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Malignant catarrhal fever: recent update

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ABSTRACT

Malignant catarrhal fever (MCF) is a serious, usually fatal disease affecting many species of ungulates of the subfamily Bovinae and family Cervidae including pigs and caused by a herpesvirus under the genus *Macavirus* in the subfamily Gammaherpesvirinae. Ten *Macaviruses* have been identified to date and 6 were found to be associated with clinical MCF. Alcelaphine herpesvirus 1 (AlHV-1), which causes inapparent infection in wildebeest and ovine herpesvirus 2 (OvHV-2), which is associated with subclinical infections in sheep are the two most important herpes viruses that cause clinical wildebeest associated MCF (WA-MCF) and sheep-associated MCF (SA-MCF), respectively. The disease is characterized by accumulation of lymphocytes (predominantly $CD8^+$ T cells) in a variety of organs, often associated with tissue necrosis. AIHV-1 can be recovered from animals, while OvHV-2 has never been recovered from affected animals, only OvHV-2 specific DNA is detected in cultured lymphoblastoid cells from infected animals. Diagnosis is normally achieved by observing the clinical signs, characteristic histopathological changes, ELISA and detection of viral DNA in the infected animals. Detection of viral DNA by PCR is becoming the method of choice for diagnosing the SA-MCF. Currently, there is no effective disease control measure. Attenuated AlHV-1 virus vaccine has been developed with varying degree of success for control of WA-MCF in Africa. Separation of reservoir host from susceptible host or raising of OvHV-2 free sheep is the only solution for control of SA-MCF. In India, our group first confirmed SA-MCF in Kashmir. The present article updates current epidemiology, diagnosis, prevention and control of MCF with special reference to India.

Key words: Diagnosis, Epidemiology, Malignant catarrhal fever, Prevention and control, Treatment, Vaccine.

Malignant catarrhal fever (MCF) is a serious, usually fatal disease affecting many species of ungulates of the subfamily Bovinae and family Cervidae including cattle, bison, deer, moose, water buffalo, other wild ruminants, pigs, giraffe and species of antelope belonging to the subfamily Tragelaphinae, which is caused by a herpesvirus under the genus *Macavirus* in the subfamily Gammaherpesvirinae (Reid *et al.* 1984, Plowright 1990, Loken *et al.* 1998, Crawford *et al.* 1999, Clauss *et al.* 2002, Martucciello *et al.* 2006, Gasper *et al.* 2012, OIE 2013a). MCF is increasingly being recognized as the cause of significant economic losses in several major ruminant species (Li *et al*. 2006, Moore *et al*. 2010), as well as a threat to certain other susceptible species held as mixed population in zoos and wildlife parks (Heuschele 1982, Li *et al*. 1999, Cooley *et al.* 2008). Among 10 different *Macaviruses* that have been identified, currently six have been found to be associated with clinical disease (Li *et al.* 2005a, Sood *et al.* 2013). These viruses infect their reservoir hosts efficiently and without apparent-disease but cause lymphoproliferative disease, that is generally fatal when they infect susceptible hosts. MCF is found worldwide wherever susceptible hosts mix with reservoir species (Russell *et al.* 2009). Alcelaphine herpesvirus 1 (AlHV-1) and ovine herpesvirus 2 (OvHV-2) are the major causative agents responsible for wildebeest-associated MCF (WA-MCF) (Plowright *et al.* 1986) and sheep-associated MCF (SA-MCF) (Reid and Buxton 1989), respectively in cattle and other ruminant species. WA-MCF is an economically important disease of cattle in Africa, where wildebeest are present and SA-MCF is prevalent worldwide where sheep husbandry is practiced while animals in zoos or zoological parks may be affected by either of the two forms of the disease (Russell *et al.* 2009, Li *et al.* 2011). Sheep associated MCF is a particular problem in farmed bison, deer and Bali cattle (Li *et al.* 2006, Russell *et al.* 2009). It is also enzootic in India where sheep are raised (Wani *et al.* 2004, 2006, Vinod *et al.* 2014, Premkrishnan *et al.* 2015). MCF is a very complex disease and is difficult to control as the infections are symptomless and widespread in reservoir hosts. The only reliable method of control is to separate

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susceptible animals from carriers or to raise virus free reservoir hosts. This article highlights the importance of MCF, its current epidemiology, prevention and control of the disease with special reference to India.

MCF viruses

Out of 10 different MCF viruses that have been described, 6 have been found to be associated with clinical MCF in different animal species to date. AlHV-1 and OvHV-2 are the two most widely prevalent causative organism of MCF (Plowright *et al.* 1986, Reid and Buxton 1989). AlHV-1 is enzootic in wildebeest and cause inapparent infection, while OvHV-2 is associated with subclinical disease in sheep under natural conditions. The AlHV-1 and OvHV-2 genomes have been completely sequenced and revealed that they are closely related viruses (Ensser *et al.* 1997, Hart *et al.* 2007). Russell *et al*. (2009) described in detailed about the genome structure of MCF viruses. Russell *et al*. (2014) observed variations in gene sequences of OvHV-2 in clinically affected animals with varied clinical manifestations.

The other viruses known to cause MCF include caprine herpesvirus-2 (CpHV-2), which is enzootic in domestic goats (Li *et al.* 2001a, Chmielewicz *et al.* 2001) causing MCF in several ruminants including sika deer (*Cervus nippon*), white tailed deer (*Odocolieus virginianus*), moose (*Alces alces*), roe deer (*Capreolus capreolus*), water buffalo and captive pudu (*Pudu puda*) (Crawford *et al*. 2002, Keel *et al.* 2003, Vikoren *et al.* 2006, Stahel *et al.* 2013, Modesto *et al.* 2015); a virus of possibly goat origin causing MCF in white-tailed deer (MCFV-WTD) and red brocket deer (*Mazama americana*) (Li *et al*. 2013); ibex MCF virus (MCFV-ibex) associated with MCF in bongo antelope (*Tragelaphus eurycerus*) (Gasper *et al.* 2012) and an AlHV-2-like virus of Jackson hartebeest (*Alcelaphus buselaphus jacksoni*) origin causing MCF like disease in Barbary red deer (*Cervus elaphus barbarus*) (Klieforth *et al.* 2002). The remaining four viruses that have been identified in asymptomatic carriers such as hippottraigne herpesvirus 1 (HiHV-1), MCFV-muskox, MCFV-oryx and MCFV-aoudad carried by roan antelope (*Hippotragus eguinus* D), muskox (*Ovibos moschatus*), oryx (*Oryx gazella*) and aoudad, respectively (Reid and Bridgen 1991, Li *et al*. 2003) have not yet been associated with disease. Most MCF viruses are named after their reservoir hosts, however, the reservoir of MCFV-WTD is uncertain, but goats may carry this virus (Li *et al*. 2013, Matzat *et al.* 2015).

The MCF viruses are mostly stable between pH 5.5 to 8.5. They are rapidly inactivated by sunlight. Cell-associated viruses may survive 72 h outside the host while cell-free virus is inactivated quickly in dry environments but may survive over 13 days in humid environments. They are also inactivated by common disinfectants including sodium hypochlorite and 3% solution recommended if heavy organic debris is present (OIE 2013b)

Epidemiology

The MCF viruses are prevalent worldwide, but illness occurs only where a carrier species can transmit a virus to susceptible hosts. Consequently, disease caused by AIHV-1 is restricted to those areas of Africa and in zoological collections where wildebeest are found and OvHV-2 form of the disease occurs world-wide wherever sheep husbandry is practiced. Most ruminants, apart from antelopes of the subfamilies Alcelaphine and Hippotraginae are susceptible to AlHV-1 (OIE 2013). Significant numbers of cattle become ill if they are exposed to this virus. Wildebeest (*Connochaetes* spp) are the carriers for AlHV-1. The blue wildebeest (*Connochaetes taurinus*) is the major reservoir host, but black wildebeest (*Connochaetes gnou*) are also carriers (Reid and Van Vuuren 2004). All or most wildebeest appear to be infected with AlHV-1 and both vertical and horizontal transmissions occur in wildebeest. In East Africa, the seasonal occurrence of MCF in cattle which is mostly in March and April in northern Tanzania and from April to July in southern Kenya, has been associated with blue wildebeest calving seasons and the disease is more common when the wildebeest calves are two to three-months-old (Cleaveland *et al.* 2001). In South Africa, two peaks of blue wildebeest associated MCF have been encountered; one in January to May (highest number of cases in early April) following the wildebeest calving season in December to February, and a second, in which the prevalence is higher, from September to November (highest number of cases in mid-September) when the wildebeest calves are 9–11 months old (Barnard and Van de Pypekamp 1988, Mlilo *et al.* 2015). The principal source of free virus in wildebeest is in the tears and nasal secretions (Mushi *et al.* 1981). The ages of cattle (excluding congenital cases) that develop clinical signs vary from 4.5 months to a few years with the majority being between 8 and 18 months old. South Africa is the only natural habitat of the black wildebeest. Although the blue wildebeest has thus far been regarded as the most important carrier of AlHV-1, indications are that black wildebeest are equally important transmitters of MCF virus. This increase can be ascribed to the increase in the number of farms on which black wildebeest are kept including increase in area distribution, which is bigger than that of blue wildebeest. All black wildebeest herds tested so far in South Africa were serologically positive for antibodies against AlHV-1 (Pretorius *et al.* 2008). Wambua *et al*. (2016) described in detailed the incidence and geographic distribution of WA-MCF.

Domestic and wild sheep are the reservoir host for OvHV-2 and most individuals are affected (Russel *et al.* 2009). Horizontal transmission is the predominant mode in sheep and it is not well documented in clinically susceptible species. OvHV-2 viral DNA also has been detected in samples from the alimentary, respiratory and urogenital tracts of sheep (Hussy *et al.* 2002). This may account for some infection of offspring occurring during or shortly after lambing. There is a wide variation of susceptibility to OvHV-2-induced disease. *Bos taurus* and *B. indicus* cattle are relatively resistant, while most species of deer, bison (*Bison bison*) and water buffalo (*Bubalus bubalis*) are more susceptible to OvHV-2. Bali cattle (*Bos*

javanicus) and Père David's deer (*Elaphurus davidianus*) are much more susceptible to OvHV-2. Experimental studies on OvHV-2 infection indicate that bison are approximately 1,000 times more susceptible to clinical MCF than cattle (Li *et al.* 2006, Taus *et al.* 2006). Similarly, bison were found 6 times more susceptible than domestic sheep (Li *et al.* 2005c, O'Toole *et al.* 2007). The more resistant species tend to experience a more protracted illness with florid lesions, while in the more susceptible species, the disease course tends to be shorter and the clinical signs are less remarkable. Sub-clinical or latent infection with OvHV-2 can also occur in cattle and other cervids like moose, roe deer, and red deer (Powers *et al.* 2005, Vikoren *et al.* 2006). In addition to sheep and wildebeest, some other species, including goats, musk oxen (*Ovibos moschatus*), may act as inapparent carriers of MCF viruses (Li *et al.* 1995a, 1996, Zarnke *et al.* 2002). Rare clinical cases have been tentatively attributed to OvHV-2 in domesticated goats, Stone's sheep (*Ovis dalli stonei*) and Barbary sheep (*Ammotragus lervia*) (Yeruham *et al.* 2004, Jacobsen *et al.* 2007, Himsworth *et al.* 2008). Although MCF is usually fatal once clinical signs develop, subclinical infections with an MCF group of virus in bison and other species such as deer and cattle have been documented (Zarnke *et al.* 2002, Powers *et al.* 2005, O'Toole *et al.* 2007, Loken *et al.* 2009). There is also molecular and serological evidence that a few infected animals may recover following mild or even quite severe clinical reactions (Michel and Aspeling 1994). Furthermore, animals that develop clinical MCF are usually dead end hosts.

MCF viruses, like other herpesviruses, establish lifelong, latent infections. AlHV-1 is spread mainly by wildebeest calves, which can become infected *in utero*, by direct contact with other wildebeest, through aerosols in close contact or from contaminated pastures and remain carriers for life (Mushi and Rurangirwa 1981, Plowright 1986). The infected animals then shed cell-free virus in nasal and ocular secretions intensely during the first 3–4 months of life, and most calves are thought to become infected in the group. Neutralizing antibodies usually develop by approximately 3 months of age and shedding of viruses declines thereafter (Mushi and Rurangirwa 1981). After this, the virus occurs mainly in the cell-associated form, which is transmitted only rarely to other animals. However, cell-free virus can be isolated from the nasal secretions of some animals that are stressed or given corticosteroids or during parturition. Most cases of wildebeest-associated MCF are seen when susceptible animals are exposed to parturient wildebeest or young calves or pasture contaminated by them. This usually occurs after close contact, but transmission has been reported when the animals were separated by at least 100 meters. There is no definitive evidence that MCF-affected animals transmit the disease horizontally to others. Congenital transmission of AlHV-1 within infected domestic cows can occur with varying disease latency periods in newborn calves (Mushi and Rurangirwa 1981). Inhalation is thought to be the primary means of transmission for all MCF viruses, although ingestion might also be possible.

The SA-MCF was first confirmed in cow and sheep in Kashmir by our group (Wani *et al.* 2004, 2006) with the help of OIE recommended PCR assay although histopathological evidence was provided much earlier in Punjab (Parihar *et al.* 1975). Subsequently, OvHV-2 have been detected in sheep and goat in southern India and death of a captive bison due to SA-MCF was recorded in Bangalore (Sood *et al.* 2013). The cases in cows were found to be sporadic, however, an outbreak occurred in the Military Dairy Farm, Bemina, Srinagar in 2010, where 22 animals (cows and heifers) out of around 250 animals died due to SA-MCF (Unpublished data). Since then, we also confirmed 14 sporadic cases of SA-MCF linked death in crossbred cows in different district of Kashmir. Kumar *et al*. (2014) also reported an outbreak of SA-MCF in cattle in a village in Andhra Pradesh in which thirteen adult cows and two calves died out of a population of forty animals. Recently, Premkrishnan *et al.* (2015) reported that nearly a quarter of sheep population in Karnataka state of India is infected with OvHV-2. The disease is generally infrequent in countries where *Bos indicus* and *Bos taurus* are predominant species. But it is common among Bali cattle and a serious problem in countries where bison and cervids are reared as farm animals as these are highly susceptible (Li *et al.* 2006, Russell *et al.* 2009). Pigs are also infected with SA-MCF virus, which was reported mainly from Norway, however, reports have been pouring from other countries too (Loken *et al.* 1998, Syrjala *et al.* 2006, Alcaraz *et al.* 2009, Azevedo *et al.* 2010, Lapp *et al.* 2015). Circumstantial evidence (antibodies to MCF viruses in some gnotobiotic and specific pathogen-free sheep) and the identification of virus-infected cells in colostrum and milk, suggest that vertical transmission of OvHV-2 is possible (Rossiter 1981). However, transmission by these routes seems to be uncommon. Viral DNA has also been reported in the semen of rams (OIE 2013b). There is also evidence of transplacental transmission of OvHV-2 in cattle with SA-MCF (Headley *et al.* 2015). A Canadian study found that there was greater risk of MCF deaths in bison herds within 1.0 km of sheep operations than in herds more than 1.0 km away (Epp *et al.* 2016). Previous studies documented spread of OvHV-2 over a distance upto 5 km (Li *et al.* 2008). Recrudescence of latent infections is also possible and must be considered for cases with no known history of contact with carriers (Heuschele *et al.* 1985). Laboratory animals like rabbit and hamsters may be experimentally infected with either AlHV-1 or OvHV-2 and develop a MCF-like syndrome that is very similar to that seen in species naturally susceptible to MCF (Buxton and Reid 1980, Reid *et al.* 1989, Anderson *et al.* 2007).

Little is known about the epidemiology of other viruses in the MCFV group. However, goats are carriers of CpHV-2 and they may also carry OvHV-2 (Li *et al.* 2001, Chmielewicz *et al.* 2001). Alcephaline herpesvirus-2 is carried subclinically in hartebeest and topi (*Damaliscus*

korrigum) (Klieforth *et al.* 2002). Based on phylogenetic analysis of a portion of the DNA polymerase gene, which is relatively conserved among herpesviruses, all MCFVs identified to date can be clustered into two major groups viz. the Alcelaphinae/Hippotraginae group, which includes AlHV-1, AlHV-2, HiHV-1, and MCFV-oryx; and the Caprinae group including OvHV-2, CpHV-2, MCFV-WTD, MCFV-ibex, MCFV-muskox and MCFV-aoudad (Li *et al.* 2005a). These data suggest the epidemiology of these viruses within the groups may be similar. The viruses within the group share certain biological properties; for example, the viruses in the Alcelaphinae/Hippotraginae group can propagate in cell culture, and a study on CpHV-2 transmission among goats showed that CpHV-2 has a similar transmission pattern as OvHV-2 (Li *et al.* 2005b).

Diagnosis of MCF

Diagnosis of MCF poses significant challenges to veterinarians due to clinical resemblance to many of the viral diseases and toxicity such as bovine viral diarrhoea, mucosal disease, infectious bovine rhinotracheitis, bluetongue, epizootic haemorrhagic disease, foot and mouth disease, vesicular stomatitis, theileriosis, ingestion of caustic materials or some toxic plants etc (OIE 2013b). Therefore, laboratory confirmation of a clinical diagnosis of MCF is important. The diagnostic approaches may vary in different clinically affected animals and reservoir hosts due to biology of the MCF viruses and host responses to the viruses. Clinical signs and different assays such as serological tests, PCR, histopathology, isolation and identification of virus (eg.AlHV-1) including experimental infection to laboratory animals either alone or in combination may be used for detection of MCFVs or diagnosis of the disease caused by the viruses.

Reservoir hosts

Isolation of virus: In wildebeest calves, cell-free virus can be found in nasal secretions for a short period after infection. The virus can also be isolated from peripheral blood leukocytes at this time. It is less likely to be successful in older wildebeest, except when they are immunosuppressed (e.g., by stress or drug treatment). Cell-associated AlHV-1 can be isolated by establishing cultures of tissues from wildebeest. The viability of the host cells must be maintained after sample collection, as the virus cannot be recovered from dead cells. Most monolayer cultures of ruminant origin are probably susceptible and develop cytopathic effect (CPE). Bovine thyroid have been used extensively (Plowright 1986, OIE 2013b). Primary isolates typically produce multinucleated CPE in which viral antigen can be identified by immunofluorescence or immunocytochemistry. OvHV-2 and CpHV-2 have never been propagated in monolayer culture, although an incompletely enveloped virus has been detected by electron microscopy (EM) from an OvHV-2 infected rabbit large granular lymphocyte (LGL) lysate (Rosbottom *et al.* 2002).

Serological tests

Several serological assays have been developed for detection of antibodies against MCFVs, and all the assays use the alcelaphine herpesviruses as antigens, predominantly AlHV-1, because these viruses can be propagated *in vitro*. These assays include virus neutralization (VN), enzyme-linked immunosorbent assay (ELISA)/competitive-inhibition ELISA (CI-ELISA), immunofluorescence assay (IFA)/immunoperoxidase test (IPT), and complement fixation test (Rossiter 1981, Sentsui *et al.* 1996, Li *et al.* 2001b, Fraser *et al.* 2006, OIE 2013a). These tests can be divided into three categories: neutralizing antibody-, polyclonal antibody- and monoclonal antibody-based assays. Viral neutralization tests have been developed for detection of antibodies to AlHV-1 or other viruses in the Alcelaphinae/Hippotraginae group of both reservoir and clinically-affected hosts (Reid *et al*. 1975). Infected wildebeest develop antibody to AIHV-1, which can be detected by the above assays. The VN tests are highly specific and work well for the detection of infected wildebeest or other related hosts, such as hartebeest and topi. Infected sheep usually develop no or low neutralizing antibody responses to AlHV-1 (Heuschele *et al.* 1984); therefore, the viral neutralization test is of very limited use in detection of antibodies in animals infected with OvHV-2 or the other related viruses carried by *Caprinae* species. Polyclonal antibody-based assays, including ELISA, IFA, and IPT among others, detect antibodies against multiple epitopes of AlHV-1. Generally, these tests have good sensitivity, but reduced specificity, due to cross-reactivity with other herpesviruses, such as bovine herpesviruses 1 and 4 (Dubuisson *et al.* 1989, Li *et al.* 1995b). The monoclonal antibody (15A) based CI-ELISA which detects a conserved epitope of all the MCFVs was found to be highly specific and sensitive (Li *et al.* 2001). Fraser *et al*. (2006) has developed a direct ELISA, which seems to be a simple and inexpensive alternative to other serological tests.

PCR assays

The use of PCR allows sensitive confirmation of the presence of MCF viruses in infected animals and may also be useful for phylogenetic and epidemiological studies in both natural and MCF-susceptible hosts. Both conventional and quantitative real-time PCR assays have been developed for the detection of OvHV-2 and AlHV-1 viral DNA (Baxter *et al.* 1993, Hussy *et al.* 2001, Traul *et al.* 2005, Cunha *et al.* 2009). The OIE approved nested-PCR (Baxter *et al.* 1993) was found to be 10-fold more sensitive than quantitative PCR. However, real-time PCR assays have the potential to define viral loads in a range of tissues from both natural and MCF-susceptible hosts. Tissues for PCR may comprise anticoagulated blood, kidney, lymph nodes, intestinal wall, brain and other tissues. PCR also found to be more sensitive than CI-ELISA either in reservoir or

susceptible host (Li *et al.* 1995a, Muller-Doblies *et al.* 1998).

Diseased animals

Clinical signs and gross pathology: The clinical signs of MCF are highly variable and many overlapping but distinct clinical patterns viz. peracute, head and eye, alimentary, neurological and cutaneous have been described (OIE 2013a). In peracute cases, either no clinical signs are observed, or depression followed by diarrhoea and dysentery may develop 12–24 h prior to death. In general, there is high fever, increased serous lachrymation and nasal exudate that progress to profuse mucopurulent discharge, inappetance, and decreased milk yields. Progressive bilateral corneal opacity, starting at the periphery is characteristic of MCF. There may be enlargement of superficial lymph nodes including swelling of limb joints. Nervous signs, viz. hyperaesthesia, incoordination, nystagmus and head pressing may develop either alone or with other clinical signs.

Gross pathological changes are generally widespread and may involve most organ systems. Salivation and oral hyperaemia may be an early sign and may progress to erosions of the tongue, hard palate, gums and characteristically the tips of the buccal papillae. Sometimes skin ulceration and necrosis may develop, which may be extensive or restricted to the udder and teats. Erosions and haemorrhages in the gastrointestinal tract may be evident. Lymph nodes are enlarged, but the degree varies within an animal. Catarrhal exudate, erosions and diphtheritic membranes are often observed in the respiratory tract. Urinary bladder often has characteristic ecchymotic haemorrhages of the epithelial lining, especially in bison. In kidney, extensive multiple raised white foci, each 1–5 mm in diameter may appear. The brain may also show signs characteristics of nonsuppurative meningoencephalitis.

Isolation of virus

AlHV-1 can only be isolated from clinically infected hosts in cell cultures mentioned above. These viruses are inactivated quickly in dead animals and samples should be taken as soon as possible. The most useful samples are collected immediately after euthanasia of a dying animal. Tissues for virus isolation may include anticoagulated blood (10–20 ml in EDTA), spleen, lung, lymph nodes, and adrenal glands. As the viral cause of SA-MCF cannot be isolated *in vitro*, evidence for OvHV-2 must rely on the presence of antibody and detection of DNA amplicons unique to OvHV2.

Serology

Most of the serological tests can be used in sick animals; however, the VN test cannot be employed, as these animals do not usually develop neutralizing antibodies. Nevertheless, their utility in the routine diagnosis of MCF cases is limited by the rapid and high case fatality rates, most animals die before a detectable antibody response has been raised (Cleaveland *et al.* 2001). However, the degree of seropositivity in MCF-susceptible species, including cattle, bison, deer, caribou (*Rangifer tarandus*), elk (*Cervus elaphus*) and moose, ranges from a few percent to 50% (Li *et al.* 1996, Frolich *et al.* 1998, Zarnke *et al.* 2002, Powers *et al.* 2005). On other hand, due to cross-reactivity with other herpesviruses, the polyclonal antibody based tests have limited use for final diagnosis. Furthermore, serological or PCR-based testing of apparently healthy cattle and free-living bison and caribou has demonstrated infection in the absence of clinical signs (Zarnke *et al.* 2002, Powers *et al.* 2005); therefore, serology should be used in conjunction with histopathology and clinical findings. Samples for serology should be paired when possible and taken first during the acute phase of disease and then during convalescence 3–4 weeks later or at death.

Histopathology

The World Organization for Animal Health (OIE) recognizes histopathology as the definitive diagnostic test. The pathological features of MCF, irrespective of the agent involved, are essentially similar. Tissues from cattle may include lung, liver, lymph nodes, skin (if lesions are present), kidney, adrenal gland, eye, oral epithelium, oesophagus, Peyer's patches, urinary bladder, thyroid, heart muscle, carotid rete and brain. In case of bison, urogenital and intestinal tract tissue are particularly important. For other species, a wide range of tissues may be collected (OIE 2013b). Histological changes are characterized by epithelial degeneration, vasculitis, hyperplasia and necrosis of lymphoid organs, and widespread interstitial accumulations of lymphoid cells in nonlymphoid organs. The interstitial accumulation of lymphoid cells in nonlymphoid organs, in particular, the renal cortex and periportal areas of the liver, is typical; and in the case of the kidney, may be very extensive with development of multiple raised white foci, each 1–5 mm in diameter. The brain may also show a nonsuppurative meningoencephalitis with lymphocytic perivascular cuffing and a marked increase in the cellularity of the cerebrospinal fluid (OIE 2013a). Experimental MCF in rabbits revealed specific differences between MCF caused by OvHV-2 and AlHV-1 (Anderson *et al.* 2007). OvHV-2-associated lesions were more apparent in visceral lymphoid tissue (e.g., mesenteric lymph nodes), whereas lesions associated with AlHV-1 were more frequent in peripheral lymph nodes. In addition, OvHV-2 associated lesions contained more areas of necrosis than those of AlHV-1. However, with both viruses, lymphoid cell infiltrations consisted mainly of T cells, of which CD8+ T cells predominated, with very few $CD4^+$ T cells (Anderson *et al.* 2007, Dewals *et al.* 2008). $CD8^+$ T cell proliferation is detectable as early as 15 days post inoculation, while the viral load in peripheral blood mononuclear cells remains below the detection level during most of the incubation period, which increases drastically few days before death.

PCR assays

Both, the nested-PCR as well as realtime-PCR can be

employed for detection of MCFVs. The higher sensitivity of the nested PCR assays may make them an attractive alternative where viral load is low or in difficult samples, such as fixed or paraffin-embedded tissue (Crawford *et al.* 1999). For routine PCR assays, unfixed tissues or peripheral blood leukocytes are preferred, but formalin- or ethanol fixed tissue held less than 3–4 weeks can also be used. The levels of OvHV-2 DNA are very low in subclinically infected bison and cattle, and may not be detected readily by PCR. However, such infections are not expected to be clinically significant, as these animals are expected to be dead end hosts for the virus. In surveillance, such animals can be detected more readily by serology than PCR.

Treatment, prevention and control

No treatment has been found to provide any consistent benefit against MCF. Stress reduction of subclinical or mildly affected animals is advisable. Occasionally, supportive care with fluids and treatment with steroids and antibiotics has been effective in helping animals recover (Penny 1998). The recent availability of derivatives of acyclovir compounds that inhibit replication of herpesviruses shows promise in potential treatment regimens. A report of inhibition of the replication of the alcelaphine herpesvirus by using recombinant interferons could be considered in development of a treatment regimen for valuable animals (Wan *et al*. 1988). Very recently, intravenous IL-2 administration was found to be associated with clinical recovery in some MCF affected cows (Braun *et al.* 2015).

Cattle surviving natural infection remained immune, despite having lower titres of serum neutralizing antibody than immunized animals (Plowright *et al.* 1975). These observations suggest that serum neutralizing antibody is not a critical component of a protective immune response in cattle. However, cell-free high passage attenuated AlHV-1 in tissue culture along with Freunds' adjuvant as a vaccine candidate was found to protect immunized cattle against intranasal challenge (Haig *et al.* 2008). The vaccine was hypothesized to induce a protective barrier of virus-neutralizing antibody in the oro-nasal region, supported by the observation of high titre neutralizing antibodies in nasal secretions of protected animals. The same group also evaluated the vaccine, but with a licensed adjuvant for duration of immunity and degree of protection in relation to virus specific antibody level locally (nasal secretions) or systemically (Russell *et al.* 2012). The vaccine was found to protect cattle from fatal intranasal challenge with pathogenic AlHV-1 at three or six months. Animals protected from MCF had significantly higher initial anti-viral antibody titres than animals that succumbed to disease; and these antibody titres remained relatively stable after challenge, while titres in vaccinated animals with MCF increased significantly prior to the onset of clinical disease. These data support the view that a mucosal barrier of neutralizing antibody blocks infection of vaccinated animals and suggests that the magnitude of the initial response may correlate with long-term protection. Interestingly, the high titre virus-neutralizing antibody responses seen in animals that succumbed to MCF after vaccination were not protective. Similarly, an attenuated AlHV-1 virus vaccine reduced infection rates by 56% in cattle exposed to wildebeest in Tanzania (Lankester *et al.* 2016). As OvHV-2 cannot be successfully propagated in the laboratory, no attempts at developing a vaccine have been attempted. These studies may allow the development of a protective vaccine for WA-MCF. Furthermore, the protective antigens in AlHV-1 can be identified and the equivalent antigens in OvHV-2 isolated to attempt vaccination control of SA-MCF. In contrast, work on cellular immunity to MCF virus has been hampered by the lack of a good experimental system in which animals can be immunized and challenged and by the severe T cell hyperplasia induced by MCF virus, which is a central part of disease pathology. Therefore, avoidance of interaction between carriers and susceptible animals remains the only control strategy for MCF before any suitable vaccine is developed. As such, susceptible animals should be separated from sheep, goats, wildebeest or other suspected reservoir hosts. Wildebeest appear to transmit AlHV-1 readily, and should always be separated from cattle. Cattle should not graze pastures where wildebeest have grazed and given birth. Wildebeest should also be segregated in zoos. Cattle rarely develop the sheep-associated form of MCF, but separation from sheep would be advisable, particularly from lambs actively shedding virus. Co-housing of sheep and cattle should be avoided. Bison, some deer and other highly susceptible species should not be allowed near sheep. Separation by longer distances is particularly important when the host is highly susceptible and the concentration of virus is high (e.g. bison and lambs in feedlot). Further, access to contaminated fomites must be avoided, especially when the species is highly susceptible. OvHV-2 free sheep can be produced by early weaning and isolation (Li and Crawford 1999). During outbreaks, susceptible animals should be separated immediately from the suspected source. As cattle and other incidental hosts are thought to be dead end hosts, they do not need any culling.

Conclusion

Malignant catarrhal fever is an important and interesting disease with many unanswered questions concerning sporadic occurrence of the disease, transmission, inability to cultivate OvHV-2 and different host response exhibited by the closely related species to the same virus. Due to the complexities of pathogenesis and its epidemiology, clinicians and veterinarians face significant challenges in diagnosing MCFV infection and/or disease. However, molecular diagnostic assays have improved the detection and differentiation of MCF causative viruses, and increased accuracy of laboratory assays in confirming MCFV infection and/or disease in various species. The importance of MCF as a pathogen especially for pastoralist cattle, farmed deer and bison, as well as other wild ruminants is

driving research for improved diagnostic tools and development of effective vaccines. The resistance of certain species/breed of animals against MCF is another area of research which needs attention. Although the SA-MCF is sporadic in cattle, outbreak can occur in dairy herds. The recent sequencing of the OvHV-2 and AlHV-1 genome, the production of recombinant AlHV-1 viruses and developments in the use of intranasal challenges, for both OvHV-2 and AlHV-1 and vaccine trials in cattle with attenuated AlHV-1 constitute important steps forward in the development of vaccine strategies to protect against MCF.

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REFERENCES

Alcaraz A, Warren A, Jackson C, Gold J, McCoy M, Cheong S H, Kimball S, Sells S, Taus N S, Divers T and Li H. 2009. Naturally occurring sheep-associated malignant catarrhal fever in North American pigs. *Journal of Veterinary Diagnostic Investigation* **21**: 250–53.

Anderson I E, Buxton D, Campbell I, Russell G, Davis W C, Hamilton M J and Haig D M. 2007. Immuno-histochemical study of experimental malignant catarrhal fever in rabbits. *Journal of Comparative Pathology* **136**: 156–66.

Azevedo Costa É, de Marco Viott A, de Souza Machado G, Quaresma Bomfim M R, Magalhães Coelho F, Portela Lobato Z I, Resende M and Carvalho Guedes R M. 2010. Transmission of ovine herpesvirus 2 from asymptomatic boars to sows. *Emerging Infectious Disease* **16**: 2011–12.

Barnard B J and Van de Pypekamp H E. 1988. Wildebeest-derived malignant catarrhal fever: unusual epidemiology in South Africa. *Onderstepoort Journal of Veterinary Research* **55**: 69–71.

Baxter S I F, Pow I, Bridgen A and Reid H W. 1993. PCR detection of the sheep-associated agent of malignant catarrhal fever. *Archives of Virology* **132**: 145–59.

Braun U, Hässig M, Previtali M, Franchini M, Vögtlin A, Storset A K and Ackermann M. 2015. Interukin-2 for the treatment of cows with malignant catarrhal fever. *Schweizer Archiv Fur Tierheilkunde* **157**: 31–8.

Buxton D and Reid H W. 1980. Transmission of malignant catarrhal fever to rabbits. *Veterinary Record* **106**: 243–45.

Chmielewicz B, Goltz M and Ehlers B. 2001. Detection and multigenic characterization of a novel gamma herpesvirus in goats. *Virus Research* **75**: 87–94.

Clauss M, Kienzle E and Wiesner H. 2002. Importance of the wasting syndrome complex in captive moose (*Alces alces*). *Zoo Biology* **21**: 499–506.

Cleaveland S, Lughano K, Ole Kuwai J, Bell C and Kazwala R. 2001. Assessing the impact of malignant catarrhal fever in Ngorongoro district, Tanzania. Department for International Development, Animal Health Programme, pp 1–57. (http:/ agris. fao.org/agris-search search.do?recordID= GB2013202238).

Cooley A J, Taus N S and Li H. 2008. Development of a management program for a mixed species wildlife park following an occurrence of malignant catarrhal fever. *Journal of Zoo and Wildlife Medicine* **39**: 380–85.

Crawford T B, Li H and O´Tool D. 1999. Diagnosis of malignant catarrhal fever by PCR using formalin fixed, paraffin-embedded tissues. *Journal of Veterinary Diagnostic Investigation* **11**: 111–16.

Crawford T B, Li H, Rosenberg S R, Norhausen R W and Garner M M. 2002. Mural folliculitis and alopecia caused by infection with goat-associated malignant catarrhal fever virus in two Sika deer. *Journal of American Veterinary Medical Association* **221**: 843–47.

Crawford T B, O'Toole D T and Li H. 1999. Malignant catarrhal fever. Current Veterinary Therapy: Food Animal Practice, 4th ed, Howell J and Smith R A (Eds), W.B. Saunders Company, Oklahoma, OK, USA, pp. 306–9.

Cunha C W, Otto L, Taus N S, Knowles D P and Li H. 2009. Development of a multiplex real-time PCR for detection and differentiation of malignant catarrhal fever viruses in clinical samples. *Journal of Clinical Microbiology* **47**: 2586–89.

Dewals B, Boudry C, Gillet L, Markine-Goriaynoff N, de Leval L, Haig D M and Vanderplasschen A. 2006. Cloning of the genome of alcelaphine herpesvirus 1 as an infectious and pathogenic bacterial artificial chromosome. *Journal of General Virology* **87**: 509–17.

Dubuisson J, Thiry E, Bublot M, Sneyers M, Boulanger D, Guillaume J and Pastoret P P. 1989. Production and characterization of monoclonal antibodies to bovid herpesvirus-4. *Veterinary Microbiology* **19**: 305–15.

Ensser A, Pflanz R and Fleckenstein B. 1997. Primary structure of the alcelaphine herpesvirus 1 genome. *Journal of Virology* **71**: 6517–25.

Epp T, Waldner C and Woodbury M. 2016. An observational study of mortality on bison farms in Saskatchewan with special emphasis on malignant catarrhal fever. *Canadian Veterinary Journal* **57**: 37–45.

Fraser S J, Nettleton P F, Dutia B M, Haig D M and Russell G C. 2006. Development of an enzyme-linked immunosorbent assay for the detection of antibodies against malignant catarrhal fever viruses in cattle serum. *Veterinary Microbiology* **116**: 21–28.

Frolich K, Li H and Muller-Doblies U. 1998. Serosurvey for antibodies to malignant catarrhal fever-associated viruses in free-living and captive cervids in Germany. *Journal of Wildlife Diseases* **34**: 777–82.

Gasper D, Barr B, Li H, Taus N, Peterson R, Benjamin G, Hunt T and Pesavento P A. 2012. Ibex-associated malignant catarrhal fever-like disease in a group of bongo antelope (*Tragelaphus eurycerus*). *Veterinary Pathology* **49**: 492–97.

Haig D M, Grant D, Deane D, Campbell I, Thomson J, Jepson C, Buxton D and Russell G C. 2008. An immunisation strategy for the protection of cattle against alcelaphine herpesvirus-1-induced malignant catarrhal fever. *Vaccine* **26**: 4461–68.

Hart J, Ackermann M, Jayawardane G, Russell G, Haig D M, Reid H and Stewart J P. 2007. Complete sequence and analysis of the ovine herpesvirus 2 genome. *Journal of General Virology* **88**: 28–39.

Headley S A, Pimentel L A, Oliveira V H, Toma H S, Alfieri A F, Carvalho A M, dos Santos M D and Alfieri A A. 2015. Transplacental transmission of ovine herpesvirus 2 in cattle with sheep-associated malignant catarrhal fever. *Journal of Comparative Pathology* **153**: 206–11.

Heuschele W P. 1982. Malignant catarrhal fever in wild ruminants-A review and current status report. *Proceedings of the United States Animal Health Association*, Nashville, TN, USA, 7–12 November 1982.

Heuschele W P, Nielsen N O, Oosterhuis J E and Castro A E. 1985. Dexamethasone-induced recrudescence of malignant catarrhal fever and associated lymphosarcoma and granulomatous disease in a Formosan sika deer (*Cervus nippon taiouanus*). *American Journal of Veterinary Research* **46**: 1578–83.

Heuschele W P, Fletcher H R, Oosterhuis J E, Jansenn D and Robinson P T. 1984. Epidemiologic aspects of malignant catarrhal fever in the USA. *Proceedings of the United States Animal Health Association* **88**: 640–51.

Himsworth C G, Harms N J, Wobeser G and Hill J. 2008. Bilateral perirenal hemorrhage in two Stone's sheep (*Ovis dalli stonei*): a possible manifestation of malignant catarrhal fever. *Journal of Veterinary Diagnostic Investigation* **20**: 676–78.

Hussy D, Janett F, Albini S, Stauber N, Thun R and Ackermann M. 2002. Analysis of the pathogenetic basis for shedding and transmission of ovine gamma herpesvirus 2. *Journal of Clinical Microbiology* **40**: 4700–04.

Hussy D, Stauber N, Leutenegger C M, Rieder S and Ackermann M. 2001. Quantitative fluorogenic PCR assay for measuring ovine herpesvirus 2 replication in sheep. *Clinical and Diagnostic Laboratory Immunology* **8**: 123–28.

Jacobsen B, Thies K, von Altrock A, Forster C, Konig M and Baumgartner W. 2007. Malignant catarrhal fever-like lesions associated with ovine herpesvirus–2 infection in three goats. *Veterinary Microbiology* **124**: 353–57.

Keel M K, Patterson J G, Noon T H, Bradley G A and Collins J K. 2003. Caprine herpesvirus-2 in association with naturally occurring malignant catarrhal fever in captive Sika deer (*Cervus nippon*). *Journal of Veterinary Diagnostic Investigation* **15:** 179–83.

Klieforth R, Maalouf G, Stalis I, Terio K, Janssen D and Schrenzel M. 2002. Malignant catarrhal fever-like disease in Barbary red deer (*Cervuselaphus barbarus*) naturally infected with a virus resembling alcelaphine herpesvirus 2. *Journal of Clinical Microbiology* **40**: 3381–90.

Lankester F, Russell G C, Lugelo A, Ndabigaye A, Mnyambwa N, Keyyu J, Kazwala R, Grant D, Percival A, Deane D, Haig D M and Cleaveland S. 2016. A field vaccine trial in Tanzania demonstrates partial protection against malignant catarrhal fever in cattle. *Vaccine* **34**: 831–38.

Lapp S, Forster C, Kummrow M, Wohlsein P and Haist V. 2015. Malignant catarrhal fever in a Vietnamese pot-bellied pig. A potential threat to pigs in mixed-species exhibits? *Tierärztliche Praxis Ausgabe G Grosstiere/Nutztiere* **43**: 165–68.

Li H, Brooking A, Cunha C W, Highland M A, O'Toole D, Knowles D P and Taus N S. 2013. Goats are potential reservoir of herpesvirus (MCFV-WTD), causing malignant catarrhal fever in deer. *Zoo and Wildlife Medicine* **44**: 484–86.

Li H and Crawford T B. 1999. Production of malignant catarrhal fever virus-free sheep. *Veterinary Microbiology* **65**: 167–72.

Li H, Cunha C W and Taus N S. 2011. Malignant catarrhal fever: understanding molecular diagnostics in context of epidemiology. *International Journal of Molecular Sciences* **12**: 6881–93.

Li H, Gailbreath K, Bender L C, West K, Keller J and Crawford T B. 2003. Evidence of three new members of malignant catarrhal fever virus group in muskox (*Ovibos moschatus*), Nubian ibex (*Capra nubiana*), and gemsbok (*Oryx gazella*). *Journal of Wildlife Diseases* **39**: 875–80.

Li H, Gailbreath K, Flach E J, Taus N S, Cooley J, Keller J, Russell G C, Knowles D P, Haig D M, Oaks J L, Traul D L and Crawford T B. 2005a. A novel subgroup of rhadinoviruses in ruminants. *Journal of General Virology* **86**: 3021–26.

Li H, Karney G, OToole D and Crawford T B. 2008. Long distance spread of malignant catarrhal fever virus from feedlot lambs to ranch bison. *Canadian Veterinary Journal* **9**:183–85.

Li H, Keller J, Knowles D P and Crawford T B. 2001a. Recognition of another member of the malignant catarrhal fever virus group: an endemic gammaherpesvirus in domestic goats. *Journal of General Virology* **82**: 227–32.

Li H, Keller J, Knowles D P, Taus N S, Oaks J L and Crawford T B. 2005b. Transmission of caprine herpesvirus 2 in domestic goats. *Veterinary Microbiology* **107**: 23–29.

Li H, McGuire T C, Muller-Doblies U U and Crawford T B. 2001b. A simpler, more sensitive competitive inhibition ELISA for detection of antibody to malignant catarrhal fever viruses. *Journal of Veterinary Diagnostic Investigation* **13:** 361–64.

Li H, O'Toole D, Kim O, Oaks L and Crawford T B. 2005c. Malignant catarrhal fever-like disease in sheep after intranasal inoculation with ovine herpesvirus-2. *Journal of Veterinary Diagnostic Investigation* **17:** 171–75.

Li H, Shen D T, Davis W C, Knowles D P, Gorham J R and Crawford T B. 1995b. Identification and characterization of the major proteins of malignant catarrhal fever virus. *Journal of General Virology* **76**: 123–29.

Li H, Shen D T, Jessup D A, Knowles D P, Gorham J R, Thorne T, O'Toole D and Crawford T B. 1996. Prevalence of antibody to malignant catarrhal fever virus in wild and domestic ruminants by competitive-inhibition ELISA. *Journal of Wildlife Diseases* **32:** 437–43.

Li H, Shen D T, O'Toole D, Knowles D P, Gorham J R and Crawford T B. 1995a. Investigation of sheep-associated malignant catarrhal fever virus-infection in ruminants by PCR and competitive-inhibition enzyme-linked-immunosorbent-assay. *Journal of Clinical Microbiology* **33**: 2048–53.

Li H, Taus N S, Jones C, Murphy B, Evermann J F and Crawford T B. 2006. A devastating outbreak of malignant catarrhal fever in a bison feedlot. *Journal of Veterinary Diagnostic Investigation* **18**: 119–23.

Li H, Westover W C and Crawford T B. 1999. Sheep-associated malignant catarrhal fever in a petting zoo. *Journal of Zoo and Wildlife Medicine* **30**: 408–12.

Loken T, Aleksandersen M, Reid H and Pow I. 1998. Malignant catarrhal fever caused by Ovine herpesvirus-2 in pigs in Norway. *Veterinary Record* **143**: 464–67.

Loken T, Bosman A M and van Vuuren M. 2009. Infection with Ovine herpesvirus 2 in Norwegian herds with a history of previous outbreaks of malignant catarrhal fever. *Journal of Veterinary Diagnostic Investigation* **21**: 257–61.

Martucciello A, Marianelli C, Capuano M, Astarita S, Alfano D and Galiero G. 2006. An outbreak of malignant catarrhal fever in Mediterranean water buffalo (*Bubalus bubalis*). *Large Animal Review* **12**: 21–24.

Matzat T, Eulenberger K and Muller H. 2015. Investigation of the presence of the etiological agents of malignant catarrhal fever in clinically healthy ruminants in zoological gardens. *Berliner Und Münchener Tierärztliche Wochenschrift* **128**: 218–24.

Michel A L and Aspeling I A. 1994. Evidence of persistent malignant catarrhal fever infection in a cow, obtained by nucleic acid hybridisation. *Journal of the South African Veterinary Association* **65**: 26–27.

Mlilo D, Mhlanga M, Mwembe R, Sisito G, Moyo B and Sibanda B. 2015. The epidemiology of malignant catarrhal fever (MCF) and contribution to cattle losses in farms around

Rhodes Matopos National Park, Zimbabwe. *Tropical Animal Health and Production* **47**: 989–94.

Modesto P, Grattarola C, Biolatti C, Varello K, Casalone C, Mandola M L, Caruso C, Dondo A, Goria M, Rocca F, Decaro N, Leonardi C, Iulini B and Acutis P L. 2015. First report of malignant catarrhal fever in a captive pudu (*Pudu puda*). *Research in Veterinary Science* **99**: 212–14.

Moore D A, Kohrs P, Baszler T, Faux C, Sathre P, Wenz J R, Eldridge L and Li H. 2010. Outbreak of malignant catarrhal fever among cattle associated with a state livestock exhibition. *Journal of American Veterinary Medical Association* **237**: 87–92.

Muller-Doblies U U, Li H, Hauser B, Adler H and Ackermann M. 1998. Field validation of laboratory tests for clinical diagnosis of sheep-associated malignant catarrhal fever. *Journal of Clinical Microbiology* **36**: 2970–72.

Mushi E Z and Rurangirwa F R. 1981. Epidemiology of bovine malignant catarrhal fevers, a review. *Veterinary Research Communication* **5**: 127–42.

O'Toole D, Taus D N, Montgomery D L, Oaks J L, Crawford T B and Li H. 2007. Intra-nasal inoculation of American bison (*Bison bison*) with OvHV-2 reliably reproduces malignant catarrhal fever. *Veterinary Pathology* **44**: 655–62.

Parihar N S, Rajya B S and Gill B S. 1975. Occurrence of malignant catarrhal fever in India. *Indian Veterinary Journal* **52**: 857–59.

Penny C. 1998. Recovery of cattle from malignant catarrhal fever. *Veterinary Record* **142**: 227.

Plowright W. 1990. Malignant catarrhal fever virus. Virus Infections of Ruminants, 3rd ed, Dinter Z and Morein B (Eds). Elsevier Science Publishers, New York, USA, pp. 123–150.

Plowright W. 1986. Malignant catarrhal fever. *Review of Scientific and Technical Off. Int. Epiz.* **5**: 897–58.

Powers J G, VanMetre D C, Collins J K, Dinsmore R P, Carman J, Patterson G, Brahmbhatt D and Callan R J. 2005. Evaluation of ovine herpesvirus type 2 infections, as detected by competitive inhibition ELISA and polymerase chain reaction assay, in dairy cattle without clinical signs of malignant catarrhal fever. *Journal of American Veterinary Medical Association* **227**: 606–11.

Premkrishnan G N, Sood R, Hemadri D, Chanu Kh V, Khandia R, Bhat S, Dimri U and Bhatia S. 2015. Cross-sectional study indicates nearly a quarter of sheep population in Karnataka state of India is infected with ovine herpesvirus 2. *Virus Disease* **26**:180–88.

Pretorius J A, Oosthuizen M C and van Vuuren M. 2008. Gammaherpesvirus carrier status of black wildebeest (*Connochaetes gnou*) in South Africa. *Journal of South African Veterinary Association* **79**: 136–41.

Reid H W and Bridgen A. 1991. Recovery of a herpesvirus from a roan antelope (*Hippotragus equinus*). *Veterinary Microbiology* **28**: 269–78.

Reid H W and Buxton D. 1989. Malignant catarrhal fever and the Gammaherpesvirinae of Bovidae. Wittmann G (Ed). Herpesvirus Diseases of Cattle, Horses, and Pigs. Kluwer Academic Publishers, Boston, pp. 116–62.

Reid H W, Buxton D, Berrie E, Pow I and Finlayson J. 1984. Malignant catarrhal fever. *Veterinary Record* **114**: 581–83.

Reid H W, Plowright W and Rowe L W. 1975. Neutralising antibody to herpesviruses derived from wildebeest and hartebeest in wild animals in East Africa. *Research in Veterinary Science* **18**: 269–73.

Reid H W, Pow I and Buxton D. 1989. Antibody to alcelaphine herpesvirus-1 (AHV-1) in hamsters experimentally infected with AHV-1 and the sheep-associated agent of malignant catarrhal fever. *Research in Veterinary Science* **47**: 383–86.

Reid H W and Van Vuuren M. 2004. Bovine malignant catarrhal fever. Coetzer J A W and Tustin R C (Eds). Infectious Diseases of Livestock. Second edition. Oxford University Press, Cape Town.

Rosbottom J, Dalziel R G, Reid H W and Stewart J P. 2002. Ovine herpesvirus 2 lytic cycle replication and capsid production. *Journal of General Virology* **83**: 2999–02.

Rossiter P B. 1981. Antibodies to malignant catarrhal fever virus in sheep sera. *Journal of Comparative Pathology* **91**: 303–11.

Russell G C, Benavides J, Grant D, Todd H, Deane D, Percival A, Thomson J, Connelly M and Haig D M. 2012. Duration of protective immunity and antibody responses in cattle immunised against alcelaphine herpesvirus-1-induced malignant catarrhal fever. *Veterinary Research* **43**: 51.

Russell G C, Scholes S F, Twomey D F, Courtenay A E, Grant D M, Lamond B, Norris D, Willoughby K, Haig D M and Stewart J P. 2014. Analysis of the genetic diversity of ovine herpesvirus 2 in samples from livestock with malignant catarrhal fever. *Veterinary Microbiology* **172**: 63–71.

Russell G C, Stewart J P and Haig D M. 2009. Malignant catarrhal fever: a review. *The Veterinary Journal* **179**: 324–35.

Sentsui H, Nishimori T, Nagai I and Nishioka N. 1996. Detection of sheep-associated malignant catarrhal fever virus antibodies by complement fixation tests. *Journal of Veterinary Medical Science* **58**: 1–5.

Stahel A B J, Baggenstos R, Engels M, Friess M and Ackermann M. 2013. Two different *Macaviruses*, ovine herpesvirus-2 and caprine herpesvirus-2, behave differently in water buffaloes than in cattle or in their respective reservoir species. *PLOS One* **8**: e83695.

Syrjala P, Saarinen H, Laine T, Kokkonen T and Veijalainen P. 2006. Malignant catarrhal fever in pigs and a genetic comparison of porcine and ruminant virus isolates in Finland. *Veterinary Record* **159**: 406–09.

Traul D L, Elias S, Taus N S, Herrmann L M, Oaks J L and Li H. 2005. A real-time PCR assay for measuring alcelaphine herpesvirus-1 DNA. *Journal of Virological Methods* **129**: 186–90.

Taus N S, Oaks J L, Gailbreath K, Traul D L, O'Toole D and Li H. 2006. Experimental aerosol infection of cattle (*Bos taurus*) with ovine herpesvirus 2 using nasal secretions from infected sheep. *Veterinary Microbiology* **116**: 29–36.

Vikoren T, Li H, Lillehaug A, Jonassen C M, Bockerman I and Handeland K. 2006. Malignant catarrhal fever in free-ranging cervids associated with OvHV-2 and CpHV-2 DNA. *Journal of Wildlife Diseases* **42**: 797–07.

Vinod Kumar N, Sreedevi B, Karthik A, Vijaya Lakshmi S, Geetha Reddy A and Sreenivasulu D. 2014. Detection of OvHV-2 from an outbreak of sheep associated malignant catarrhal fever from crossbred cattle of Southern India. *Veterinary Research Communication* **38**: 323–28.

Wan S K, Castro A E and Fulton R W. 1988. Effect of interferons on the replication of alcelaphine herpesvirus-1 of malignant catarrhal fever. *Journal of Wildlife Disease* **24**: 484–90.

Wani S A, Bhat M A, Samanta I, Buchoo B A, Ishaq S M, Pandit F, Shah G U and Buchh A S. 2004. Clinical, serological and molecular evidence of sheep-associated malignant catarrhal fever in India. *Veterinary Record* **155**: 242–44.

Wani S A, Samanta I, Pandit F, Buchoo B A, Peer F and Bhat M A. 2006. Molecular epidemiology of ovine herpesvirus type 2

infection in Kashmir, India. *Veterinary Record* **159**: 587–90.

World Organization for Animal Health (OIE). 2013a. Manual of Diagnostic Tests and Vaccines for Terrestrial Animals [online]. Paris: OIE; 2013a. Malignant catarrhal fever. Available at: http://www.oie.int/ fileadmin/Home/fr/Health_standards/tahm/ 2.04.15_MCF.pdf.

World Organization for Animal Health (OIE). 2013b. OIE Technical Disease Cards: Malignant catarrhal fever. Avaialble at http://www.oie.int/fileadmin/Home/eng/ Animal_Health_ in_the_ World/docs/pdf/Disease_cards/ MALIGNANT_CATHARRAL_FEVER.pdf. Accessed 3 June 2016.

Wambua L, Wambua P N, Ramogo A M, Domnic Mijele D and Otiende M Y. 2016. Wildebeest-associated malignant catarrhal fever: perspectives for integrated control of a lymphoproliferative disease of cattle in sub-Saharan Africa. *Archive of Virology* **161**: 1–10.

Yeruham I, David D, Brenner J, Goshen T and Perl S. 2004. Malignant catarrhal fever in a Barbary sheep (*Ammotragus lervia*). *Veterinary Record* **155**: 463–65.

Zarnke R L, Li H and Crawford T B. 2002. Serum antibody prevalence of malignant catarrhal fever viruses in seven wildlife species from Alaska. *Journal of Wildlife Diseases* **38**: 500–04.