Epidemiology, disease and control of infections in ruminants by herpesviruses – An overview

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ABSTRACT
There are at least 16 recognised herpesviruses that naturally infect cattle, sheep, goats and various species of deer and antelopes. Six of the viruses are recognised as distinct alphaherpesviruses and 9 as gammaherpesviruses. Buffalo herpesvirus (BiHV) and ovine herpesvirus-1 (OvHV-1) remain officially unclassified. The prevalence of ruminant herpesviruses varies from worldwide to geographically restricted in distribution. Viruses in both subfamilies Alphaherpesvirinae and Gammaherpesvirinae cause mild to moderate and severe disease in respective natural or secondary ruminant hosts. Accordingly, the economic and ecological impact of the viruses is also variable. The molecular characteristics of some members have been investigated in detail. This has led to the identification of virulence-associated genes and construction of deletion mutants and recombinant viruses. Some of the latter have been developed as commercial vaccines. This paper aims to give an overview of the epidemiology and pathogenesis of infection by these viruses, immuno-prophylaxis and mechanisms of recovery from infection. Since there are 128 ruminant species in the family Bovidae, it is likely that some herpesviruses remain undiscovered. We conclude that currently known ruminant herpesviruses occur only in their natural hosts and do not cross stably into other ruminant species. By contrast, gammaherpesviruses have a much broader host range as evidenced by the fact that antibodies reactive to alcelaphine herpesvirus type 1 have been detected in 4 subfamilies in the family Bovidae, namely Alcelaphinae, Hippotraginae, Ovibovinae and Caprinae. New gammaherpesviruses within these subfamilies are likely to be discovered in the future.

Key words: disease and immunoprophylaxis, epidemiology, herpesviruses, pathogenesis, ruminant.


INTRODUCTION
This paper gives an overview of the biology of infections by currently recognised ruminant herpesviruses. There are 128 ruminant species in the family Bovidae. The family Bovidae contains 3 subfamilies, the Alpha-, Beta- and Gamma-herpesvirinae based on their biological characteristics. Alphaherpesviruses are characterised by rapid, lytic growth cycles; they primarily establish latency in neurons of sensory ganglia and have a variable but broad host range. Betaherpesviruses are slow-growing, cause enlargement of infected cells (cytomegaly), have a restricted host range and establish latency in lymphoid cells. Gammaherpesviruses may be oncogenic, are slow-growing and have specificity for either T or B lymphocytes and establish latency in lymphoid cells. There are at least 16 recognised herpesviruses affecting ruminants. Of the 16 recognised viruses, 6 belong to the subfamily Alphaherpesvirinae and 8 to the subfamily Gammaherpesvirinae while buffalo herpesvirus (BiHV) and ovine herpesvirus type 1 (OvHV-1) remain officially unclassified. These unclassified viruses do not appear to be important pathogens and will not be considered further as little published information is available for them. It should be emphasised that BiHV is antigenically related to bovine herpesvirus-1 (BHV-1) but the viruses have distinct restriction endonuclease DNA fingerprints. The recognised ruminant alphaherpesviruses are BHV-1, BHV-2, BHV-5, caprine herpesvirus-1 (CapHV-1), cervine herpesvirus-1 (CerHV-1), and CerHV-2.

The currently known gammaherpesviruses comprise 8 malignant catarrhal fever (MCF)-related viruses and BHV-4. The MCF-related virus group comprises 4 viruses known as alcelaphine herpesvirus-1 (AlHV-1), -2 (AlHV-2), hippotragine herpesvirus-1 (HipHV-1), ovine herpesvirus-2 (OvHV-2) and 4 recently identified viruses. These newly discovered lymphotropic viruses have been provisionally named caprine herpesvirus-2 (CapHV-2), cervine herpesvirus-3 (CerHV-3), bovine lymphotropic herpesvirus (BLHV) and caprine lymphotropic herpesvirus (CapLHV). These viruses cause either no illness, mild to moderate or fatal disease in spite of sharing some common pathogenetic mechanisms (see below). Accordingly, the economic impact of infection in the respective natural hosts by these viruses also varies. This paper will concentrate on diseases, epidemiology, and latency of these viruses and available immunoprophylaxis in natural hosts. There are more than likely herpesviruses, particularly in wild ruminants, that remain undiscovered since systematic surveys and monitoring of wild ruminants is costly and difficult to conduct.

RUMINANT HERPESVIRUSES – DISEASE AND EPIDEMIOLOGY
Alphaherpesviruses
Infection by alphaherpesviruses mostly occurs through the respiratory tract via virus aerosol, while infection of genital tract surfaces usually occurs after viraemia resulting from the respiratory tract infection. At both these sites virus replicates in epithelial cells. The released progeny virus infects fresh epithelial cells. This results in viraemia. The process continues for several days until immune intervention. Infected cells are usually destroyed. This damages the mucous and results in inflammation.

Bovine herpesvirus-1 (BHV-1), commonly known as infectious bovine rhinotracheitis virus (IBR), is arguably the most important respiratory tract disease of cattle globally. IBR due to BHV-1 infection is an important cause of economic losses to the cattle industry worldwide. BHV-1 causes IBR, infectious pustular vulvovaginitis (IPV) and infectious balanoposthitis (IPB) and infrequently other diseases in cattle. The progeny virus shed by epithelial cells can also invade local neurons whose endings are...
embedded in the mucosae. Brain invasion is not a common consequence of BHV-1 infection\(^9\). There are conflicting reports as to whether the respiratory and the genital isolates of BHV-1 can be distinguished by restriction endonuclease DNA fingerprints\(^7\). These authors did not find obvious differences between the respiratory and the genital BHV-1 isolates. Besides cattle, BHV-1 also naturally infects sheep, goats\(^4\), and pigs and a number of wild ruminants\(^2,10\). There is scanty published data on the prevalence, incidence and economic impact of BHV-1 infection of these other species. There is evidence of antibody to BHV-1 in sera from 20 species of free-living African ruminants, Australian water buffaloes (Bubalus bubalis) and American prong horn antelope (Antillocapra americana) but the antibody could be due to related ruminant alphaherpesviruses\(^8\). In cattle the main route of transmission is by virus aerosol\(^3,9\). This route is also likely to be the main mode of virus transmission in deer\(^5\). Experimentally, BHV-1 is transmissible to goats by intranasal inoculation and although infected goats shed virus in nasal mucus for 3–10 days they remained clinically normal\(^6\). BHV-1 is also transmissible to mule deer\(^9\).

Bovine herpesvirus-2 (BHV-2) mammillitis is not a common disease in temperate countries but the incidence is high in cattle in the tropics\(^8\). BHV-2 in the tropics or warmer countries is associated with a generalised skin disease known as pseudo-lumpy skin disease. Furthermore antibody to BHV-2 has been detected in 17 species of African wild ruminants\(^8\). BHV-2 causes mammillitis in heifers and young cows\(^8\). BHV-2 infection produces widespread erosive skin lesions on teats and udders. Erosion and ulceration leads to the formation of scabbed pustules. Similar lesions in the buccal mucosa may occur in suckling calves. Unlike other alphaherpesviruses, BHV-2 transmission occurs mechanically by milking machines and dairy personnel\(^8\).

Geographically, fatal encephalitis in calves due to bovine herpesvirus-5 (BHV-5) is restricted to Australia\(^9\), Argentina and United States of America (USA) and sporadically in other countries\(^8\). BHV-5 encephalitis is a sporadic and uncommon disease of cattle\(^5\). Encephalitis usually occurs without other clinical signs\(^8\). Similar to the closely related BHV-1 the main mode of BHV-5 transmission is via the aerosol route. The incidence of BHV-5 induced disease and the associated economic loss in countries where the virus is most prevalent is poorly documented. However, unlike BHV-1, upper respiratory tract infection by the closely related BHV-5 can lead to brain invasion via the trigeminal pathway even though BHV-1 and BHV-5 have similar growth profiles (extent and duration) in the nasopharynx of calves\(^8\). The inflammatory responses in the upper respiratory tract due to BHV-1 and BHV-5 are also different in infected calves. Thus, in BHV-5 infection of calves, unlike that of BHV-1 infection, pyrexia and nasal discharge are not commonly observed\(^5\).

Natural caprine herpesvirus-1 (CapHV-1) infections have only been recognised in goats\(^5,7\). CapHV-1 was isolated from goat kids (Capra hircus)\(^9\) and the virus is distributed worldwide\(^10\). Cattle and sheep are susceptible to experimental infection by CapHV-1\(^11,12\). In adult goats most CapHV-1 infections are subclinical. Abortions due to CapHV-1 have been recorded after experimental intranasal or intravenous infection of pregnant does\(^13\). Natural or experimental infection of neonatal kids with CapHV-1 is often fatal\(^5,14\). Ten-to-16-day-old Boer goat kids died showing depression, abdominal pain, anorexia, nasal and ocular discharge, ulceration of the nasal septum, erosions in the nasal cavity and diarrhoea\(^15\). In natural fatal cases in kids ulcerative and necrotic lesions were found in the ileum, colon and caecum while experimentally these lesions were seen in the caecum and colon\(^9\). CapHV-1 is non-pathogenic for bovine cows\(^16\) and nonpathogenic\(^5\) or mildly pathogenic\(^5\) for lambs. However, information on the prevalence and epidemiology of CapHV-1 is limited\(^5,17\). Since goats can be infected by both the intranasal and the intravaginal routes and virus from the respiratory infection can spread to the genital site, the mode of CapHV-1 transmission is likely to be via the oronasal route\(^9,18\). Experimentally, CapHV-1 causes an IBR-like disease in goats with shorter (1–6 days) periods of viral shedding compared to the 1–12 days of shedding in nasal mucus of calves infected by BHV-1 or BHV-5\(^19,20\). Importantly, the economic impact of CapHV-1 infection in goat rearing areas remains unreported but there could be considerable loss of goat kids due to CapHV-1 infection\(^5\).

Cervine herpesvirus-1 (CerHV-1) is widespread in free-living and farmed red deer (Cervus elaphus)\(^5\). It was isolated from an outbreak of ocular disease primarily involving conjunctival mucopurulent discharge and supraorbital oedema\(^5\). CerHV-1 can also cause respiratory disease, notably ulcerative erosions of the nares and muzzle, fever, mucopurulent nasal discharge and conjunctivitis. Infected deer shed virus in eye and nasal secretions\(^8\). Experimentally, CerHV-1 was not transmissible to bovine calves by means of intranasal inoculation\(^21\).

The prevalence of rangeferine herpesvirus-1 (CerHV-2) is poorly documented and the virus is not associated with an overt clinical disease in reindeer, the natural host\(^22\). However, experimentally CerHV-2 does cause mild rhinitis in bovine calves accompanied by viral shedding for 6–9 days\(^23\).

A key mechanism in the disease process caused by some alphaherpesviruses in ruminants is progeny virus viraemia initiated from the site of primary mucosal replication (usually upper respiratory tract mucus) to secondary sites within the body of the infected host. In general the systemic spread is by means of lymphocytes\(^24\). It should, however, be pointed out that the level of viraemia is low since experimentally it could barely be detected even in cases of BHV-1 and BHV-5 infections of calves where there is a significant (8–9 log\(_{10}\)) median tissue culture infective dose (TCID\(_{50}\)) infective per mill nasal swab) virus shedding by almost all infected calves. Systemic disease has been recorded in the case of BHV-1, BHV-2, BHV-5, CapHV-1, and CerHV-1 albeit with varying incidence rates and severity.

Gammaherpesviruses

Gammaherpesviruses have a tropism for either T or B lymphocytes\(^25\). A feature of gammaherpesvirus infection is the induction of lymphoproliferation which may manifest itself as infectious mononucelosis, splenomegaly, or malignant catarrhal fever (MCF). In free-ranging animals, MCF is a fatal disease of cattle, deer, bison (Bison bison) and moose (Alces alces). Many other ruminant species become susceptible when in captivity. The presence of antibodies that react with ALHV-1 has consistently been detected in species belonging to 4 subfamilies of the family Bovidae although there is no evidence that any of them naturally spread to susceptible species and cause MCF. In natural hosts, MCF viruses are endogenous without causing disease but often cause disease in other secondary ruminant hosts\(^26,27\). The characteristic pathology in MCF is a widespread lymphoid cell proliferation and cell necrosis in which the pathognomonic lesions are widespread arteritis characterised by segmental fibrinoid necrosis\(^28,29\). MCF is caused by several different gammaherpesviruses, namely ALHV-1, OvHV-2, CaHV-2 and MCF virus of white tailed deer. In Africa, MCF is mainly caused by the wildebeest-associated ALHV-1 while outside Africa ovine herpesvirus-2 (OvHV-2) is the main cause of sheep-associated
MCF	extsuperscript{10,12,20}. OvHV-2 is also present in Africa. AlHV-1 grows in tissue culture	extsuperscript{15} thus allowing virus isolation and virus antibody tests required for virus epidemiology and pathogenetic studies. By contrast, OvHV-2 is at present not culturable in tissue culture and hence studies of OvHV-2 have relied on tests using virus specific DNA probes	extsuperscript{12,15} and recently a new monoclonal antibody based ELISA test	extsuperscript{12,20}.

In Africa, AlHV-1 is carried by blue and black wildebeest (Connochaetes taurinus and Connochaetes gnou) in which it is innocuous and is shed in nasal mucus	extsuperscript{20}. In cattle, sporadic but fatal cases occur at the time of wildebeest calving, the route of virus transmission being virus containing aerosol from shedding wildebeest. Wildebeest have been the source of AlHV-1 transmission to deer and many other antelope species in zoos	extsuperscript{20,32,33}. OvHV-1-induced fatal MCF was reported in sika deer (Cervus nippon)	extsuperscript{34}, barasingha deer (Cervus duvaucelli)	extsuperscript{35}, Père David’s deer (Elaphurus davidianus)	extsuperscript{36}, reindeer	extsuperscript{37}, and white-tailed deer (Odocoileus virginianus)	extsuperscript{31,32,36}.

Sheep older than 6 months are the healthy carriers of OvHV-2	extsuperscript{2}, and are the source of OvHV-2 transmission to dead-end, secondary ruminant hosts worldwide wherever sheep are in contact with them	extsuperscript{20,32,33}. Goats are also a source of transmission of OvHV-2	extsuperscript{24,48,72}. Fatal cases of sheep-associated OvHV-2 MCF have been recorded in cattle and deer species (see below). Recent data	extsuperscript{39} show that OvHV-2 is not invariably fatal in cattle. OvHV-2 is reported to cause disease in pigs	extsuperscript{40}. The mode of OvHV-2 transmission between sheep is via nasal secretions and the highest amounts of OvHV-2 DNA were detected in nasal secretions of sheep	extsuperscript{41}, which could also be indicative of oronasal transmission to cattle, deer and other susceptible species. This has been directly demonstrated by intranasal inoculation of cattle (Bos taurus) and American bison (Bison bison) with sheep nasal secretions containing OvHV-2 DNA. Inoculated cattle and bison developed clinical MCF	extsuperscript{42}. Experimental intranasal OvHV-2 transmission to sheep was also demonstrated using nasal secretions from infected sheep	extsuperscript{42}. Losses in cattle are sporadic but those in deer are extensive. Unlike the situation in cattle, transmission from farmed red deer to other deer and rabbits has proved relatively easy	extsuperscript{43,44}. The deer species susceptible to OvHV-2 are: farmed red deer	extsuperscript{45,46}, rusa deer (Cervus timorensis)	extsuperscript{47}, axis deer (Axis axis)	extsuperscript{48}, mule deer	extsuperscript{49} and Père David’s deer	extsuperscript{40}.

In cattle, OvHV-2-induced MCF occurs mainly over several weeks following inoculation but was not tested in cattle	extsuperscript{40}. The natural host of AlHV-2 is the red hartebeest (Alcelaphus buselaphus)	extsuperscript{44}. Experimentally AIHV-2 is transmissible to cattle and other ruminant species but produces a mild form of MCF	extsuperscript{16}.

In addition to the known MCF-causing viruses namely AlHV-1, OvHV-2, CapHV-2, and MCF virus of white tailed deer	extsuperscript{16} described above, 4 new novel gammaherpesviruses related to AlHV-1 and OvHV-2 were discovered recently. The new viruses are BLHV	extsuperscript{19}, CerHV-3	extsuperscript{20}, CapHV-3	extsuperscript{32} and CapLVH	extsuperscript{45}. Discovery of novel MCF viruses has depended on targeting viral DNA polymerase gene with specific sequences for the PCR-based detection of new herpesviruses	extsuperscript{35}. CerHV-3 causes classical MCF in white-tailed deer (Odocoileus virginianus)	extsuperscript{35} while CapHV-2 which is carried by goats, causes chronic dermatitis and weight loss in sika deer (Cervus nippon)	extsuperscript{14}, but how common these diseases are is unknown. For BLHV and CapLHV we are unable to find published literature for disease incidence and prevalence and also if other ruminant species are affected or not. This related group of gammaherpesviruses also includes HipHV-1	extsuperscript{17}.

The pathogenesis of fatal MCF due to AlHV-1 and OvHV-2 in secondary ruminant hosts is suggested to arise from infection of a specific subset of lymphocytes which undergoes uncontrolled interleukin driven hyperplasia, mainly of CD8 cells	extsuperscript{16} and consequent widespread autoimmune destruction of tissues. It was suggested that AlHV-1, OvHV-2, HipHV-1 interfere with the immune system in a subtly different way	extsuperscript{46}. In AlHV-1-induced MCF, there is deposition of immune complexes in lesions	extsuperscript{50}. Consistent with the T-lymphocyte hyperplasia hypothesis, the fact that every little virus antigen expression is detected in lesions of AlHV-1-induced MCF. Thus, approximately 1 cell in 100 000 was positive for AlHV-1 antigen	extsuperscript{50} or DNA	extsuperscript{16}.

Bovine herpesvirus-4 (BHV-4) is a ubiquitous virus of cattle. Based on restriction enzyme cleavage pattern analysis of virus genomic DNA, BHV-4 isolates have been classified as American and European strains. However, BHV-4 isolates do not always comply with this geographical classification	extsuperscript{9}. The mode of virus transmission in cattle and possibly other hosts such as American bison (Bison bison), water buffaloes (Bubalus bubalis) and African buffaloes (Syncerus caffer) is likely to be via the respiratory route since the virus is shed in nasal and ocular secretions	extsuperscript{61}. BHV-4 infection in cattle is not associated with a significant disease and its economic impact is therefore not clear. Epidemiologically, the significance of the virus either alone or in association with other cattle viruses is difficult to assess despite considerable knowledge of BHV-4 molecular virology	extsuperscript{5,35,60}.

**ANTIGENIC AND GENETIC RELATEDNESS**

**Alphaherpesviruses**

Some glycoproteins of BHV-1, BHV-5, CapHV-1, CerHV-1 and CapHV-2 share common epitopes and these viruses cross-react in several serological tests including also the most virus specific test namely the virus neutralisation (VN) test	extsuperscript{10,28,60}. Limited data also confirm the serological findings of cross relationships at the level of genomic relatedness to a varying degree	extsuperscript{16}. There is indeed shared homology of the genomic sequences and structure among these viruses but the data are limited to allow conclusions about their evolution and genetic changes in adaptation to their respective natural hosts	extsuperscript{10,28,60}. Although most of the ruminant alphaherpesviruses share antigenic and genetic components there are differences between them. The genomic DNA of CerHV-1 and CerHV-2 are distinct from each other and also from the BHV-1 genome	extsuperscript{10}. It also applies to CapHV-1 and BHV-4	extsuperscript{16,60}. However, the closest antigenic and genetic similarity is between BHV-5 and BHV-1 and yet they vary markedly in the diseases they cause. The former can cause a fatal brain infection while the latter is an acute febrile respiratory disease	extsuperscript{20,16}.

**Gammaherpesviruses**

Recent studies suggested that ruminant MCF viruses should be defined by the presence of the 15-A antigen epitope and base sequence similarity of conserved regions of viral DNA polymerase gene	extsuperscript{21,43}. The 15-A antigen epitope is present on all known MCF viruses	extsuperscript{29,45}. An ELISA kit for serological detection of MCF using a monoclonal antibody to the 15-A MCF epitope is available	extsuperscript{14}. Prior to these
recent tests and probes, relatedness of MCF viruses was established by serological tests using polyclonal antisera from hyperimmunised and/or infected animals.\textsuperscript{56,57,58}

We should, however, point out that not all of these viruses have been shown to induce MCF.

The ubiquitous BHV-4, despite considerable investigation of its genome and the protein makeup\textsuperscript{93,94} remains the least understood with respect to its relationship with other ruminant gammaherpesviruses. BHV-4 has a genomic structure and arrangement closely resembling herpesvirus saimiri and the prototype virus of the subfamily Gammaherpesvirinae namely Epstein Barr virus.\textsuperscript{93,94} Epidemiologically the significance of the virus either alone or in association with other cattle viruses is not clear despite much work.

**LATENCY AND VIRULENCE MODULATING GENES**

**Latency**

All herpesviruses are able to establish latent infections. A requirement for an effective latent infection is that the cell harboring the virus is long-lived and is not destroyed either through apoptosis or immune elimination. Long living, non-dividing, terminally differentiated cells such as neurons and lymphocytes fulfill this requirement. Whilst the mechanisms central to the establishment and maintenance of a state of latency remain yet to be fully defined, it is clear that latently infected cells are not eliminated by the host’s immune responses. Mechanisms triggering reactivation have also not been identified.\textsuperscript{95} However, dysfunction of the cellular immune system and/or immunosuppression appears to be involved in this process.\textsuperscript{96} The site of latency by most analysed alphaherpesviruses is primarily in neurons of the sensory ganglia close to the primary site of virus infection and replication. For some gammaherpesviruses notably AHV-1 and OvHV-2, lymphocytes are probably the site of latent infection in carrier hosts. Virus reactivated from such cells after productive virus replication, usually in the mucosa of the respiratory tract, is considered the source for transmission to other susceptible hosts both natural and unnatural. Reactivation of HipHV-1 in explanted diced fragments of submandibular lymph node from an African roan antelope (Hippotragus equinus) was suggested as the mechanism of productive virus growth and CPE in these cultures which eventually produced a cell monolayer.\textsuperscript{17} However, the molecular events leading to reactivation and those of transport of reactivated infectious progeny virus back to the portal of entry at the primary infection site from where virus is shed and transmitted to susceptible hosts are undefined. Thus, latency represents a long-term reservoir in an otherwise immune host. In this case of BHV-1 reactivation, infectious virus is transported intra-axomally back to the original portal of virus entry where virus replicates and is shed and may thus be transmitted.\textsuperscript{18}

**Vireulence modulating genes**

For alphaherpesviruses, mutations of some non-essential and essential genes were found to modulate virulence of the virus for the natural host. Deletion of several non-essential genes has led to decreased virulence of the mutated virus for the natural host. Notable examples are genes encoding glycoproteins (g) C, E, I, and M\textsuperscript{18,27,40}, and virus-encoded enzymes such as thymidine kinase.\textsuperscript{95} The vireulence-associated genes of gammaherpesviruses currently remain uninvestigated.

**IMMUNOPROPHYLAXIS**

**Alphaherpesviruses**

With respect to control of disease and economic loss due to infection by ruminant alphaherpesviruses, the major effort has been against BHV-1. The first live, attenuated BHV-1 vaccine was developed soon after the first report of BHV-1 isolation.\textsuperscript{93,94} Scores of BHV-1 vaccines have been developed commercially and new products are still being offered to the market place.\textsuperscript{85,86} Single and/or combined BHV-1 vaccines are available as both live and killed formulations. Subunit gD or gC and marker gE deletion (gE) mutant virus vaccines have also been produced.\textsuperscript{85,86,99} The reader should be made aware that none of the currently available BHV-1 vaccines completely prevents viral shedding and respiratory disease due to BHV-1 challenge.\textsuperscript{56,57,96} Normally, natural BHV-1 outbreaks of combined respiratory and genital diseases are rare.\textsuperscript{31,32} In spite of the fact that the respiratory BHV-1 isolates can produce genital disease and conversely, the genital isolates typically produce respiratory disease,\textsuperscript{11,12} the efficacy of BHV-1 vaccines has largely been assessed against the respiratory disease.\textsuperscript{56,57,96} With respect to vaccine efficacy, live BHV-1 vaccines are superior under some circumstances.\textsuperscript{96} This is with respect to quicker onset of immunity and therefore live vaccines are more suitable for use in the face of an outbreak compared to killed BHV-1 vaccines.\textsuperscript{56,57,96} Secondly, live BHV-1 vaccines afford better protection to unweaned passively immune calves.\textsuperscript{61,62}

Interestingly, a BHV-1 vaccine cross-protected bovine calves against BHV-5 meningio-encephalitis.\textsuperscript{100} This was, however, not the case in a recent controlled efficacy study with an experimental, live gE BHV-1 vaccine.\textsuperscript{31} Despite these contradictory findings, BHV-1 vaccines are in use in Latin America to immunise cattle against BHV-5 infection. Notwithstanding antigenic cross-reactivity between BHV-1 and CerHV-1 the prospect of protecting farmed red deer against CerHV-1 ocular disease\textsuperscript{96} with BHV-1 vaccines needs to be experimentally demonstrated.

There are few examples of vaccines for other ruminant alphaherpesviruses. A live non-attenuated tissue culture grown BHV-2 vaccine has been used on farm premises where BHV-2 mammillitis is a persistent problem.\textsuperscript{99} An experimental killed CapHV-1 vaccine, containing Montanide ISA 740 adjuvant, after 2 subcutaneous injections was found to protect goats against vaginal lesions and vaginal virus shedding after intravaginal challenge.\textsuperscript{95} It was, however, not determined if the vaccine protected goat kids from fatal disease.

**Gammaherpesviruses**

To our knowledge, there is no immunoprophylaxis currently offered against ruminant gammaherpesviruses. A vaccine to prevent fatal MCF in cattle and deer due to AHV-1, OvHV-2 and some of the new MCF-causing viruses would be a major step forward.

**RECOVERY FROM INFECTION**

**Alphaherpesviruses**

BHV-1 infection in cattle is the most studied in this respect. Aspects of the immune response investigated comprise: (i) those following primary infection, (ii) re-infection (secondary infection), (iii) latent virus reactivation and after vaccinations with different (live, killed, subunit and DNA plasmids of virus glycoproteins and respective genes) BHV-1 vaccines.\textsuperscript{96} BHV-1 infection normally induces a balanced Th2 (antibody) and Th1 (cellular) immunity. The latter is the key response in recovery from primary infection, while the former and particularly VN antibody has a role in limiting virus spread and generalisation within the infected host during secondary infection. The role of the many BHV-1 proteins in conferring immunity and aiding in recovery from an ongoing infection remains to be elucidated. It is, however, known that the major BHV-1 glycoproteins (gB, gC and
gD) are important in stimulating protective antibody and cellular antiviral activities. BHV-1 gC and to a lesser degree gB and gD are involved in virus attachment to cell receptor(s) and also have VN antibody epitopes. Neutralised virus is prevented from attaching to and hence gaining entry into the cell. Therefore virus replication is blocked. BHV-1 VN antibody is significantly effective in reducing virus replication in vivo. This was experimentally demonstrated in BHV-1 naïve bovine calves that were inoculated intramuscularly with BHV-1 VN antibody globulin fractionated from serum pooled from 3 hyperimmunised calves. This protective effect was also seen in calves with maternally derived antibody (MDA). In secondary infection (re-infection or latent virus reactivation) and in revaccinated cattle BHV-1 antibody neutralises extracellular virus and also virus inside damaged cells and thus restricts virus spread. BHV-1 antibody also has a pivotal role in binding to virus glycoproteins on surfaces of infected cells which are lysed by polymorphonuclear neutrophils (PMNs), macrophages and NK cells via antibody-dependent cell cytotoxicity (ADCC). Both interferon and complement also enhance the ability of PMNs to lyse virus infected cells by ADCC. In addition to antibody, cellular immunity also plays an important role in recovery from secondary BHV-1 infection. There is limited or no published data on protective immune responses by other ruminant herpesviruses in their respective natural hosts. Notwithstanding this limitation, it is reasonable to conclude that some of the above described mechanisms for BHV-1 are likely to be involved in controlling infections by related viruses such as BHV-5, CerHV-1, CapHV-1 and CerHV-2.

Gammaherpesviruses

The immunology of the T-lymphotropic gammaherpesviruses AlHV-1 and OvHV-2 is of particular interest since they are asymptomatic in their natural carrier host while causing a fatal disease in susceptible hosts. AlHV-1 in wildebeest, the natural reservoir host, induces VN antibody but AlHV-1 infected cattle produce poor or no VN antibody. The relevance of these observations is not clear. There is also an antibody response against HpiHV-1 in its natural host, the roan antelope. It should be stated that AlHV-1 infected cattle do produce other AlHV-1 specific antibodies. In fatally affected hosts, AlHV1 and OvHV-2 interfere with the homeostasis of cell-mediated immunity (CMI). More specifically, a hypothesis suggests that the hyperplasia in affected animals is mainly due to CD8+ lymphocytes in response to excessive IL-2 production resulting from deregulation of natural killer (NK) cells and the IL-2 activity. The NK cell dysfunction progressively increases as the infection generalises. The end result of the CMI system dysfunction is a widespread destruction of normal tissues. This antibody is also involved in this destructive process is indicated by the formation of immune complexes in the terminal disease in cattle. Cattle infected with BHV-4 produce circulating antibodies but they are poorly neutralising. No information is available on CMI induced by BHV-4.

CONCLUSION

In conclusion, much effort has been devoted to the study of BHV-1 biology at all levels and our knowledge of the virus is fast catching up with our understanding of herpes simplex virus, the archetype for the Alphaherpesvirinae. There are 128 ruminant species in the family Bovidae and therefore it is likely that some herpesviruses, particularly those in wild ruminants, remain undiscovered. Currently 6 known alphaherpesviruses occur only in their natural hosts and do not cross stably into other ruminant species. By contrast, 9 ruminant gammaherpesviruses appear to have a much broader host range which is probably, along with their biology, not fully unravelled at present. The MCF-causing viruses can cause disease under natural conditions in cattle, pigs, domesticated buffaloes, free-ranging deer and moose. In captivity, many different antelope species, African buffaloes and bison are developing antelopine gammaherpesviruses. Gammaherpesviruses are innocuous in their natural hosts but have the potential to cause serious diseases in secondary ruminant hosts.

However, a disproportionately smaller effort has been made to understanding immune-pathological mechanisms causing MCF in cattle and deer following infection by AlHV-1 and OvHV-2. This is surprising since a well characterised animal model namely the rabbit exists for MCF caused by both AlHV-1 and OvHV-2. An interesting question is whether the MCF-causing viruses are evolving, which is very likely. Such findings may also aid our understanding of human lymphoproliferative disorders due to gammaherpesviruses.

REFERENCES
