalitis induced by bovine herpesvirus 5 and protection by prior vaccination or infection with bovine herpesvirus 1, J. Vet. Diagn. Invest. 11 (1999) 134–139.

[19] Chenier S., Montpetit C., Helie P., Caprine herpesvirus-1 abortion storm in a goat herd in Quebec, Can. Vet. J. 45 (2004) 241–243.

[20] Chowdhury S.I., Lee B.J., Ozkul A., Weiss M.L., Bovine herpesvirus 5 glycoprotein E is important for neuroinvasiveness and neurovirulence in the olfactory pathway of the rabbit, J. Virol. 74 (2000) 2094–2106.

[21] Chowdhury S.I., Lee B.J., Onderci M., Weiss M.L., Mosier D., Neurovirulence of glycoprotein C(gC)-deleted bovine herpesvirus type-5 (BHV-5) and BHV-5 expressing BHV-1 gC in a rabbit seizure model, J. Neurovirol. 6 (2000) 284–295.

[22] Collins J.K., Ayers V.K., Whetstone C.A., van Drunen Littel-van den Hurk S., Antigenic differences between the major glycoproteins of bovine herpesvirus type 1.1 and bovine encephalitis herpesvirus type 1.3, J. Gen. Virol. 74 (1993) 1509–1517.

[23] D'Arce R.C., Almeida R.S., Silva T.C., Franco A.C., Spilki F., Roehe P.M., Arns C.W., Restriction endonuclease and monoclonal antibody analysis of Brazilian isolates of bovine herpesviruses types 1 and 5, Vet. Microbiol. 88 (2002) 315–324.

[24] Davison A.J., Evolution of the herpesviruses, Vet. Microbiol. 86 (2002) 69–88.

[25] De Carlo E., Re G.N., Letteriello R., Del Vecchio V., Giordanelli M.P., Magnino S., Fabbi M., Bazzocchi C., Bandi C., Galiero G., Molecular characterisation of a field strain of bubaline herpesvirus isolated from buffaloes (*Bubalus bubalis*) after pharmacological reactivation, Vet. Rec. 154 (2004) 171–174.

[26] Delhon G., Moraes M.P., Lu Z., Afonso C.L., Flores E.F., Weiblen R., Kutish G.F., Rock D.L., Genome of bovine herpesvirus 5, J. Virol. 77 (2003) 10339–10347.

[27] Deregt D., Jordan L.T., van Drunen Littel-van den Hurk S., Masri S.A., Tessaro S.V., Gilbert S.A., Antigenic and molecular characterization of a herpesvirus isolated from a North American elk, Am. J. Vet. Res. 61 (2000) 1614–1618.

[28] Deregt D., Tessaro S.V., Gilbert S.A., Serological evidence of latency in cattle experimentally infected with elk herpesvirus, Vet. Rec. 156 (2005) 610–611.

[29] Deregt D., Gilbert S.A., Campbell I., Burton K.M., Reid H.W., Hurk S.V., Penniket C., Baxi M.K., Phylogeny and antigenic relationships of three cervid herpesviruses, Virus Res. 114 (2005) 140–148.

[30] Dietrich R.A., Respiratory viruses, in: Dietrich R.A. (Ed.), Alaskan wild life diseases, University of Alaska, Fairbanks, 1981, pp. 28–29.

[31] D'Offay J.M., Mock R.E., Fulton R.W., Isolation and characterization of encephalitic bovine herpesvirus type 1 isolates from cattle in North America, Am. J. Vet. Res. 54 (1993) 534–539.

[32] Egyed L., Brocchi E., Rusvai M., Bartha A., Study of bovine herpesvirus type 1 strains with monoclonal antibodies, Acta Vet. Hung. 40 (1992) 225–230.

[33] Ek-Kommonen C., Veijalainen P., Rantala M., Neuvonen E., Neutralizing antibodies to bovine herpesvirus 1 in reindeer, Acta Vet. Scand. 23 (1982) 565–569.

[34] Ek-Kommonen C., Pelkonen S., Nettleton P.F., Isolation of a herpesvirus serologically related to bovine herpesvirus 1 from a reindeer (*Rangifer tarandus*), Acta Vet. Scand. 27 (1986) 299–301.

[35] El Azhary M.A., Roy R.S., Frechette J.L., Serological evidence of IBR and BVD infection in caribou (*Rangifer tarandus*), Vet. Rec. 105 (1979) 336.

[36] Engels M., Ackermann M., Pathogenesis of ruminant herpesvirus infections, Vet. Microbiol. 53 (1996) 3–15.

[37] Engels M., Thiry E., L'infection de la chèvre par l'herpèsvirus caprin de type 1, Point Vét. 31 (2000) 37–42.

[38] Engels M., Steck F., Wyler R., Comparison of the genomes of infectious bovine rhinotracheitis and infectious pustular vulvovaginitis virus strains by restriction endonuclease analysis, Arch. Virol. 6 (1981) 169–174.

[39] Engels M., Gelderblom H., Darai G., Ludwig H., Goat herpesviruses: biological and physicochemical properties, J. Gen. Virol. 64 (1983) 2237–2247.

[40] Engels M., Giuliani C., Wild P., Beck T.M., Loepfe E., Wyler R., The genome of bovine herpesvirus 1 (BHV-1) strains exhibiting a neuropathogenic potential compared to known BHV-1 strains by restriction site mapping and cross-hybridization, Virus Res. 6 (1986) 57–73.

[41] Engels M., Loepfe E., Wild P., Schraner E., Wyler R., The genome of caprine herpesvirus 1: genome structure and relatedness to bovine herpesvirus 1, J. Gen. Virol. 68 (1987) 2019–2023.

[42] Engels M., Palatini M., Metzler A.E., Probst U., Kihm U., Ackermann M., Interactions of bovine and caprine herpesviruses with the natural and the foreign hosts, Vet. Microbiol. 33 (1992) 69–78.

[43] Favoreel H.W., Van de Walle G.R., Nauwynck H.J., Pensaert M.B., Virus complement evasion strategies, J. Gen. Virol. 84 (2003) 1–15.

[44] Fehler F., Herrmann J.M., Saalmuller A., Mettenleiter T.C., Keil G.M., Glycoprotein IV of bovine herpesvirus 1-expressing cell line complements and rescues a conditionally lethal viral mutant, J. Virol. 66 (1992) 831–839.

[45] Friedli K., Metzler A.E., Reactivity of monoclonal antibodies to proteins of a neurotropic bovine herpesvirus 1 (BHV-1) strain and to proteins of representative BHV-1 strains, Arch. Virol. 94 (1987) 109–122.

[46] Gompels U.A., Craxton M.A., Honess R.W., Conservation of glycoprotein H (gH) in herpesviruses: nucleotide sequence of the gH gene from herpesvirus saimiri, J. Gen. Virol. 69 (1988) 2819–2829.

[47] Grewal A.S., Wells R., Vulvovaginitis of goats due to a herpesvirus, Aust. Vet. J. 63 (1986) 79–82.

[48] Griffin A.M., The nucleotide sequence of the glycoprotein gB gene of infectious laryngotracheitis virus: analysis and evolutionary relationship to the homologous gene from other herpesviruses, J. Gen. Virol. 72 (1991) 393–398.

[49] Guercio A., Greco G., Lanizzoto G., Di Marco V., Todaro M., Valutazione della diffusione di anticorpi anti Herpes Virus della capra in allevamenti caprini della Sicilia, Atti. SIPAOC 12 (1998) 138–142.

[50] Hage J.J., Vellema P., Schukken Y.H., Barkema H.W., Rijsewijk F.A., van Oirschot J.T., Wentink G.H., Sheep do not have a major role in bovine herpesvirus 1 transmission, Vet. Microbiol. 57 (1997) 41–54.

[51] Hall W.T., Simmons G.C., French E.L., Snowdon W.A., Asdell M., The pathogenesis of encephalitis caused by the infectious bovine rhinotracheitis virus, Aust. Vet. J. 42 (1966) 229–237.

[52] Horner G.W., Hunter R., Day A.M., An outbreak of vulvovaginitis in goats caused by a caprine herpesvirus, N. Z. Vet. J. 30 (1982) 152.

[53] Hubner S.O., Oliveira A.P., Franco A.C., Esteves P.A., Silva A.D., Spilki F.R., Rijsewijk F.A., Roehe P.M., Experimental infection of calves with gI, gE, US9 negative bovine herpesvirus type 5, Comp. Immunol. Microbiol. Infect. Dis. 28 (2005) 187–196.

[54] Hutchinson L., Goldsmith K., Snoddy D., Ghosh H., Graham F.L., Johnson D.C., Identification and characterization of a novel herpes simplex virus glycoprotein, gK, involved in cell fusion, J. Virol. 66 (1992) 5603–5609.

[55] Hyllseth B., Stuen S., Rimstad E., Dahle H.K., Tyler J.C., Serologiske undersokelser over herpesvirus infecksjoner hos reain fra Finnmark og Svalbard, Norsk Veterinaertidsskrift 105 (1993) 733–736.

[56] Inglis D.M., Bowie J.M., Allan M.J., Nettleton P.F., Ocular disease in red deer calves associated with a herpesvirus infection, Vet. Rec. 113 (1983) 182–183.

[57] Johnston L., Simmons G., McGavin M., A viral meningo-encephalitis in calves, Aust. Vet. J. 38 (1962) 207–215.

[58] Jones C., Herpes simplex virus type 1 and bovine herpesvirus 1 latency, Clin. Microbiol. Rev. 16 (2003) 79–95.

[59] Jordan L.T., Rettie W.J., Tessaro S.V., Evidence of herpesvirus infection in Woodland Caribou in Saskatchewan, J. Wildl. Dis. 39 (2003) 216–220.

[60] Keuser V., Thiry E., Conséquences de l'infection des cervidés par des alpha-herpèsvirus apparentés au virus de l'IBR, Point Vét. 31 (2000) 219–223.

[61] Keuser V., Gogev S., Schynts F., Thiry E., Demonstration of generalized infection with caprine herpesvirus 1 diagnosed in an aborted caprine fetus by PCR, Vet. Res. Commun. 26 (2002) 221–226.

[62] Keuser V., Schynts F., Detry B., Collard A., Robert B., Vanderplasschen A., Pastoret P.-P., Thiry E., Improved antigenic methods for differential diagnosis of bovine, caprine, and cervine alphaherpesviruses related to bovine

herpesvirus 1, J. Clin. Microbiol. 42 (2004) 1228–1235.

[63] Keuser V., Espejo-Serrano J., Schynts F., Georgin J.P., Thiry E., Isolation of caprine herpesvirus type 1 in Spain, Vet. Rec. 154 (2004) 395–399.

[64] Keuser V., Detry B., Thiry J., de Fays K., Schynts F., Pastoret P.-P., Vanderplasschen A., Thiry E., Characterization of caprine herpesvirus 1 glycoprotein D gene and its translation product, Virus Res. 115 (2006) 112–121.

[65] Konig P., Giesow K., Keil G.M., Glycoprotein M of bovine herpesvirus 1 (BHV-1) is nonessential for replication in cell culture and is involved in inhibition of bovine respiratory syncytial virus F protein induced syncytium formation in recombinant BHV-1 infected cells, Vet. Microbiol. 86 (2002) 37–49.

[66] Koppers-Lalic D., Reits E.A.J., Ressing M.E., Lipinska A.D., Abele R., Koch J., Rezende M.M., Admiraal P., van Leeuwen D., Bienkowska-Szewczyk K., Mettenleiter T.C., Rijsewijk F.A.M., Tampe R., Neefjes J., Wiertz E.J.H.J., Varicelloviruses avoid T cell recognition by UL49.5-mediated inactivation of the transporter associated with antigen processing, Proc. Natl. Acad. Sci. USA 102 (2005) 5144–5149.

[67] Koptopoulos G., Papanastasopoulou M., Papadopoulos O., Ludwig H., The epizootiology of caprine herpesvirus (BHV-6) infections in goat populations in Greece, Comp. Immunol. Microbiol. Infect. Dis. 11 (1988) 199–205.

[68] Lee B.J., Weiss M.L., Mosier D., Chowdhury S.I., Spread of bovine herpesvirus type 5 (BHV-5) in the rabbit brain after intranasal inoculation, J. Neurovirol. 5 (1999) 474–484.

[69] Lehmkuhl H.D., Cutlip R.C., Protection from parainfluenza-3 virus and persistence of infectious bovine rhinotracheitis virus in sheep vaccinated with modified live IBR-PI-3 vaccine, Can. J. Comp. Med. 49 (1985) 58–62.

[70] Lillehaug A., Vikoren T., Larsen I.L., Akerstedt J., Tharaldsen J., Handeland K., Antibodies to ruminant alpha-herpesviruses and pestiviruses in Norwegian cervids, J. Wildl. Dis. 39 (2003) 779–786.

[71] Liman A., Engels M., Meyer G., Ackermann M., Glycoprotein C of bovine herpesvirus 5 (BHV-5) confers a distinct heparin-binding phenotype to BHV-1, Arch. Virol. 145 (2000) 2047–2059.

[72] Lyaku J.R., Nettleton P.F., Mardsen H., A comparison of serological relationships among five ruminant alphaherpesviruses by ELISA, Arch. Virol. 124 (1992) 333–341.

[73] Lyaku J.R., Vilcek S., Nettleton P.F., Marsden H.S., The distinction of serologically related ruminant alphaherpesviruses by the polymerase chain reaction (PCR) and restriction endonuclease analysis, Vet. Microbiol. 48 (1996) 135–142.

[74] Martin W.B., Castrucci G., Frigeri F., Ferrari M., A serological comparison of some animal herpesviruses, Comp. Immunol. Microbiol. Infect. Dis. 13 (1990) 75–84.

[75] Mettler F., Engels M., Wild P., Bivetti A., Herpesvirus infection in kids in Switzerland, Schweiz. Arch. Tierheilkd. 121 (1979) 655–662 (in German).

[76] Metzler A.E., Schudel A.A., Engels M., Bovine herpesvirus 1: molecular and antigenic characteristics of variant viruses isolated from calves with neurological disease, Arch. Virol. 87 (1986) 205–217.

[77] Meurens F., Schynts F., Keil G.M., Muylkens B., Vanderplasschen A., Gallego P., Thiry E., Superinfection prevents recombination of the alphaherpesvirus bovine herpesvirus 1, J. Virol. 78 (2004) 3872–3879.

[78] Meurens F., Keil G.M., Muylkens B., Gogev S., Schynts F., Negro S., Wiggers L., Thiry E., Interspecific recombination between two ruminant alphaherpesviruses, bovine herpesviruses 1 and 5, J. Virol. 78 (2004) 9828–9836.

[79] Meyer G., Vilcek C., Paces V., O'Hara M.K., Pastoret P.-P., Thiry E., Schwyzer M., Sequence analysis of the bovine herpesvirus type 1 genes homologous to the DNA polymerase (UL30), the major DNA-binding protein (UL29) and the ICP 18.5 assembly protein (UL28) genes of herpes simplex virus, Arch. Virol. 142 (1997) 89–102.

[80] Meyer G., Hanon E., Georlette D., Pastoret P.-P., Thiry E., Bovine herpesvirus type 1 glycoprotein H is essential for penetration and propagation in cell culture, J. Gen. Virol. 79 (1998) 1983–1987.

[81] Meyer G., Bare O., Thiry E., Identification and characterization of bovine herpesvirus type 5 glycoprotein H gene and gene products, J. Gen. Virol. 80 (1999) 2849–2859.

[82] Meyer G., d'Offay J., Thiry E., Les encéphalites à herpèsvirus bovins, Point Vét. 31 (2000) 417–424.

[83] Meyer G., Lemaire M., Ros C., Belak K., Gabriel A., Cassart D., Coignoul F., Belak S., Thiry E., Comparative pathogenesis of acute and latent infections of calves with bovine herpesvirus types 1 and 5, Arch. Virol. 146 (2001) 633–652.

[84] Muluneh A., Liebermann H., Occurrence of caprine herpesvirus (BHV-6) infection in goat population of the GDR, Arch. Exp. Veterinarmed. 44 (1990) 254–257.

[85] Nettleton P.F., Sinclair J.A., Herring J.A., Inglis D.M., Fletcher T.J., Ross H.M., Bonniwell M.A., Prevalence of herpesvirus infection in British red deer and investigations of further disease outbreaks, Vet. Rec. 118 (1986) 267–270.

[86] Nettleton P.F., Thiry E., Reid H.W., Pastoret P.-P., Herpesvirus infections in cervidae, Rev. Sci. Tech. Off. Int. Epizoot. 7 (1988) 977–988.

[87] Nettleton P.F., Ek-Kommonen C., Tanskanen R., Reid H.W., Sinclair J.A., Herring J.A., Studies in the epidemiology and pathogenesis of alphaherpesviruses from red deer (*cervus elaphus*) and reindeer (*rangifer tarandus*), in: Reid H.W. (Ed.), The management and Health of Farmed deer, Kluwer Academic Publishers, Dordrecht, 1988, pp. 143–147.

[88] Nixon P., Edwards S., White H., Serological comparisons of antigenically related herpesviruses in cattle, red deer and goats, Vet. Res. Commun. 12 (1988) 355–362.

[89] Oldoni I., Weiblen R., Inkelmann M.A., Flores E.F., Production and characterization of monoclonal antibodies to a Brazilian bovine herpesvirus type 5, Braz. J. Med. Biol. Res. 37 (2004) 213–221.

[90] Papanastasopoulou M., Koptopoulos G., Lekkas S., Papadopoulos O., Ludwig H., An experimental study on the pathogenicity of the caprine herpesvirus type 1 (CHV-1), Comp. Immunol. Microbiol. Infect. Dis. 14 (1991) 47–53.

[91] Pastoret P.-P., Thiry E., Brochier B., Derboven G., Bovid herpesvirus 1 infection of cattle: pathogenesis, latency, consequences of latency, Ann. Rech. Vét. 13 (1982) 221–235.

[92] Perez S.E., Bretschneider G., Leunda M.R., Osorio E.A., Flores E.F., Odeon A.C., Primary infection, latency, and reactivation of bovine herpesvirus type 5 in the bovine nervous system, Vet. Pathol. 39 (2002) 437–444.

[93] Perez S.E., Vagnozzi A., Sur J.H., Odriozola E., Campero C.M., Odeon A.C., Análisis retrospectivo de casos con diagnóstico de necrosis cerebrocortical y su relación com herpesvirus bovino tipo 5, Rev. Argent. Microbiol. 35 (2003) 69–73.

[94] Pidone C.L., Galosi C.M., Echeverria M.G., Nosetto E.O., Etcheverrigaray M.E., Restriction endonuclease analysis of BHV-1 and BHV-5 strains isolated in Argentina, Zentralbl. Veterinarmed. B 46 (1999) 453–456.

[95] Pirak M., Thiry E., Brochier B., Pastoret P.-P., Infection expérimentale de la chèvre par le virus de la rhinotrachéite infectieuse bovine (Bovine herpesvirus type 1) et tentative de réactivation virale, Rec. Méd. Vét. (1983) 1103–1106.

[96] Plebani G.F., Engels M., Metzler A.E., Wyler R., Caprine herpesvirus in Switzerland: distribution, incidence and latency of infection, Schweiz. Arch. Tierheilkd. 125 (1983) 395–411 (in German).

[97] Pospisil Z., Vyvlecka R., Cihal P., Lany P., Zendulkova D., Detection of herpesvirus serum antibodies in red deer (*Cervus elaphus*) imported into the Czech Republic, Vet. Med. 41 (1996) 279–282.

[98] Pratelli A., Greco G., Dall'Ara P., Engels M., Tempesta M., Buonavoglia C., Restriction endonuclease analysis of the genome of two Italian caprine herpesvirus 1 strains, Arch. Virol. 145 (2000) 845–851.

[99] Reid H.W., Nettleton P.F., Pow I., Sinclair J.A., Experimental infection of red deer (*Cervus elaphus*) and cattle with a herpesvirus isolated from red deer, Vet. Rec. 119 (1986) 156–158.

[100] Rimstad E., Krona R., Hyllseth B., Comparison of herpesviruses isolated from reindeer, goats, and cattle by restriction endonuclease analysis, Arch. Virol. 123 (1992) 389–397.

[101] Roizman B., Knipe M.D., Herpes simplex virus and their replication, in: Knipe D.M., Howley P.M. (Eds.), Fields Virology, 4th ed., Lippincott Williams and Wilkins publishers, Philadelphia, 2001, pp. 2399–2461.

[102] Roizman B., Pellett P.E., The family Herpesviridae: A brief introduction, in: Knipe D.M., Howley P.M. (Eds.), Fields Virology, 4th ed., Lippincott Williams and Wilkins publishers, Philadelphia, 2001, pp. 2381–2398.

[103] Ronsholt L., Christensen L.S., Bitsch V., Latent herpesvirus infection in red deer: characterization of a specific deer herpesvirus including comparison of genomic restriction fragment patterns, Acta Vet. Scand. 28 (1987) 23–31.

[104] Roop C., Hutchinson L., Johnson D.C., A mutant herpes simplex virus type 1 unable to express glycoprotein L cannot enter cells, and its particles lack glycoprotein H, J. Virol. 67 (1993) 2285–2297.

[105] Roperto F., Pratelli A., Guarino G., Ambrosio V., Tempesta M., Galati P., Iovane G., Buonavoglia C., Natural caprine herpesvirus 1

(CpHV-1) infection in kids, J. Comp. Pathol. 122 (2000) 298–302.

[106] Ros C., Belak S., Studies of genetic relationships between bovine, caprine, cervine, and rangiferine alphaherpesviruses and improved molecular methods for virus detection and identification, J. Clin. Microbiol. 37 (1999) 1247–1253.

[107] Ros C., Belak S., Characterization of the glycoprotein B gene from ruminant alphaherpesviruses, Virus Genes 24 (2002) 99–105.

[108] Ros C., Riquelme M.E., Forslund K.O., Belak S., Improved detection of five closely related ruminant alphaherpesviruses by specific amplification of viral genomic sequences, J. Virol. Methods 83 (1999) 55–65.

[109] Saito J.K., Gribble D.H., Berrios P.E., Knight H.D., Mc Kercher D.G., A new herpesvirus isolate from goats: Preliminary report, Am. J. Vet. Res. 35 (1974) 847–848.

[110] Salvador S.C., Lemos R.A.A., Riet-Correa F., Osorio A.L.A.R., Meningoencefalite em bovinos causada por bovino-5 no Mato Grosso do Sul and São Paulo, Pesqui. Vet. Bras. 18 (1998) 76–83.

[111] Schudel A.A., Carrillo B.J., Wyler R., Metzler A.E., Infection of calves with antigenic variants of bovine herpesvirus 1 (BHV-1) and neurological disease, J. Vet. Med. B 33 (1986) 303–310.

[112] Schwyzer M., Ackermann M., Molecular virology of ruminant herpesviruses, Vet. Microbiol. 53 (1996) 17–29.

[113] Schynts F., McVoy M.A., Meurens F., Detry B., Epstein A.L., Thiry E., The structures of bovine herpesvirus 1 virion and concatemeric DNA: implications for cleavage and packaging of herpesvirus genomes, Virology 314 (2003) 326–335.

[114] Schynts F., Meurens F., Detry B., Vanderplasschen A., Thiry E., Rise and survival of bovine herpesvirus 1 recombinants after primary infection and reactivation from latency, J. Virol. 77 (2003) 12535–12542.

[115] Silva A.M., Weiblen R., Irigoyen L.F., Roehe P.M., Sur H.J., Osorio F.A., Flores E.F. Experimental infection of sheep with bovine herpesvirus type-5 (BHV-5): acute and latent infection, Vet. Microbiol. 66 (1999) 89–99.

[116] Six A., Banks M., Engels M., Bascunana C.R., Ackermann M., Latency and reactivation of bovine herpesvirus 1 (BHV-1) in goats and of caprine herpesvirus 1 (CapHV-1) in calves, Arch. Virol. 146 (2001) 1325–1335.

[117] Spilki F.R., Silva A.D., Hubner S., Esteves P.A., Franco A.C., Driemeier D., Roehea P.M., Partial protection induced by a BHV-1 recombinant vaccine against challenge with BHV-5, Ann. NY Acad. Sci. 1026 (2004) 247–250.

[118] St George T.D., Philpott M., Isolation of infectious bovine rhinotracheitis virus from the prepuce of water buffalo bulls in Australia, Aust. Vet. J. 48 (1972) 126.

[119] Tempesta M., Cavalli A., Voigt V., Buonavoglia D., Presenza di anticorpi per caprine herpesvirus 1 (CapHV.1) in allevamenti caprini dell'Italia meridionale, Atti. SIPAOC 11 (1994) 121–122.

[120] Tempesta M., Buonavoglia D., Sagazio P., Pratelli A., Buonavoglia C., Natural reactivation of caprine herpesvirus 1 in latently infected goats, Vet. Rec. 143 (1998) 200.

[121] Tempesta M., Pratelli A., Corrente M., Buonavoglia C., A preliminary study on the pathogenicity of a strain of caprine herpesvirus-1, Comp. Immunol. Microbiol. Infect. Dis. 22 (1999) 137–143.

[122] Tempesta M., Pratelli A., Greco G., Martella V., Buonavoglia C., Detection of caprine herpesvirus 1 in sacral ganglia of latently infected goats by PCR, J. Clin. Microbiol. 37 (1999) 1598–1599.

[123] Tempesta M., Pratelli A., Normanno G., Camero M., Buonavoglia D., Greco G., Buonavoglia C., Experimental intravaginal infection of goats with caprine herpesvirus 1, J. Vet. Med. B Infect. Dis. Vet. Public Health 47 (2000) 197–201.

[124] Tempesta M., Camero M., Greco G., Pratelli A., Martella V., Buonavoglia C., A classical inactivated vaccine induces protection against caprine herpesvirus 1 infection in goats, Vaccine 19 (2001) 3860–3864.

[125] Tempesta M., Greco G., Pratelli A., Buonavoglia D., Camero M., Martella V., Buonavoglia C., Reactivation of caprine herpesvirus 1 in experimentally infected goats, Vet. Rec. 150 (2002) 116–117.

[126] Tempesta M., Camero M., Sciorsci R.L., Greco G., Minoia R., Martella V., Pratelli A., Buonavoglia C., Experimental infection of goats at different stages of pregnancy with caprine herpesvirus 1, Comp. Immunol. Microbiol. Infect. Dis. 27 (2004) 25–32.

[127] Thiry E., Lemaire M., Infection de ruminants par des herpèsvirus hétérologues, Point Vét. 207 (2001) 20–25.

[128] Thiry E., Vercouter M., Dubuisson J., Barrat J., Sepulchre C., Gerardy C., Meersschaert C., Collin B., Blancou J., Pastoret P.-P., Serological survey of herpesvirus infections in wild ruminants of France and Belgium, J. Wildl. Dis. 24 (1988) 268–273.

[129] Thiry E., Lemaire M., Schynts F., Meyer G., Dispas M., Gogev S., Les conséquences de l'infection des bovins par le virus de la rhinotrachéite infectieuse bovine, Point Vét. 199 (1999) 279–285.

[130] Thiry E., Meurens F., Muylkens B., McVoy M., Gogev S., Thiry J., Vanderplasschen A., Epstein A., Keil G., Schynts F., Recombination in alphaherpesviruses, Rev. Med. Virol. 15 (2005) 89–103.

[131] Thiry E., Muylkens B., Meurens F., Gogev S., Thiry J., Vanderplasschen A., Schynts F., Recombination in the alphaherpesvirus bovine herpesvirus 1, Vet. Microbiol. (2005) in press.

[132] Thiry J., Tempesta M., Camero M., Tarsitano E., Bellacicco A.L., Thiry E., Buonavoglia C., A live attenuated glycoprotein E negative bovine herpesvirus 1 vaccine induces a partial cross-protection against caprine herpesvirus 1 infection in goats, Vet. Microbiol. (2005) in press.

[133] Tikoo S.K., Campos M., Babiuk L.A., Bovine herpesvirus 1 (BHV-1): biology, pathogenesis, and control, Adv. Virus. Res. 45 (1995) 191–223.

[134] Tisdall D.J., Rowe S.M., Isolation and characterisation of cervine herpesvirus-1 from red deer semen, N. Z. Vet. J. 64 (2001) 111–114.

[135] Tolari F., White H., Nixon P., Isolation and reactivation of bovid herpesvirus 1 in goats, Microbiologica 13 (1990) 67–71.

[136] Uzal F.A., Woods L., Stillian M., Nordhausen R., Read D.H., Van Kampen H., Odani J., Hietala S., Hurley E.J., Vickers M.L., Gard S.M., Abortion and ulcerative posthitis associated with caprine herpesvirus-1 infection in goats in California, J. Vet. Diagn. Invest. 16 (2004) 478–484.

[137] Vanderplasschen A., Bublot M., Pastoret P.-P., Thiry E., Restriction maps of the DNA of cervid herpesvirus 1 and cervid herpesvirus 2, two viruses related to bovine herpesvirus 1, Arch. Virol. 128 (1993) 379–388.

[138] Vogel F.S., Caron L., Flores E.F., Weiblen R., Winkelmann E.R., Mayer S.V., Bastos R.G., Distribution of bovine herpesvirus type 5 DNA in the central nervous systems of latently, experimentally infected calves, J. Clin. Microbiol. 41 (2003) 4512–4520.

[139] Vossen M.T., Westerhout E.M., Soderberg-Naucler C., Wiertz E.J., Viral immune evasion: a masterpiece of evolution, Immunogenetics 54 (2002) 527–542.

[140] Wafula J.S., Mushi E.Z., Wamwayi H., Reaction of goats to infection with infectious bovine rhinotracheitis virus, Res. Vet. Sci. 39 (1985) 84–86.

[141] Waldvogel A., Engels M., Wild P., Stunzi H., Wyler R., Caprine herpesvirus infection in Switzerland: some aspects of its pathogenicity, Zentralbl. Veterinarmed. B 28 (1981) 612–623.

[142] Weiblen R., de Barros C.S., Canabarro T.F., Flores I.E., Bovine meningoencephalitis from IBR virus, Vet. Rec. 24 (1989) 666–667.

[143] Wellenberg G.J., Mars M.H., van Oirschot J.T., Antibodies against bovine herpesvirus (BHV) 5 may be differentiated from antibodies against BHV1 in a BHV1 glycoprotein E blocking ELISA, Vet. Microbiol. 78 (2001) 79–84.

[144] Whetstone C.A., Evermann J.F., Characterization of bovine herpesviruses isolated from six sheep and four goats by restriction endonuclease analysis and radioimmunoprecipitation, Am. J. Vet. Res. 49 (1988) 781–785.

[145] Williams N.M., Vickers M.L., Tramontin R.R., Petrites-Murphy M.B., Allen G.P., Multiple abortions associated with caprine herpesvirus infection in a goat herd, J. Am. Vet. Med. Assoc. 211 (1997) 89–91.