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GAMMAHERPESVIRUS INFECTION IN SEMIDOMESTICATED REINDEER (*RANGIFER TARANDUS TARANDUS*): A CROSS-SECTIONAL, SEROLOGIC STUDY IN NORTHERN NORWAY

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ABSTRACT: Malignant catarrhal fever (MCF) is caused by a group of gammaherpesviruses that primarily affect domestic and wild ruminants. Using competitive-inhibition enzyme-linked immunosorbent assay, we screened 3,339 apparently healthy, semidomesticated reindeer (*Rangifer tarandus tarandus*) from Finnmark County, Norway, sampled during slaughter. The overall antibody prevalence was 3.5% and varied among reindeer herding districts in Finnmark (0–6.7%), the largest reindeer herding region in Norway. The risk of exposure to gammaherpesvirus (i.e., seroconversion) was significantly higher for adult reindeer than it was for calves ≤1 yr, for reindeer in east Finnmark (3.8%) compared with west Finnmark (3.3%), and with increasing population density. No evidence of disease associated with this virus was detected in reindeer sampled for this study, but because samples were collected at slaughterhouses, one cannot discard the possibility of these events happening in the field. The low antibody prevalence could indicate occasional infection of reindeer with another ruminant gammaherpesvirus or the presence of a yet-unknown, specific, low-pathogenic reindeer gammaherpesvirus. Further studies should aim at characterizing the virus circulating in reindeer and address the potential clinical impact of this virus.

Key words: cELISA, gammaherpesvirus, malignant catarrhal fever, *Ovine herpesvirus 2*, PCR, reindeer.

INTRODUCTION

The subfamily *Gammaherpesvirinae* is a large group of viruses affecting humans and other vertebrates. This subfamily of the *Herpesvirales* order, the *Herpesviridae* family, is divided into four genera: *Lymphocryptovirus*, *Rhadinovirus*, *Percavirus*, and *Macavirus*. The genus *Macavirus* contains nine formally recognized species (Davison et al., 2009), and several others have also been reported (Li et al., 2000, 2003a). Most viruses in this genus are closely related genetically and antigenically and are associated with malignant catarrhal fever (MCF) in several ruminant species. *Alcelaphine herpesvirus 1* (AlHV1) was the first MCF virus (MCFV) recognized; for which, the carrier species is the blue wildebeest (*Connochaetes taurinus*; Plowright et al., 1960), although the virus causes MCF in several other ruminant species in Africa. A major causative agent of MCF worldwide is *Ovine herpesvirus 2* (OvHV2). Domestic sheep (*Ovis aries*) are healthy carriers of OvHV2 and transmit the virus to various wild and domestic ruminant species and to domestic pigs (*Sus scrofa*; Løken et al., 1998; Syrjälä et al., 2006). *Caprine herpesvirus 2* (CpHV2) is a more recently discovered and apparently less-virulent virus, which is enzootic in domestic goats (*Capra aegagrus hircus*; Chmielewicz et al., 2001; Li et al., 2001a) and can cause MCF in moose (*Alces alces*) and various species of deer (*Cervidae*; Crawford et al., 2002; Keel et al., 2003; Li et al., 2003b; Vikoren et al., 2006). Many other MCF-associated viruses have been reported, for example in muskox (*Ovibos moschatus*; Li et al., 2003a). Included in the genus *Macavirus* are also the viruses that are not associated with MCF including, among

others, *Bovine herpesvirus 6* (BoHV6), previously known as bovine lymphotrophic herpesvirus (Rovnak et al., 1998).

Malignant catarrhal fever is usually a fatal disease that occurs in a range of animal species worldwide, with sporadic appearance of epidemics affecting domestic and wild ruminants. Nevertheless, chronic cases and recovery have been reported (Baxter et al., 1993; O'Toole et al., 1995, 1997). The disease is characterized by lymphoproliferation, vasculitis, and erosive-ulcerative lesions in the mucosa and skin (Heuschele and Reid, 2001). Typical clinical signs include fever, inappetence, ocular and nasal discharge, diarrhea, and depression. The mode of transmission of these viruses between carriers and susceptible ruminants is uncertain, but transmission via nasal secretions from sheep to other ruminants may be the most likely route for OvHV2 (Li et al., 2004).

A wide range of clinically susceptible ruminant species, including cattle (*Bos taurus*), bison (*Bison bison*), moose, reindeer (*Rangifer tarandus*), roe deer (*Capreolus capreolus*), and red deer (*Cervus elaphus*) may, instead of developing clinical MCF, establish lifelong, subclinical or latent infection (Li et al., 2001a; Zarnke et al., 2002; Vikoren et al., 2006). The mechanisms of establishment, maintenance, and reactivation of latency are not well known for the MCFV group (Ackermann, 2006).

In Norway, MCF has been reported in more than 100 cattle and an unknown number of domestic pigs each year (Løken et al., 2009), and fatalities associated to MCFV have been reported in wild cervids, including moose, roe deer, and red deer (Vikoren et al. 2006). A serosurvey of sheep and goats in Norway indicated a prevalence of antibodies to MCFV of approximately 100% in both species (Løken et al., 2009). The only two viruses belonging to the MCFV group that have been identified in Norway are OvHV2 and CpHV2. A few cases of fatal MCF have been reported in captive reindeer (Li et al., 1999; Kiupel et al., 2004), but no cases of MCF have been reported in wild or semidomesticated reindeer under normal herding conditions. However, because antibodies against gammaherpesviruses in the MCFV group have been documented in wild reindeer in southern Norway and caribou in Alaska (Zarnke et al., 2002; Vikoren et al., 2006), circulation of a gammaherpesvirus in semidomesticated reindeer is possible.

Finnmark County is the largest reindeer-herding region in Norway (Fig. 1); the estimated population was 167,811 reindeer in 2005–2006, when most of the samples in this study were obtained. With few exceptions, reindeer husbandry is an exclusive right of the indigenous Saami people in northern Norway. The reindeer are semidomesticated and range freely within defined herding districts, often demarcated by mountain ranges, fjords, rivers, or extensive fences to prevent mixing of animals between herds and districts. Reindeer are kept under seminomadic conditions, often on pastures shared with other ruminants. Contact between reindeer and livestock occurs, but the transmission of pathogenic viruses has only been reported for *Parapoxvirus* spp. (Klein and Tryland, 2005). The only *Herpesvirus* so far identified in reindeer is *Cervid herpesvirus 2*, an alphaherpesvirus potentially associated with ocular and respiratory disease (Das Neves et al., 2009; Tryland et al., 2009).

The only previous study of gammaherpesvirus infections in reindeer in Norway was carried out exclusively in wild reindeer in southern Norway on a small number of animals ($n=250$; Vikoren et al. 2006). Because most reindeer are semidomesticated, live in northern Norway, are of great economic and cultural importance for the country, and often share pastures with other ruminants, we conducted a large-scale survey to determine the prevalence of antibodies against gammaherpesvirus in reindeer in Finnmark County, Norway, and to evaluate whether the risk of being exposed to the virus was influenced by

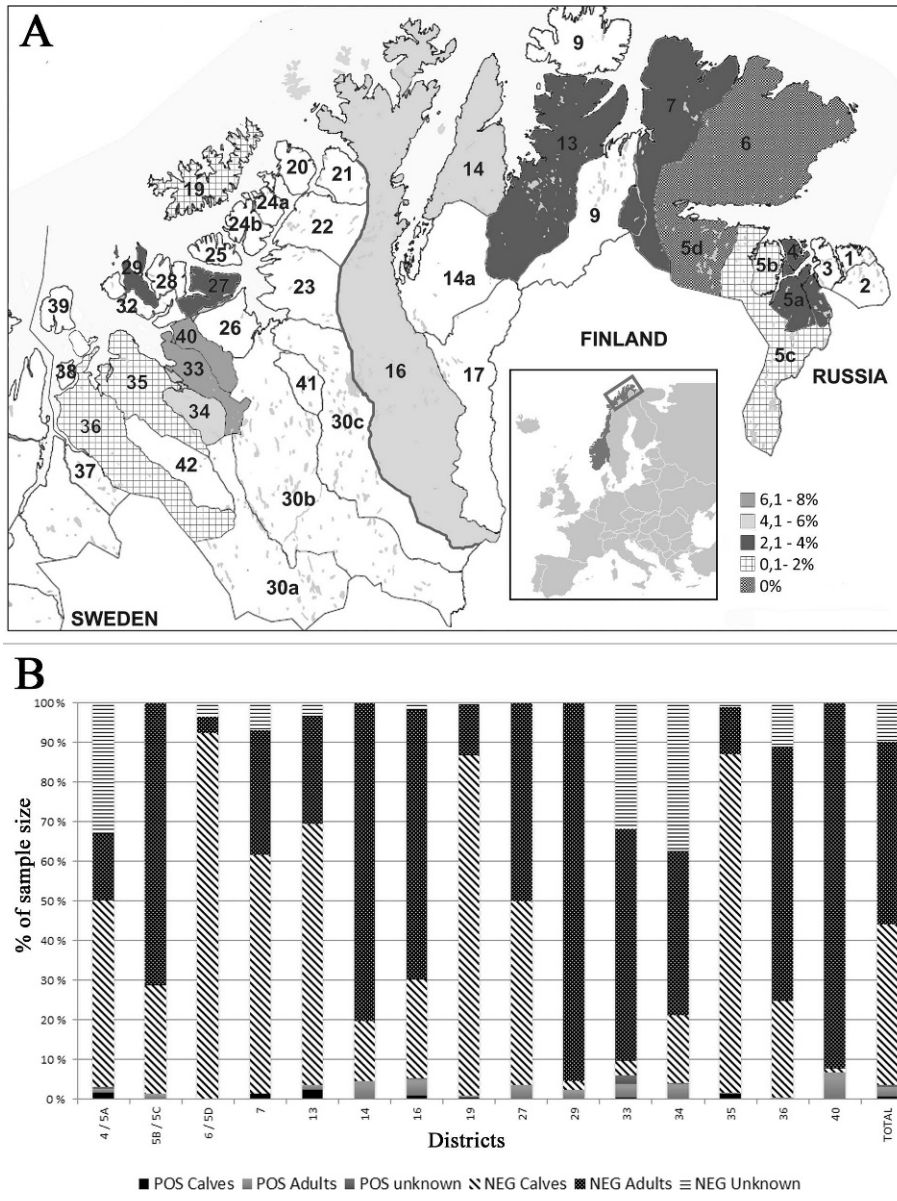

FIGURE 1. Prevalence of antibody to gammaherpesvirus in semidomesticated reindeer (*Rangifer tarandus tarandus*) categorized by reindeer-herding district in Finnmark County, Norway. (A) The map shows total antibody prevalence per husbandry district (thicker line to the left of district 16 marks the division between east and west). (B) The graph displays prevalence per district by gender and age group.

factors such as location, age, gender, carcass weight, and population density.

MATERIALS AND METHODS

Sampling

Blood samples (n=3,339), from reindeer representing 15 summer-herding districts, were collected during the winter slaughter periods from 2004 to 2006 and in 2009, in slaughterhouses in Finnmark County, Norway (Kautokeino, Karasjok, Šuoššjāvri, and Varangerbotn slaughterhouses). After centrifugation, sera and the leukocyte fraction (buffy coat) were stored separately at −20 C until tested.

Age, gender, carcass weight, district of origin, and year of sampling were obtained

from the slaughter lists. Animals were grouped into calves (≤1 yr old) and adults, according to classification by the abattoir staff. The size of the reindeer-herding districts and the number of reindeer for each district were obtained from the 2008 Reindeer Husbandry Authority Report (Reindriftsforvaltningen, 2008), and population density (number of reindeer per square kilometer) in each summer-herding district was calculated.

Serologic testing

Sera were tested for specific antibodies to the MCFV group by a direct competitive-inhibition enzyme-linked immunosorbent assay (cELISA; Li et al., 2001a, b). The cELISA test is based on a monoclonal antibody (15-A) against an epitope highly conserved among all MCFVs identified, including AlHV1, AlHV2, OvHV2, CpHV2, and *Hippotragine herpesvirus 1* (HiHV1), the virus that causes MCF in white-tailed deer (*Odocoileus virginianus*; Li et al., 2000), and the viruses carried by muskox, Nubian ibex (*Capra nubiana*), gemsbok (*Oryx gazella*) (Li et al., 2003a), and aoudad (*Ammotragus lervia*) (Li et al., 2005), respectively. Sera were scored by optical density (OD), based on the ability of each sample to inhibit binding of the 15-A monoclonal antibody to the AlHV1 antigen. Sera were considered positive if binding of the monoclonal antibody was inhibited ≥25% compared with the negative control. Samples were tested in duplicate, and the mean OD was used to evaluate the result. If duplicates were classified as one positive and one negative, they were retested. Samples with reconfirmed contrary results were considered negative.

Statistical methods

Prevalence estimates were established using the survey commands of STATA 11 (StataCorp, College Station, Texas, USA). *District* was the primary sampling unit for the model, and data were stratified according to *geographic area*. Estimates were corrected using a sample-weighting procedure: $1/n$ (sampled reindeer/N total reindeer/district).

A nonparametric kernel-density estimation of the probability density function for antibody prevalence was performed to analyze the distribution of samples classified as positive or negative and as a support for confirming the ELISA cutoff. Age was determined by the abattoir staff by visual evaluation. To avoid potential misclassifications, the relationship between age and carcass weight was verified by dividing weight into 10 quantiles, correlating it with age, and tabulating it with age and antibody prevalence.

For assessing risk factors affecting antibody prevalence, a logistic-regression model was compiled using a backward-selection procedure, adding, initially, all biologic and ecologic variables (gender, age, weight, geographic area, and population density) that could affect the response variable (prevalence) and, subsequently, removing those variables whose effects were not significant. The model assumed a binomial distribution for the binary response variable (gammaherpesvirus antibody status, positive or negative). *District* was used as a cluster variable in estimating prevalence, and sample weighting was performed.

The logistic model was compiled using the likelihood-ratio test with a threshold of $P=0.05$. A Hosmer and Lemeshow χ^2 test of the goodness-of-fit for the survey data was carried out with data grouped into 10 quantiles (Hosmer and Lemeshow, 1989). Finally, a classification table for sensitivity and specificity and a receiver operating characteristic (ROC) curve were calculated to assess the predictive qualities of the model.

RESULTS

Serology

Overall antibody prevalence was 3.5%, varying from 0% to 6.7% among reindeer-herding districts (Table 1). Prevalence was 3.8% in eastern Finnmark and 3.3% in western Finnmark, Norway. Prevalence values per herding district are depicted in Figure 1A and discriminated by age over districts in Figure 1B. After extrapolation, the tested samples represented 115,224 animals, approximately 69% of the reindeer population in Finnmark. The extrapolated overall antibody prevalence was 3.54%.

Age classification and weight classes

When carcass weight was stratified into 10 quantiles (Table 2), antibody-prevalence was low in both low- and high-weight quantiles and reached a maximum around 23–28 kg (quantiles 6–8; antibody prevalence=4.8–8.0%). Most antibody-positive adult animals had low carcass weights, whereas most positive calves had high

TABLE 1. Gammaherpesvirus antibody prevalence in semidomesticated reindeer (*Rangifer tarandus tarandus*) from Finnmark County, Norway. Results are presented by region (east and west) and by husbandry districts.

Region	District	Population density[a]	Antibody prevalence		
			N positive/total	%	95% CI[b]
East	4/5A	1.0	6/185	3.2	1.5–6.9
East	5B/C	4.2	1/73	1	0.2–7.4
East	5D/6	2.1	0/119	0.0	0–0
East	7	1.4	1/73	1	0.2–7.4
East	13	4.4	9/256	3.5	1.9–6.5
East	14	4.3	3/66	5	1.6–12.5
East	16	7.9	31/588	5.3	3.7–7.4
Subtotal east		3.3	51/1,360	3.8	2.9–4.9
West	19	4.7	3/283	1.1	0.4–3.1
West	27	14.9	16/452	3.5	2.2–5.7
West	29	6.0	1/43	2	0.4–12.1
West	33	11.2	14/234	6.0	3.6–9.8
West	34	11.5	15/362	4.1	2.5–6.7
West	35	5.5	3/224	1.3	0.5–3.9
West	36	3.9	1/202	0.5	0.1–2.8
West	40	15.9	12/179	6.7	3.9–11.4
Subtotal west		6.4	65/1,979	3.3	2.6–4.2
Grand total		4.4	116/3,339	3.5	2.9–4.1

[a] No. of animals divided by total area of each summer-pasture district.

[b] CI = confidence interval.

carcass weights for their group (Fig. 2), which could indicate some misclassifications, as seen from Table 2 for calves.

Factors associated with serologic status

The logistic-regression model showed that the following parameters had a significant effect on the risk of becoming infected with a gammaherpesvirus: region (east vs. west; odds ratio [OR]=2.215, SE=0.497, $P<0.001$), age (adults vs. calves; OR=2.190, SE=0.651, $P<0.008$), and animal density (OR=1.131, SE=0.334, $P<0.001$). Year of sampling, carcass weight, and gender were

TABLE 2. Distribution of antibody prevalence in 10 carcass-weight quantiles and classification of age (calves and adults) as conducted at the abattoir for semidomesticated reindeer (*Rangifer tarandus tarandus*) from Finnmark County, Norway. Data from 3,005 animals were used because information on weight and age were not available for all 3,339 animals.

Quantiles	Weight (kg)		No. of animals[a]		Seroprevalence		
	Mean	Min–max	Calves	Adults	*N*	%	95% CI[b]
1	13.6	9.2–15.1	300	3	4/304	1.3	0.03–2.6
2	16.5	15.4–17.5	283	15	6/298	2.0	0.4–3.6
3	18.6	17.5–19.6	262	41	6/303	2.0	0.4–3.6
4	20.4	9.6–21.2	194	104	7/298	2.3	0.6–4.1
5	22.1	21.3–23.0	137	171	8/308	2.6	0.8–4.4
6	23.7	23.0–24.5	96	198	14/294	4.8	2.3–7.2
7	25.4	24.5–26.4	65	235	14/300	4.7	2.3–7.1
8	27.4	26.4–28.4	18	283	24/301	8.0	4.9–11.0
9	29.9	28.4–31.8	15	286	9/301	3.0	1.1–4.9
10	38.2	31.9–69.7	3	296	15/99	15.2	0.5–7.5

[a] Calves = ≤1 yr old; adults = >1 yr old.

[b] CI = confidence interval; min = minimum; max = maximum.

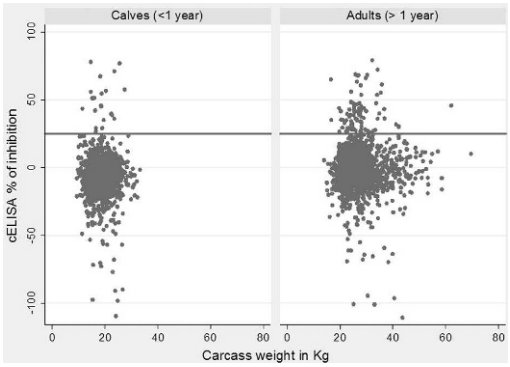

FIGURE 2. Scatterplot of the relationship between carcass weight and the percentage of inhibition by competitive-inhibition enzyme-linked immunosorbent assay (cELISA) to detect antibodies to gammaherpesvirus in sera from 3,339 semidomesticated reindeer from Finnmark County, Norway. The cELISA cutoff value (25%) is indicated by the horizontal line.

not significant and were removed from the final model. A ROC value of the model at 0.67 was calculated (data not shown). The Hosmer and Lemeshow goodness-of-fit test had a χ^2 value of 7.44 and a very satisfactory *P*-value of 0.59.

DISCUSSION

Ours is the first survey, to our knowledge, addressing gammaherpesvirus within the MCFV group by cELISA in semidomesticated reindeer, and the study documents that a relatively restricted proportion (mean=3.5%) of semidomesticated reindeer throughout the reindeer-herding districts of Finnmark County, Norway, have been exposed to gammaherpesvirus. This low antibody prevalence is consistent with previous studies on wild reindeer in southern Norway and caribou in Alaska, both revealing an antibody prevalence of 4% (Zarnke et al., 2002; Vikoren et al., 2006).

Previous studies in cattle and bison, using the same direct cELISA used in this study, revealed some sensitivity limitations and likely resulted in underestimation of true infection rates (Li et al., 2001b). Thus, the antibody prevalence found in our study may also be lower than the true infection rate. The specificity of the direct cELISA was 94% in cattle, bison, and deer (Li et al. 2001b) but was never evaluated for reindeer. A low prevalence makes the serologic assay more vulnerable to random error. However, the reliability of the direct cELISA should be considered strong in this study because of the large sample size and because all samples were tested in duplicate, although a gold standard classification test (which requires two independent survey populations and two independent laboratory assays) was not possible.

The distinct differences in antibody prevalence at the level of the reindeer-herding district (0–6.7%; Table 1) may have been influenced by differences in the proportion of calves and adults among the districts (Fig. 1B). For example, district 40 had the highest prevalence (6.7%) with 177 adults but only 2 calves, whereas district 6 had no antibody-positive animals with only 5 adults and 110 calves. The study design did not allow sampling to be completely random because reindeer owners chose which animals were sent for slaughter. This may have led to a skewed distribution of samples regarding gender, age, and health and fitness; this was accounted for by integrating the district variable into the logistic-regression model.

On a regional level, comparing east and west Finnmark, gender and age were more equally distributed. Antibody prevalence was significantly higher for reindeer in east Finnmark, Norway (3.8%), than it was for reindeer in west Finnmark (3.3%), Norway, but we cannot suggest an explanation for that difference. However, sampling had several asymmetries (e.g., age proportions), which even extrapolation models can have difficulties in compensating for and clarifying. Increasing population density was weakly correlated to a higher risk of becoming infected, but that factor may be difficult to correctly evaluate given the asymmetric sampling.

The prevalence of antibodies to gammaherpesvirus was positively correlated

with age: prevalence was less for calves (≤1 yr) than it was in older animals. The most likely explanation is that adults had a longer time to be exposed to the virus and thus become infected. However, because we were able to divide age into only two groups, we missed information on antibody prevalence throughout the life of the adult animals, which may affect the prevalence variation within the adult group as well as the prevalence associated with carcass weight.

For adult animals, antibody prevalence seemed to be higher in animals with carcass weights around 23–28 kg than it was in heavier animals (Fig. 2); the low carcass-weight animals may have been young adults or older animals in bad condition. The lack of older adults with antibodies, on the other hand, does not mean that those animals were not exposed and infected. If, after early life infection, no reactivation took place, antibody levels could fall below detection levels, as has been shown for other herpesviruses in ruminants (Kaashoek et al., 1996). Other studies have shown similar patterns with age for gammaherpesvirus carrier species, including musk ox, bighorn sheep (*Ovis canadensis*), domestic sheep, and goats (Li et al., 1996).

Ruminant species susceptible to MCF are considered not to transmit the gammaherpesvirus within their own species (O'Toole et al., 2002; Ackermann, 2006). However, if the virus causing the immune response in reindeer is species specific, horizontal virus transmission between reindeer cannot be excluded, and that would, perhaps, explain the lack of clinical symptoms.

Indirectly, increasing population density may increase density-dependent factors, such as increased infection risk. Resource limitations may influence biologic factors directly, by affecting life history traits such as body mass, survival, and recruitment (Fowler 1981; Bonenfant et al., 2009). Reduced fitness and higher stress are factors that can make reindeer more susceptible to infections and disease.

Latent or subclinical gammaherpesvirus infection is common for several ruminant species (Li et al., 1996; Powers et al., 2005; Vikoren et al., 2006). The low antibody prevalence in the apparently healthy reindeer in this study supports that. No cases of MCF have been reported in wild or semidomesticated reindeer, but clinical symptoms have been reported in captive reindeer that had contact with sheep. Other investigators have described a variety of forms of MCF among free-ranging ruminants in Norway and other countries. Moose can suffer from subacute or acute MCF, and roe deer can suffer from a peracute or acute forms of the disease (Vikoren et al. 2006). Therefore, one cannot exclude that undiscovered cases of disease and even mortality associated with an acute form of MCF, which can take 3 days in reindeer (Kiupel et al. 2004), may occur in semidomesticated reindeer. These animals were free-ranging within the limits of their districts and were normally inspected closely or handled only a few times per year, making it difficult to identify episodes of disease.

As mentioned, one can also hypothesize circulation of a specific reindeer gammaherpesvirus in Norway. In this case, the lack of clinical symptoms would fit with previously described gammaherpesviruses, which do not cause disease in their natural host (Ackermann, 2006). Low antibody prevalence can, in this case, be the result of a very low pathogenicity, causing a restricted number of outbreaks. Likewise, a new reindeer gammaherpesvirus could have lower affinity to the MCFV cELISA, which would result in underestimation of antibody prevalence.

We believe this study raises new important questions to be addressed in the future. Because it is clear that a gammaherpesvirus is circulating among reindeer in Norway, is it specific to reindeer? Do reindeer serve as a virus reservoir and source of MCFV infection in other susceptible hosts? How does this virus establish latency, and what factors may

induce reactivation episodes? What clinical symptoms, if any, are linked to this agent in reindeer? Given the widespread exposure to a gammaherpesvirus throughout the reindeer-herding districts in Finnmark, Norway, it is essential to better characterize the agent and to develop a better understanding of the effect of such infections in reindeer and other ruminant species in the Arctic regions.

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