HEMORRHAGIC AND NECROTIZING HEPATITIS ASSOCIATED WITH ADMINISTRATION OF A MODIFIED LIVE CANINE ADENOVIRUS-2 VACCINE IN A MANED WOLF (CHRYSOCYON BRACHYURUS)

Author(s): Julie Swenson, D.V.M., Kathryn Orr, D.V.M., and Gregory A. Bradley, D.V.M., Dipl. A.C.V.P.
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HEMORRHAGIC AND NECROTIZING HEPATITIS ASSOCIATED WITH ADMINISTRATION OF A MODIFIED LIVE CANINE ADENOVIRUS-2 VACCINE IN A MANED WOLF (CHRYSOCYON BRACHYURUS)


Abstract: A 15-yr-old, female, maned wolf (Chrysocyon brachyurus) was euthanized after presenting semicomatose with severe, uncontrolled frank hemorrhage from her rectum 6 days following a routine physical examination and vaccination. Histopathology indicated severe hemorrhagic and necrotizing hepatitis with intranuclear basophilic inclusion bodies in the liver that were thought to be consistent with adenoviral infection. Further classification by polymerase chain reaction, immunohistochemical staining, virus isolation, and electron microscopy confirmed the etiologic agent to be canine adenovirus-2. A representative sample of the vaccine that had been used was submitted and sequenced along with the virus isolated from the maned wolf. The sequencing of the etiologic agent that had been isolated from the maned wolf was determined to be the same as the strain of virus used in the production of the modified live vaccine that had been administered 6 days prior to death. From this information, the diagnosis of vaccine-induced adenoviral hepatitis was made. This is the first confirmed case of vaccine-induced canine adenoviral hepatitis in a maned wolf.

Key words: Adenoviral hepatitis, Chrysocyon brachyurus, maned wolf, modified live virus vaccine, vaccine-induced.

INTRODUCTION

Maned wolves (Chrysocyon brachyurus) are an omnivorous member of the Canidae family distributed in the scrub forests and grasslands of central South America. According to the International Union for Conservation of Nature’s (IUCN) Red List of Threatened Species, the maned wolf is considered to be near threatened. The most significant threat to their survival in the wild is habitat loss, primarily caused by conversion of habitat into agricultural land. In addition, the species is also threatened by direct interactions with humans, including vehicular trauma and removal by farmers to protect livestock, as well as by the spread of infectious diseases from domestic canids.

Infectious diseases are also of concern to the captive population of maned wolves. Infectious diseases have been reported as the second leading cause of death in captivity. Of particular importance, because of the potential to avoid infection by use of vaccination, are the infectious canine viral diseases. Deaths of maned wolves in zoologic institutions have been attributed to many domestic canine viral diseases including canine distemper virus (CDV), canine parvovirus (CPV), and canine adenovirus (CAV), specifically canine adenovirus 1 (CAV-1). In one report, CDV and CPV infections were the most frequent infections seen in captive maned wolves and were responsible for 4% of captive maned wolf deaths from 1980 to 1997.

Based on the importance of these diseases in the mortality rates of captive maned wolves, many zoologic institutions choose vaccination as a means to decrease the risk to the collection animals. Currently, the maned-wolf species survival plan (SSP) recommends that captive maned wolves be vaccinated against CDV, CPV, and rabies.

In 2009, the Phoenix Zoo housed a single nonbreeding pair of maned wolves. The male was castrated because of neurologic abnormalities noted at birth. The female was intact, but geriatric at 15 yr of age and likely past breeding age. Both animals were vaccinated yearly for rabies using a killed rabies vaccine (Imrab® 3, Merial Inc., Athens, Georgia 30601, USA) and CDV using either a recombinant canary pox-vectored CDV vaccine (Purevax® Ferret Distemper, Merial Inc.) or, prior to the availability of the Purevax vaccine, a single-agent modified live CDV vaccine (Galaxy D®, Schering-Plough Ani-
CASE REPORT

A 15-yr-old, female, maned wolf (Chrysocyon brachyurus) presented to the veterinary staff of the Animal Care Center at the Phoenix Zoo for emergency treatment. The wolf was noted to be nonresponsive by the keepers at morning rounds. Prior history of this animal included a hind limb amputation due to a nonhealing fracture of the femur 5 yr prior, renal disease of 4-yr duration, cardiac disease of 2-yr duration, and a fracture of the mandible that had occurred 11 mo prior.

Six days prior to becoming nonresponsive, the animal had been evaluated by the veterinary staff for a recheck of the previously fractured mandible. The animal was immobilized via dart with a mixture of ketamine hydrochloride (Ketaset®, Fort Dodge Laboratories; 4 mg/kg i.m.) and medetomidine hydrochloride (Domitor®, Pfizer Animal Health, Exton, Pennsylvania 19341, USA; 0.065 mg/kg i.m.), and then maintained on isoflurane (IsoFlo®, Abbott Animal Health, Abbott Park, Illinois 60064, USA) via mask during the examination. Physical examination findings included a fractured upper carnassial tooth with extensive undermining of the posterior root, an irregular heart rhythm, underweight body condition, and a swollen vulva likely associated with estrus. The previously fractured mandible felt stable on palpation.

Blood was drawn from a cephalic vein and submitted for a complete blood count (CBC), serum chemistry panel, and coccidioidomycosis titer. Dorsoventral and lateral radiographs were taken of the chest and abdomen with no significant findings. The fractured tooth was manually extracted. The wolf was given 1,300 ml (65 ml/kg) of lactated Ringer’s solution, 1,200,000 IU of a combination penicillin product (Twin Pen® long-acting penicillin, Agrilabs, St. Joseph, Missouri 64505, USA; 150,000 units penicillin G benzathine and 150,000 units penicillin G procaine per ml, 60,000 IU/kg s.c.), and was vaccinated for rabies (Imrab 3, Merial, Inc.; 1 ml s.c.) and for canine distemper using a combination vaccine labeled for use against CDV, canine adenovirus type 2 (CAV-2), canine parainfluenza, and CPV (Duramune Max 5, Boehringer Ingelheim Vetmedica, Inc., St. Joseph, Missouri 64506, USA; 1 ml s.c.). Recovery was uneventful.

Blood work results were compared with normal values from the International Species Information System (ISIS). The CBC showed no significant findings. Serum chemistry panel findings included mild hypoalbuminemia (albumin = 2.5 g/dl; normal range, 2.8–3.4 g/dl) and hypoproteinemia (total protein = 5.7 g/dl; normal range, 6.0–7.2 g/dl). This was suspected to be secondary to the previously diagnosed renal disease. An elevated blood urea nitrogen was present (BUN = 74 mg/dl; normal range, 18–34 mg/dl), which was also consistent with a previous diagnosis of renal disease, but could have been secondary to dehydration as well since a concomitant rise in creatinine was not noted. A mild stress hyperglycemia (glucose = 174 mg/dl; normal range, 82–132 mg/dl) was also present. The coccidioidomycosis titer was a weak positive with an immunodiffusion titer of 1:2. An in-house fecal with direct microscopic examination and flotation exam was negative.

The animal was returned to the exhibit for further monitoring by the keeper. Doxycycline (Diamondback Drugs, Scottsdale, Arizona 85257, USA; 5 mg/kg, 100 mg p.o. s.i.d. × 10 days) was started to decrease the risk of secondary bacteremia following the tooth extraction. Over the next several days, the animal continued to decline and began refusing all diet. Six days following the exam, the maned wolf was found on exhibit semicomatose at morning check and was brought to the Animal Care Center for another examination.

At presentation, the animal was hypothermic (31.6°C), nonresponsive, with pale mucous membranes and a delayed capillary refill time. A large amount of frank blood and hemorrhagic fluid was leaking from the rectum. Because of an inability to stop the excessive bleeding from the rectum despite emergency treatment for shock and hypothermia, humane euthanasia was determined to be the most appropriate course.
Blood was taken prior to euthanasia for a CBC and serum chemistry panel. Results were compared with ISIS normal ranges as described previously. Multiple abnormalities were noted as elevated, including alkaline phosphatase (ALKP = 724 IU/L; normal range, 0–84 IU/L), alanine aminotransferase (ALT = 11,814 IU/L; normal range, 12–178 IU/L), and aspartate aminotransferase (AST = 10,622 IU/L; normal range, 13–75 IU/L), indicating likely acute hepatic failure. Total bilirubin (Tbili = 3 mg/dl; normal range, 0.1–0.5 mg/dl), direct bilirubin (Dbili = 2.4 mg/dl; normal range, 0–0.2 mg/dl), and indirect bilirubin (Ibili = 0.6 mg/dl; normal range, 0–0.4 mg/dl) were also elevated, which was also likely due to hepatic failure and/or biliary tree obstruction. The previously noted hypoproteinemia had worsened (total protein = 5.2 g/dl) with both a hypoalbuminemia (Alb = 2.3 g/dl) and hypoglobulinemia (Glob = 2.9 g/dl; normal range, 3.0–4.0). The hypoproteinemias were considered to be attributed to decreased production secondary to hepatic failure and/or increased loss. The increased loss may have been through the abnormalities noted in the gastrointestinal tract on physical exam (severe hemorrhagic diarrhea/discharge) or the previously diagnosed renal disease or, more likely, a combination of both. There was a severe hyperphosphatemia (Phos = 14.9 mg/dl; normal range, 3.5–5.1 mg/dl) likely due to worsening of the previously diagnosed renal disease. The previous azotemia had also worsened since the last exam, with both an elevated BUN (BUN = 83 mg/dl) and an elevated creatinine (Crea = 3.9 mg/dl; normal range, 1.2–1.8 mg/dl), likely caused by either worsening renal disease and/or dehydration. Last, a severe hypoglycemia (Glu = 29 mg/dl; normal range, 82–132 mg/dl) was also noted and attributed to the state of shock the animal had been presented in, the previous anorexia, as well as the apparent hepatic failure.

On gross necropsy, there was significant muscle wasting in spite of adequate fat. The abdomen was full of serosanguinous fluid (Fig. 1). The liver was firm with numerous multicolored foci approximately 2–3 mm in diameter (Fig. 1).
gastrointestinal tract, there were mucosal hemor-
 rhages noted from the level of the duodenum
 through the gastrointestinal tract down to the
 level of the rectum (Fig. 2). Both the bladder and
 the kidneys contained multiple small calculi, and
 both kidneys contained areas of cystic structures.
 Concerning the reproductive tract, both ovaries
 contained multiple cystic structures, and an
 intrauterine mass was noted in one uterine horn.
 A firm white nodule was noted in one thyroid
gland, and the left adrenal gland appeared mildly
 enlarged compared with the right. The previously
 fractured mandible was unstable at the time of
 necropsy. Samples from multiple organ tissues
 were submitted in formalin to the diagnostic lab
 at the University of Arizona for histopathology.

 On histopathology, the heart had multifocal
 areas of fibrosis in the myocardium and large
 mural deposits of amyloid in the coronary arter-
 ies. There was mild myxomatous degeneration of
 the valves. One adrenal gland had a focus of
cortical nodular hyperplasia. The ovaries con-
tained multiple cysts filled with pale eosinophilic
 fluid and lined by low cuboidal epithelium. There
 were scattered corpora lutea. The serosal and
 submucosal vessels of the colon were congested,
as were the mucosal blood vessels of the small
 intestines.

 There was evidence of mild, diffuse glomerulo-
nephritis with a few cystic, dilated tubules in the
 medulla containing a small amount of proteinic
 fluid and a mild increase in cellularity in the
 glomeruli. Most of the architecture was replaced
 by dense fibrous connective tissue containing
 isolated blood vessels and a few remnant glomer-
 uli. There was also a focal chronic infarct in the
cortex of the kidney.

 The cervical lymph node that was submitted
 was almost entirely effaced by a nodular neoplas-
tic mass consistent with squamous cell carcinoma.
The mass was composed of small nests and loose
 sheets of polygonal-shaped epithelial cells with
 large vesicular nuclei and prominent nucleoli.
 These epithelial cells had a moderate amount of
 eosinophilic cytoplasm and were frequently un-
dergoing intracytoplasmic keratinization. The

Figure 2. Gross necropsy photograph showing extensive hemorrhage within the intestinal tract.
primary tumor was unable to be confirmed as the previously fractured jaw was not submitted with the histopathologic samples; however, as no other primary tumor site was found, the lymph node neoplasia was suspected to be secondary to a primary tumor of the lower mandible, which may have been related to the non-union of the jaw fracture.

There was marked centrolobular necrosis with sinusoidal disruption and pooling of blood (hemorrhage) in the liver. Affected areas were infiltrated by small numbers of neutrophils. Many of the degenerating hepatocytes and hepatocytes in the adjacent intact parenchyma contained large bluish intranuclear inclusion bodies (Fig. 3). These varied from filling the entire nucleus with a thin rim of marginated chromatin to smaller central inclusion with a surrounding clear halo. These findings were consistent with hemorrhagic and necrotizing hepatitis. The intranuclear basophilic inclusion bodies were suspected to be of viral etiology, with adenovirus being the primary differential.

To better characterize the viral hepatitis, additional testing was performed. Polymerase chain reaction (PCR) testing performed at Colorado State University was negative for CAV types 1 and 2 as well as negative for canine herpesvirus. Immunohistochemistry was performed at Michigan State University, which confirmed the presence of canine adenoviral antigens in the tissues. The stained sections of liver showed multifocal, strong, diffuse and stippled, positive, intranuclear labeling for adenovirus antigen. Virus isolation from the liver was performed at Colorado State University, and electron microscopy of the virus isolated was performed at Wyoming Veterinary Diagnostic Laboratory (Fig. 4). Both of these tests also identified the virus as an adenovirus. A series of in-house PCR testing was performed at the University of Arizona including CAV type 1 and 2. The PCR was positive on the fluid from the Wyoming virus isolation (VI). This PCR product from the VI fluid was sequenced at the University of Arizona Genetics Core Facility. A BLAST sequence library search revealed that the product

Figure 3. Histopathology slide of the liver showing intranuclear inclusion bodies. H&E stain, ×400.
matched most closely with the sequence for CAV-2 strain Toronto A26/61, having 99% homology.

Fort Dodge was contacted to determine what strain of CAV-2 is used in the Duramune MLV vaccine. Fort Dodge was able to confirm that the same strain was used in all lot numbers of their Duramune vaccine. A representative vaccine sample was submitted to the Arizona Veterinary Diagnostic Laboratory for virus sequencing. The sequence of the vaccine was confirmed to have 95% homology to the same strain that was sequenced from the PCR product from the virus isolated from the maned wolf liver, CAV-2 strain Toronto A26/61. From this information, the diagnosis of vaccine-induced canine hepatitis was made.

**DISCUSSION**

This is the first reported case of vaccine-associated adenoviral hepatitis in a maned wolf. Infectious diseases are common in captive maned wolves, with the International Studbook for Maned Wolves listing infectious diseases as the second most common cause of death in captivity. Of the infectious diseases reported in captive maned wolves from 1980 to 1997, CDV and CPV were the most frequent infectious agents. Because of this propensity, many zoologic institutions regularly vaccinate their maned wolf population using combination vaccines that protect against multiple agents including CDV and CPV.

The maned wolf SSP currently recommends a regular vaccination protocol for all maned wolves. This protocol includes vaccination against rabies, CDV, and CPV. The recommended rabies vaccination is a killed vaccine. The recommended CDV vaccine is the Merial Purevax ferret distemper vaccine, which is a recombinant canary pox vector vaccine that is licensed for use in domestic ferrets. The recommendation for CPV vaccination is to use a killed feline panleukopenia virus vaccine in young pups, owing to the possibility of vaccine-induced disease in immune-suppressed juveniles, and then to switch to Duramune Max Pv (Fort Dodge Animal Health), which is an MLV vaccine for protection against CPV, once the pups are greater than 6 mo of age.

If species-specific vaccine safety information is not known, recommendations for vaccinating exotic species traditionally include the use of killed or inert vaccines. As the agents within the vaccines are no longer living, there is less risk of disease development in an animal for which the vaccine was not specifically developed. The main disadvantage to inert or killed vaccines relates to the amount of immune stimulation they trigger in the body. Since the infectious agent is chemically inactive, the immune stimulation that occurs is significantly less than that produced with live or modified live vaccines. The decrease in immune stimulation often leads to a decrease in the length of protection offered by the vaccine.

When looking at CDV vaccination in exotic carnivores, Montali et al. used a titer level of 1:100 in their study as a protective level as that is the standard for indicating immunity against CDV in domestic dogs. Protocol at the National Zoological Park, Washington, D.C., prior to the start of the study had been to vaccinate maned wolves using a killed CDV vaccine (produced specifically for use at the National Zoological Park) at 2-wk intervals 2 or 3 times after they reached 10 wk of age followed by annual or semiannual boosters. Eight maned wolves that had been previously vaccinated according to this protocol were tested to determine the efficacy of the vaccine in producing an immune response. All eight animals had serum titers of <1:25 despite multiple vaccinations, indicating a lack of protective response secondary to vaccination with a killed vaccine.

Modified live virus (MLV) vaccines have been developed to combat this lack of protective response in domestic species. MLV vaccines have been modified to no longer be virulent in the target species; however, they retain enough of the
original virus particles to stimulate a more substantial immune response in the host than most killed vaccines. Although MLV vaccines have shown promise in improving the immune response compared with killed virus vaccines, there are additional problems with their use in nonlabeled species. In exotic carnivores, these MLV vaccines have been shown to be still capable of reverting to virulence under certain situations resulting in vaccine-induced disease. Because of this possibility, careful consideration must be used in each individual exotic species to determine whether or not an MLV vaccine can be considered safe.

MLV vaccines have been reported to be safe and effective in maned wolves in multiple studies. Because of the low titer findings in the animals vaccinated with a killed vaccine at the National Zoological Park, Montali et al. vaccinates five maned wolves with an MLV CDV vaccine one to four times and retested vaccine titers within 2 to 6 mo of each vaccination. Although all the animals required multiple vaccinations to reach titers >1:100 (between 2 and 3 vaccinations were required), all five animals did reach titers >1:100, which would be consistent with a protective titer in domestic dogs. No adverse reactions to vaccination with the MLV vaccine were seen.

In the Montali et al. study, the MLV vaccine used contained only one disease agent, CDV. Multivalent vaccines are frequently used in veterinary medicine in order to vaccinate for multiple potential diseases at the same time. There is some concern that immune suppression secondary to the use of multivalent vaccines, and the increased stimulation to the immune system, could allow one of the MLV components to regain virulence. Kaufman et al. demonstrated that immunosuppression secondary to vaccination with MLV vaccines in ferrets does in fact occur. Krakowka et al. demonstrated a return to virulence in domestic dogs vaccinated with a multivalent vaccine when immune suppressed by exposure to CPV post vaccination. Both researchers concluded that immune suppression allowed for a return to virulence of a component of the multivalent vaccine. Whether or not a multivalent vaccine can cause significant enough immune suppression on its own to allow for a reversion to virulence of one of the components has still not been confirmed; however, it is a consideration particularly in young or older animals whose immune systems may not be functioning as well as their mature, nongeriatric counterparts.

In addition to single-agent MLV vaccines, multivalent combination MLV vaccines have been reported as safe in maned wolves. In a study by Maia and Gouveia, 47 maned wolves of varying ages were vaccinated with either Duramune DA,Pv,Lci (Fort Dodge Laboratories, Inc.) or Eurican (Merial Laboratories, Inc., Lyon, France) modified live combination vaccines. The Duramune DA,Pv,Lci vaccine from Fort Dodge is used to vaccinate against CDV, CPV, CAV-2, and two serovars of leptospirosis. Two different Eurican vaccines were used from Merial: CHPL and CHPLR. Eurican CHPL vaccinates against CDV, CPV, CAV-2, and two serovars of leptospirosis. Eurican CHPLR vaccinates against the same diseases as Eurican CHPL with the addition of rabies virus. There were no negative reactions seen following yearly single-dose vaccinations for adults and an initial 3-dose series of vaccinations for pups in the study. All 47 animals were monitored for 24 mo post vaccination, and no clinical evidence of disease was seen within that time frame. Based on their findings, the study recommended the use of modified live combination vaccines in maned wolves.

The animal in this case report had been vaccinated multiple times previously with the single-agent MLV vaccine Galaxy D with no negative effects noted. However, potentially due to her suspected state of significant immune suppression from advanced age and multiple concurrent diseases, including renal disease, cardiac disease, and metastatic squamous cell carcinoma, as well as the use of a multivalent MLV vaccine rather than a single-agent MLV vaccine like Galaxy D, the modified live adenovirus-2 used in the vaccine was competent enough to cause active adenoviral infection in this animal. This was confirmed by classic gross and histopathologic lesions, immunohistochemistry, virus isolation, and electron microscopy.

Adenoviral infection in domestic dogs is seen in two main forms: CAV-1 and CAV-2. CAV-1 infection leads to hepatic disease referred to as infectious canine hepatitis (ICH). ICH causes a large variety of nonspecific clinical signs including fever, tachycardia, anorexia, thirst, conjunctivitis, serous ocularonasal discharge, vomiting, subcutaneous edema, and rarely central nervous system signs. A clinical suspicion for ICH usually is reached because of the abrupt onset of bleeding that occurs secondary to clotting abnormalities that arise from the underlying disseminated intravascular coagulation that occurs. Incubation is typically 4–9 days, and mortality rates in
domestic dogs can be high, especially in young animals. Lesions seen on postmortem examination include petechia and evidence of hemorrhage along the gastric serosa, lymph nodes, thymus, pancreas, and subcutaneous tissues, along with hepatocellular necrosis and characteristic intranuclear inclusion bodies in the liver.\textsuperscript{3,7,18,25} Vaccination with modified live strains of CAV-1 has been associated with ocular abnormalities including corneal edema and uveitis.\textsuperscript{19,21}

Infection with CAV-2 can lead to the clinical presentation of infectious tracheobronchitis, which includes mild respiratory signs as the primary clinical sign noted in affected dogs. As a vaccine component, however, CAV-2 has minimal associated side effects. Cross-protection occurs with antibodies to homologous strains of adenoviruses. Since CAV-2 cross-protects for CAV-1 but is not associated with the significant side effects seen following vaccination with CAV-1, it is typically the component that is used in vaccine production for protection against both forms of canine adenoviral disease.\textsuperscript{3,7,18,25}

In the case report presented here, many of the clinicopathologic changes common in cases of domestic dogs diagnosed with adenoviral infections were also present in the maned wolf. Severe, sudden onset of uncontrolled bleeding was noted 6 days post vaccination, which correlates well with the typical incubation length for adenoviral disease. On gross necropsy, hemorrhage was noted throughout the gastrointestinal tract, and the abdomen was full of serosanguinous ascites. The liver appeared grossly abnormal. On histopathology, hepatocellular necrosis was confirmed along with visualization of characteristic intranuclear inclusion bodies within the hepatocytes.

Diagnosis of adenoviral disease in domestic dogs is typically confirmed by virus isolation, immunofluorescence, and/or the presence of characteristic intranuclear inclusion bodies on histopathologic examination.\textsuperscript{3,7,18,25} Although the clinical signs and pathologic findings, including the intranuclear inclusion bodies, were consistent with adenoviral infection, the decision was made to pursue further confirmation owing to the suspicion that this might be a vaccine-induced disease in this animal. To this end, virus isolation with electron microscopy was performed along with immunohistochemistry. Both tests confirmed the presence of canine adenoviral antigens in the tissues.

It is unknown why the initial PCR test for CAV was negative on liver tissue. Virus isolation from the same tissue did in fact grow an adenovirus. In addition, adenovirus was localized to the lesions by immunohistochemistry performed on the formalin-fixed tissues. The product from the adenovirus PCR on the VI fluid was sequenced and compared with the sequence of the virus strain used in production of the vaccine. Because of the close homology of the two products, a diagnosis of vaccine-induced canine hepatitis was made.

Vaccine-induced disease is a significant concern in captive populations of wild carnivores. Potential causes for induction of disease following vaccination with an MLV vaccine in exotic carnivores include immune suppression of the host as a result of environmental considerations (i.e., age, social status, etc.) vs. immune suppression of the host as a result of other infectious disease processes, such as was seen in the study by Krakowka et al.\textsuperscript{12} Although no evidence was seen of a secondary infectious process that could have led to immune suppression in this animal following vaccination, the current health status of the individual was likely a state of immune suppression prior to vaccination as a result of the multiple compounding diseases that were present. These included chronic renal disease, cardiac disease, and a nonhealing mandibular fracture suspected to be the primary site for the metastatic squamous cell carcinoma. It is suspected that these multiple diseases, in addition to the animals advanced age, likely resulted in significant enough immune suppression to allow for a return to virulence of the adenoviral component of the MLV vaccine.

Based on the findings of this case and previous information concerning vaccine-induced disease in zoo animals, vaccination of maned wolves with MLV vaccines, particularly geriatric or immune suppressed animals, should be done with extreme caution and only if the risk is deemed high for natural exposure, and killed or recombinant vaccine products are not available. If MLV vaccines must be used, single-agent vaccines would likely be preferable to multivalent vaccines because of the decreased immune suppression seen when a single-agent vaccine is used.

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LITERATURE CITED


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