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Canine Distemper Spillover in Domestic Dogs from Urban Wildlife

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KEYWORDS

- Canine distemper virus genetics • Transmission
- Pathogenicity • Wildlife • Vaccines

Canine distemper virus (CDV) causes a major disease of domestic dogs that develops as a serious systemic infection in unvaccinated or improperly vaccinated dogs.¹ Domesticated dogs are the main reservoir of CDV, which is a multihost pathogen. This virus of the genus *Morbillivirus* in the family Paramyxoviridae occurs in other carnivorous species including all members of the Canidae (fox, coyote, wolf) and Mustelidae families (ferret, skunk, badger, mink, weasel, otter) and in some members of the Procyonidae (raccoon, lesser panda, kinkajou), Hyaenidae (hyenas), Ursidae (bear), and Viverridae (palm civet) families.² Canine distemper also has been reported in the Felidae family (lions, tigers) and marine mammals (river otters).^{3–9} In the United States, spillover of infection from domestic dogs with spillback from raccoons, which may serve as intermediate hosts,¹⁰ and other susceptible wildlife is well documented.¹¹ The spread and incidences of CDV epidemics in dogs and wildlife here and worldwide are increasing due to the rise in dog populations associated with growing human populations and widespread urbanization.

VIRUS PROPERTIES

CDV is a small, enveloped, nonsegmented single-stranded, negative-sense RNA virus (about 15,000 bases long) that encodes 6 structural proteins: the nucleocapsid (N) protein, 2 transcriptase-associated proteins (phosphoprotein P and large protein L), the envelope stabilizing matrix (M) protein, and 2 transmembrane glycoproteins embedded in the viral envelope, which are important immunogens of CDV, the hemagglutinin (H) and fusion (F) proteins.¹² CDV has an affinity for many cell types including epithelial, lymphocytic, neuroendocrine, and mesenchymal cells. The viral

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attachment factor, protein H, controls the host specificity and cell tropism and induces the majority of CVD-neutralizing antibodies.^{13–15} Humoral immunity due to the presence of neutralizing antibodies to CDV, elicited by either immunization or natural infection, is detectable within 10 to 14 days, providing protection against infection or reinfection. Viral infection of a susceptible host cell begins when the H protein of CDV binds to the signaling lymphocyte activation molecule (SLAM; CD150) receptor site of the cell.¹⁶ A conformational change of the H protein occurs on binding, which signals the F protein-mediated fusion of the CDV envelope with the host cell membrane. Binding between SLAM and the H protein is a high-affinity, host-virus specific interaction.^{14,17} The H and F glycoproteins may mediate fusion activity between neighboring cells leading to syncytium formation and, ultimately, to cell lysis.¹⁶ Host cell surface sites CD46 and a heparin-like receptor have been suggested as putative H protein receptors in SLAM-negative cells, but strong supporting evidence is lacking at this time.^{18,19}

DISEASE

Distemper is a highly contagious disease that poses a threat mainly to concentrated populations of previously unexposed or unvaccinated, susceptible species. In these populations, distemper is almost always fatal. The disease is complex in that it presents varying clinical symptoms and may run varying clinical courses. Outcomes of CDV infection range from complete recovery to persistent disease to death depending on the age and immune status of the animal infected.¹² Robustness of the humoral immune response correlates with the disease outcome. Canine distemper virus replicates initially in the lymphoid tissues of the upper respiratory tract followed by immune-mediated progression of the disease over a period of 1 to 2 weeks. A diphasic fever is a characteristic feature of the disease, occurring 7 or 8 days after infection, that drops rapidly and again climbs by day 11 or 12. Clinical signs of distemper are often unapparent or initially mild during this time, and disease is characterized by mucopurulent oculonasal discharges, conjunctivitis, respiratory distress, anorexia, vomiting, diarrhea and dehydration, and cutaneous rash. Anti-CDV antibody titers that develop 10 to 14 days postinfection contribute to viral elimination and recovery when a vigorous humoral response occurs characterized by highly specific anti-H protein antibodies. Cell-mediated immunity also plays a role in recovery from CDV infection, and a strong T-cell-mediated CDV-specific immune response causes viral elimination in convalescing dogs.²⁰

Weak humoral and cell-mediated responses lead to systemic intracellular spread of virus to the epithelial cells of the gastrointestinal and urinary tracts, skin, and the endocrine and central nervous systems causing direct virus-mediated damage. Additional clinical signs that may occur are localized twitching, ascending paresis/paralysis, and/or convulsions. Hyperkeratosis of the foot pads and nose may be seen. The infection may either prove fatal or persist resulting in subacute or chronic central nervous system (CNS) signs. Delayed lymphocytolysis correlates with persistence of CDV in the CNS.²¹ Within 1 to 3 weeks after recovery from gastrointestinal and respiratory signs, depression and neurologic signs indicating CNS involvement are often evident, although sometimes neurologic impairment does not occur until months later, even without a history of systemic signs.¹² Dogs that recover from acute disease with persistent infection may shed virus in urine and through the skin on the foot pads. These animals should be isolated from contact with unvaccinated animals, especially puppies.

DIAGNOSIS

Canine distemper infection can be challenging to diagnose because many diseases can cause symptoms resembling canine distemper. The respiratory symptoms of canine distemper may be mistaken as canine respiratory disease complex. Canine parvovirus, coronavirus, bacterial, and internal parasite infections should be ruled out as causes of vomiting and diarrhea. Often, CDV-infected animals that exhibit neurologic signs are mistaken as having rabies. Neurologic symptoms must be differentiated from other infections, trauma, and ingestion of toxins. Vaccination history of the affected animal, clinical symptoms, and laboratory testing support a probable diagnosis of CDV infection. State and commercial veterinary diagnostic laboratories offer testing for canine distemper and advise practitioners on appropriate specimens to submit, tests to order and the limitations of test results given the circumstances of each individual case submitted. The following 5 diagnostic methods are commonly offered:

- IFA (immunofluorescence assay) of antemortem specimens detects CDV inclusion bodies in cells from conjunctival scrapes, buffy coat (peripheral blood lymphocytes [PBL]), urine sediment, traumatic bladder catheterization, transtracheal washes, cerebrospinal fluid, and biopsies of footpads or nose when callusing is present. This test is most reliable within the first 3 weeks of infection in acute disease. Virus often persists in the CNS for 60 days or longer.
- Serology for the following:
 - IgM, present as serum antibodies, is measured by enzyme-linked immunosorbent assay (ELISA). A high IgM titer indicates recent infection or recent vaccination and may last for 3 months after detection.
 - IgG serum antibodies are measured as serial titers on 2 samples taken 14 days apart to detect rising titers. In unvaccinated dogs, rising titers indicate CDV infection. A greater than 4-fold titer increase indicates infection even in recently vaccinated dogs.
 - Distemper antibodies in cerebrospinal fluid (CSF) are highly indicative of distemper infection. Vaccine-induced antibodies do not cross the blood-brain barrier into the CSF fluid.
- Cell culture may not yield timely results as virus isolation may take up to 3 weeks. However, newer cell lines, Vero cells expressing the canine SLAM receptor (Vero.DogSLAMtag or Vero-DST cells), can provide results in few days.^{22,23} Specimen quality and origin are other limitations of this technique.
- Reverse transcription–polymerase chain reaction (RT-PCR) can detect virus in respiratory secretions, CSF, feces, urine, whole blood, and conjunctival or ocular samples. A negative result does not rule out distemper. Immunization for CDV with modified live virus (MLV) vaccine interferes with PCR testing for approximately 3 to 4 weeks, creating a false-positive result.
- Necropsy/histopathology of post-mortem specimens including spleen, tonsil, lymph node, stomach, kidney, lung, duodenum, bladder, and brain tissues are processed with conventional stains, IFA, or immunohistochemistry (IHC).

Diagnostic testing for CDV and anti-CDV antibodies presents a special challenge because results do not distinguish between naturally acquired CDV disease (wild-type strains), infection with attenuated virus vaccine strains used in modified-live (MLV) vaccines, or immune response due to the recombinant, virus-vectored vaccine. Canine distemper viruses are of a single serotype (monotypic), thus the various genotypes cannot be distinguished using classic serologic techniques with polyclonal

antibodies.¹⁵ Use of monoclonal antibodies to differentiate recent field isolates from older field isolates and vaccine strains of CDV has met with limited success and the reagents developed are not widely available.^{24,25} Currently, 2 in-clinic serologic test kits are licensed for sale in the United States, the TiterCHEK CDV/CPV ELISA-based assay (Synbiotics, San Diego, CA, USA) and the ImmunoComb Canine VacciCheck (Modern Veterinary Products, Coral Gables, FL, USA).²⁶ Both kits evaluate an immune response to CDV from vaccination or infection but neither differentiates between titers to the vaccine or infection with wild-type CDV strains.

Licensed RT-PCR kits for detection of CDV are not available in the United States. Among the commercial and state veterinary diagnostic laboratories that perform RT-PCR testing of their own design to detect CDV, one of the challenges is differentiating between vaccine strains and wild-type isolates that may be present concurrently in samples. The RT-PCR assays are typically designed to amplify a portion of the H, F, M, or N gene to verify the presence of CDV RNA in specimens. Absolute identification of strains and differentiation between vaccine and wild-type CDV may be performed by sequence analysis of the cloned RT-PCR amplified H gene region.¹⁰ Rapid methods have been designed to differentiate CDV strains as either wild-type or vaccine derived without the need to perform time-consuming gene sequencing. Two popular methods are based on RT-PCR of a specific CDV structural protein genes followed either by a restriction fragment length polymorphism (RFLP) analysis of the amplified nucleic acid or by a second round of nested PCR with analyses by electrophoresis.^{10,27-29} Other unique approaches that have been developed are multiplex RT-nested PCR (RT-nPCR) of the M protein and amplification refractory mutation system (ARMS)-PCR of the CDV M-F intergenic and untranslated, prepeptide regions of the F gene followed by RFLP.^{30,31}

VACCINATION AND PREVENTION

Most CDV vaccines in the United States, Canada, and Europe are of the American-1 (Onderstepoort) lineage with the exception of the Vanguard vaccine (Pfizer Animal Health, Madison, NJ, USA), which is of the America-2 genotype.^{27,32} The major vaccine strains were isolated in the 1930s and it is not known if they continue to circulate in nature as they have not been detected for many years.^{33,34} Although CDV vaccine strains have not changed in the past 60 years, there is potential for newer antigenic variants of CDV to emerge around the world.²³ However, the current vaccines have largely provided adequate protection against clinical disease when properly administered to healthy domesticated dogs in this country.

Core vaccination guidelines, including canine distemper MLV and recombinant canarypox vectored canine distemper virus (rCDV) vaccines, recommended by the American Animal Hospital Association Canine Vaccine Guidelines, were revised in 2006.³⁵ Recommendations for administering the rCDV and MLV vaccines are similar. Advantages of the rCDV vaccine is that it does not contain live virus that replicates and spreads from vaccinees and it is more likely to produce immunity in puppies that have passively acquired maternal antibodies. Vaccination failures can occur when MLV vaccines are used to immunize puppies that have not cleared maternal antibodies.³⁶ Maternal antibodies are adsorbed in the intestine from colostrum during the first 2 days of life and are cleared 6 to 12 weeks later. It is recommended that puppies receive a series of 3 vaccinations beginning at 6 to 16 weeks of age to achieve complete immunity to CDV followed by a booster at 1 year of age. Canine distemper virus vaccines impart long-term immunity in dogs.³⁷ Duration of immunity of 3 years has been reported for both MLV and rCDV vaccines.^{38,39} In animal shelters and high-risk environments, one dose of MLV or rCDV vaccine has been reported to

be protective in puppies already exposed to CDV.⁴⁰ Ferrets are also highly susceptible to CDV and the disease is virtually 100% fatal. The American Ferret Association recommends vaccinating ferrets with PureVax Ferret Distemper Vaccine (Merial Inc, Athens, GA, USA), the only USDA-licensed vaccine product labeled for use in ferrets, following the product label for kits or adults.⁴¹

Reasons that a vaccine may fail, in addition to the presence of maternal antibodies in puppies, are incomplete immunity due to failure to complete the puppy booster vaccination series, stressors in the physical environment, the animal's immune competence and specific responsiveness to CDV antigen or intercurrent exposure to other virulent viruses such as canine parvovirus or coronavirus or even parasites, and improper storage and handling of vaccine.^{36,42-44} A concern voiced by scientists is that new genetic CDV variants may be associated with pathogenesis changes or immune evasion in dogs vaccinated with current vaccines.⁴⁵ In infected dogs with a history of recent vaccination with MLV vaccine, exposure to wild-type CDV prior to vaccination is usually assumed to be the source of the CDV infection.¹⁰ However, CDV infections reported in previously vaccinated dogs in Japan, Mexico, and the United States were caused by novel CDV lineages distantly related to the America-1 vaccine group.^{10,44,46-49} Variation of key amino acid residues and the addition or loss of *N*-glycosylation sites on the H and F proteins may alter interaction between the H and F proteins during binding and fusion with susceptible cells, leading to changes in antigenicity, virulence, and tissues targeted by CDV variants.^{50,51} Continued surveillance, study of genetic and antigenic drift in circulating CDV strains, and molecular analysis of emerging CDV variants are warranted to ensure that vaccines for prevention of distemper continue to be potent and efficacious in preventing infection in domestic dogs.

In addition to immunization of domestic dog populations, hygienic measures are necessary. Unvaccinated puppies should be isolated from dogs other than their bitches. Strict isolation of dogs infected with CDV is the most important step in controlling the disease. Virus is shed in all body secretions and excretions during the acute systemic disease. Direct dog-to-dog contact and indirect aerosol transmission are the main routes of viral spread, but CDV can be transmitted from fomites at room temperature or lower for several hours. Disinfection of CDV in the environment, particularly in shelters and kennels, is important. Inactivation of canine distemper virus with benzalkonium chloride (0.05%), a quaternary ammonium compound, occurs in 10 minutes at room temperature.⁵² Similarly, 70% ethanol is effective against CDV.⁵³

GENOTYPES AND GENOTYPING

Nucleic acid sequence analysis of the H gene is the gold standard for phylogenetic analysis, classification, and genotyping of CDV because it has the greatest heterogeneity (about 10% amino acid variation) of the 6 structural proteins of CDV.⁵⁴ Studies of complete H gene sequences have identified 12 distinct geographically separated clusters of CDV genotypes: American-1 (including most vaccine strains), American-2 (North America), Arctic (Arctic region and Europe), Asia-1, Asia-2, Asia-3, Europe, European wildlife, South Africa, Argentina, Rockborn-like, and a new genotype of primarily Mexican strains.^{28,48,55-57} Serengeti isolates are distinctive from CDV isolates from other parts of the world.⁵ In the United States, genotypes that have been identified in dogs and wildlife in addition to the American-1 and America-2 strains are the European wildlife, EdoMex, and Arctic strains in domestic dogs.^{10,49,55} Amino acid sequence variation between the genotypes is greater than 4% and strains within each genotype have less than 2% amino acid variation.¹² Characterization of

CDV strains from South America may be of special interest. Scientific archivists point to documentation of distemper-like epizootics occurring in Peruvian dogs in the mid-1700s that may have spread to Europe circa 1760 with the importation of diseased dogs by Spanish colonials.⁵⁸

Sequence analysis of CDV strains from different geographical locations and animal species indicates that the H protein gene undergoes genetic drift.⁵⁹ Viral recombination in CDV has been documented in an isolate recovered from a giant panda.⁶⁰ Recently, a CDV genotype designated “Wildlife Europe 2006–2009 (WE/06–09)” found exclusively in wild carnivores was described that evolved and spread over a wide geographical area in Northern Italy in 10 months following its initial detection in 2006.⁶¹ Bavarian wildlife isolates collected during the 2008 distemper outbreak in the Southern Alps were 99.7% to 100% similar to the Italian isolates.⁶² The evolutionary origin of the group was estimated to have diverged from its most recent ancestor 5 months prior to identification of the first virus CDV.⁶³ The mean nucleic acid substitution rate in the new CDV genotype was estimated to be 10.53×10^{-4} subs per site per year, which was within the range typically observed for CDV.⁶³ Phylogenetic analysis of 73 CDV H gene and H protein sequences from dog and non-dog hosts indicated that amino acid residues 530 and 549 are under positive selection, and these residues are located in the regions of the H protein that are important in binding to the host cell SLAM receptor and triggering activation of the F protein cellular entry.^{17,59,64} This provides compelling evidence that repeated evolution at known functional sites of emerging strains of CDV is associated with multiple independent occurrences of disease emergence in a range of novel host species.

Facilitation of large-scale diagnostic and molecular epidemiologic studies of CDV requires rapid molecular-based methods that accurately differentiate among the genotypes and between vaccine and wild-type strains of CVD without the need to perform either full-length or partial sequencing of the H gene for each isolate. A hemi-nested PCR system was developed that can genotype 5 of the 12 CDV lineages (America-1, Europe, Asia-1, Asia-2, and Arctic) using specific primers targeted to the H gene.³² The ARMS-PCR method followed by RFLP also differentiates a broad variety of lineages.³¹ Further development of rapid protocols for distinguishing among all CDV genotypes is needed to advance epidemiologic studies of this important pathogen. Genotyping is important for tracing the relatedness of CDV isolates and cross-transmission between and within species of carnivores.

NONCANID HOSTS OF CDV

Distemper outbreaks in Rhesus monkeys (*Macaca culatta*) have occurred since 2006 at the largest monkey breeding farm in mainland China that supplies breeding stock for biomedical research facilities and zoos.⁶⁵ Over 10,000 monkeys contracted the disease and more than 4,250 died at the farm and at the facilities it serves. The entire genome of the isolated virus was sequenced. Phylogenetic analysis of the H gene places it within the larger clade of Asian genotypes yet it is unique in the number of amino acid changes to its structural proteins. Although monkeys and monkey-derived cell cultures have been experimentally infected with CDV, only one other natural CDV outbreak of monkeys (*Macaca fuscata*) occurring in Japan was reported in 1989.⁶⁶

Canine distemper is not a clinically recognized entity in domestic cats; however, large felids are susceptible to infection with CDV. Most of the large cats are threatened or endangered species; thus surveillance of pathogens that have the potential to cause their extinctions is critical. Where CDV has caused widespread distemper outbreaks in nondomestic cats, domestic dogs, raccoons, or wild canids have been implicated as reservoirs of the disease. CDV outbreaks with multiple

mortalities were reported in lions, tigers, jaguars, and leopards in zoos and wildlife safari parks in the 1980s.⁶⁷ Raccoons living in the area surrounding one suburban zoo had increased numbers of fatal distemper cases and may have transmitted the disease to the large cats. CDV isolated from large felids in the zoo was of the America-2 genotype circulating in the local feral raccoons.⁶⁴ A retrospective immunohistochemistry study of paraffin tissues from 42 necropsy cases of lions and tigers from Swiss zoo and circus cats collected from 1972 through 1992 indicated that 19 were CDV positive.⁴ Of 56 Asiatic lions from 6 captive breeding centers in western India tested in 2007 for antibodies against CDV, 88% were positive.⁶⁸ In addition to domestic dogs, urban wildlife in the United States such as raccoons, foxes, and skunks may play a role in direct transmission of distemper to large felids and other carnivores in zoos, wildlife parks, circuses, and captive breeding facilities.

Many studies of canine distemper in free-ranging large felids have been reported.^{69–75} African lions of the Serengeti are the most intensively studied of the large felids with regard to the prevalence of CDV. In 1994, a CDV epidemic in Serengeti lions caused fatalities in 30% of the population with only an estimated 2,000 lions remaining in 1996.⁶⁹ Prior to 1994, disease-related mortality due to CDV infection of lions had not been documented, although retrospective serology tests indicated that 29% of lions that were living in the area from 1984 to 1989 had titers to CDV. A single CDV genotype was common among the susceptible animal species living in the Serengeti during the 1994 CDV outbreak that included lions, hyenas, bat-eared foxes, domestic dogs, and jackals.⁵ Unowned, feral domestic dogs living in or near the Serengeti are not vaccinated, experience periodic distemper outbreaks, and likely serve as a primary reservoir of CDV. Jackals and hyenas may be amplifying species that spread CDV throughout the park to lions and other felids.^{6,76,77} A Brazilian study was performed in 2 state parks with the goal of determining the prevalence of CDV titers in wild felid populations (jaguars, pumas, and ocelots) and correlating it with the prevalence of CDV titers in, and density of, domestic dogs in the areas adjacent the parks.⁷² Dog owners in small rural settlements surrounding the parks were questioned about the CDV vaccination status of their dogs. Unvaccinated dogs were tested for CDV titers. Jaguars (60%) and pumas (11%) from one park had titers to CDV and 100% of the dogs living adjacent to the park were seropositive for CDV. None of the large felids tested at the second park had CDV titers and only 35% of the local unvaccinated dog population was seropositive for CDV. The occurrence of CDV in wild felids appears to be related with home range and close association with unvaccinated, infected domestic dogs living nearby.

PREVENTION OF CDV INFECTION IN WILDLIFE

Vaccine coverage of 95% of domesticated dogs is needed to control canine distemper in these pets.⁷⁸ Currently the best means for breaking the circulation of CDV between susceptible wildlife populations and domestic dogs is through regular vaccination of pet dogs and preventing them from roaming freely and interacting with unvaccinated dogs and wildlife that may harbor the virus. Free roaming wildlife are not vaccinated in the United States unless federal and state authorities determine that an endangered species may benefit from vaccination in captive breeding programs designed to stabilize and increase existing populations for release back into the wild. One study reported the vaccination of wild raccoons with MLV canine distemper vaccine prior to 1997 in a forest preserve near a Chicago area zoo.⁶⁴ In the 1960s through the 1980s, primarily killed vaccines (KV) were used to vaccinate endangered wildlife and zoo animals against CDV.^{79,80} Virus-neutralizing titers developed post-vaccination to the KV were generally quite low, and several exotic species that had

been vaccinated died from outbreaks of CDV infection. Use of MLV CDV vaccines is often fatal to many wildlife and zoo animals; thus they have only been used in rare situations in the United States to control disease in endangered species and display animals in zoologic parks.^{1,79–82} After the univalent canarypox vectored recombinant distemper vaccine, Purevax Ferret (Merial Inc), was licensed and marketed in 2001, many North American zoological institutions began using the rCDV vaccine to vaccinate numerous at-risk species.⁸³ Currently, the American Association of Zoo Veterinarians' Distemper Vaccine subcommittee recommends the extralabel use of the rCDV PureVax Ferret Distemper Vaccine (Merial, Inc) in all susceptible zoological display animals where CDV is endemic in local wildlife.⁸⁴

Vaccination of endangered species that are susceptible to CDV has been an important in the success of recovery programs. Initially, commercial KV and MLV CDV vaccines were used to vaccinate the endangered black-footed ferret but these products proved to be nonprotective or fatal.^{80,85,86} In 1988, an experimental canarypox vectored rCDV vaccine (Merial Inc) used to vaccinate ferrets in the captive breeding program successfully prevented distemper, one of several diseases that had threatened the species with extinction.⁸⁷ All wild-born black-footed ferrets are trapped and vaccinated. After the 1999 CDV outbreak on Santa Catalina Island, California, the native island fox population plummeted from 1,300 to less than 100 individuals. Infected domesticated dogs or stowaway raccoons from boats anchoring on the island mingling with the foxes may have caused the outbreak.⁸⁸ The federally endangered island fox was vaccinated with the rCDV vaccine to reestablish the population beginning in 1999 with permission from the California Department of Fish and Game.^{89,90} Wildlife rescue and research organizations also vaccinate CDV-susceptible animals in areas where distemper is endemic. The rCDV vaccine, PureVax, is used prevent disease in captive southern sea otters at California institutions.⁹ Free-ranging sea otters are susceptible to CDV.

Immune-stimulating complexes (ISCOMs), a novel form of adjuvant that, combined with antigens, generally induces strong activation of both the cell-mediated and humoral immunity. African wild dogs (*Lycaon pictus*), which are on the International Union for Conservation of Nature Red List of Threatened Species, cannot be vaccinated with MLV CDV vaccines, which are always fatal.⁹¹ One study reported the use of ISCOMs incorporating the F and H proteins to vaccinate African wild dogs.⁹² The dogs initially vaccinated at the beginning of the captive breeding program in 1995 developed protective immunity. However, in 2000, when the 49 of 52 dogs in the colony succumbed to distemper, neutralizing anti-CDV antibodies were not measurable despite a recent vaccination. Although the use of ISCOMs appeared to be promising for control of CDV in a variety of wildlife, the successes have been limited.⁸²

Oral bait vaccines to control zoonotic diseases like rabies and plague in wildlife are currently in use. Oral vaccines to control wildlife distemper are not yet available. Two major issues in developing an efficacious oral bait vaccine for distemper are achieving an adequate mucosal immune response in the gut and overcoming interference from maternal antibodies in infant animals. Attempts at inducing mucosal immunity using vaccinia and canarypox vectored CDV vaccines have been reported using ferrets as model animals.^{80,93–95} Highly attenuated vaccinia and canarypox virus strains expressing the H and F proteins of CDV were administered by parenteral, intranasal, and intradoudenal routes. Juvenile ferrets receiving either vaccine intramuscularly or intranasally had 100% survival rates, but intradoudenal vaccination protected only 60%.⁹³ In studies of infant ferrets with and without maternal antibody, the vaccinia and canarypox vectored vaccines were administered parenterally or intranasally. All

infant ferrets vaccinated parenterally with either vaccine in the absence of maternal antibody survived challenge. Parenteral vaccination with either vaccine in the presence of maternal antibody did not protect against death from CDV challenge. Intranasal vaccination with either vaccine, in ferrets with or without maternal antibody, was not protective against CDV.⁹⁴ Other studies have shown low efficiency in producing a protective immune response with the nonparenteral delivery of CDV canarypox vectored vaccines.^{80,95} As with the Raboral V-RG (Merial, Inc), the CDV vaccinia vectored vaccines stimulate a stronger protective mucosal immune response.⁹³ If an efficacious CDV oral bait vaccine can be developed for wildlife, vigorous domestic dog vaccination programs here and abroad will continue to be the primary means to control the disease.

DISEASE SURVEILLANCE AND CONTROL IN THE UNITED STATES

In the United States, several federal agencies are tasked with surveillance of animal diseases of wildlife. The U.S. Department of Agriculture–APHIS Wildlife Services' administers the National Wildlife Disease Program (NWDP), which participates in wildlife disease monitoring and surveillance in all regions of the United States.⁹⁶ Additionally, NWDP assists state, federal, tribal and international agencies, and nongovernment organizations, with development of local wildlife disease monitoring programs and nationally coordinated wildlife surveillance systems. Canine distemper is among diseases of interest to the surveillance program, although minor.⁹⁷ Over the past 10 years, the NWDP has assisted in distemper surveillance monitoring and research activities with state agencies and veterinary colleges.^{96,98,99} The USDA National Wildlife Research Center is currently assisting the Zambian Wildlife Authority and the African Wild Dog Conservation Trust in the development of conservation management plans for several critically endangered species including African wild dogs, African lions, bat-eared foxes, and leopards. It has been postulated that diseased village dogs are the reservoirs of distemper, rabies, parvovirus, and a number of parasites that are infecting African wildlife.^{100,101} Three programs within the U.S. Department of the Interior also monitor threats to wildlife and wildlife health in the United States: the Fish and Wildlife Service (FWS), National Park Service (NPS), and U.S. Geological Survey (USGS).¹⁰² The FWS administers health monitoring programs for endangered and threatened terrestrial and freshwater species under the Endangered Species Act of 1973. In 1988, in association with state and private organizations, the FWS began a captive breeding and vaccination program of black-footed ferrets, which were nearly extinct due to outbreaks of canine distemper and sylvatic plague.^{86,103} The FWS was involved in the captive breeding and vaccination program and continuing surveillance of the Santa Catalina Island fox population after the 1999 canine distemper outbreak. By the end of 2010, the fox population rebounded from 100 foxes to 1,008 individuals.^{88,104,105} Grey wolves reintroduced by the FWS to Yellowstone National Park are monitored for canine distemper, which caused population declines in 1999, 2005, and 2008.¹⁰⁶ The NPS Biological Resource Management Division performs surveillance and disease management of wildlife health within the federal park system. The USGS National Wildlife Health Center, which provides wildlife health and disease investigative, research, and training support to federal, state, local, and international conservation agencies, was designated as an OIE Collaborating Centre for Research and Diagnosis of Emerging and Existing Pathogens of Wildlife, by the World Organization for Animal Health (OIE) in July of 2011.

SPREAD OF CANINE DISTEMPER AMONG DOMESTIC DOGS AND WILDLIFE

The epidemiology and transmission of CDV are complicated by the wide host range of animals susceptible to distemper.² Canine distemper virus is present on all continents wherever there are carnivores. Domestic dogs are considered to be the primary reservoir of CDV, which disseminates between free-ranging, unvaccinated or incompletely vaccinated dogs (pets and feral) and urban or rural wildlife.¹ Raccoons, foxes, and skunks have adapted well to urban environments and, in the United States, raccoons, a secondary reservoir of CDV, are among the most common wildlife species found in cities and towns. Cyclical outbreaks of distemper commonly occur in North America among raccoons associated with an increase in their populations. The periodic increase in distemper outbreaks in raccoons leads to spillback to domestic and feral dogs and spillover to other wildlife (skunks, foxes, badgers, coyotes, wolves, etc.). Over the past decade, many outbreaks of canine distemper in urban wildlife have been reported in the United States and Canada, prompting health officials to issue advisories to the public to avoid feeding or otherwise attracting wildlife to their property, keep dogs current on CDV vaccinations, and confine their pets in fenced enclosures or on a leash.^{11,107}

Infection with CDV also is an important conservation threat to many carnivore species in their natural habitats, especially for small, endangered populations that already face environmental insults.^{108,109} Distemper has contributed to population declines in black-footed ferrets, Catalina Island foxes, native Florida mink, gray wolves, coyotes, sea otters, pumas, and ocelots in the United States and many other wild carnivores worldwide. Often, multiple competent hosts for CDV exist within a region, allowing localized persistence of disease.¹¹⁰ Susceptible captive animals that are held in high densities are especially vulnerable to infection; thus quarantine, vaccinations, and meticulous hygiene are important measures to take, as is reducing the potential for contact with free roaming wildlife that serve as reservoirs of disease.^{4,64–68}

Transmission of CDV between animals is via aerosol or respiratory secretions (coughing, sneezing, barking, licking) and bodily excretions (urine and feces) or through direct contact with shared, virus-contaminated food and water bowls, garbage, compost piles, and other organic materials. Other disease-causing contacts include chasing, mating, fights, simultaneous and sequential feeding events at carcasses, and grooming.⁷⁶ Wild animals with distemper have similar symptoms as infected dogs. They are often mistaken as rabid because they display unusual behavior, disorientation, aimless wandering, and/or aggression and walk with an unusual gait due to CNS involvement. The majority of cases in wildlife are most often observed in spring and summer since juveniles are more susceptible to infection, but cases occur year round.

EPIDEMIOLOGY

Studies of threatened, endangered, or reintroduced carnivore species in the Greater Yellowstone Ecosystem and in the Serengeti National Park, Tanzania, have supplied a wealth of information on the epidemiology of CDV in these expansive natural habitats over many decades.^{69,76,77,88,110,111} However, little is known of the overall health status and disease problems in free-ranging wildlife populations that have direct and regular contact with domestic dogs. The domestic dog is the most numerous of carnivores in the world with an estimated population of over 500 million worldwide.¹¹² Domestic dogs have been sources of many zoonotic viruses, bacteria, helminths, arthropods, protozoa, and fungi and have served as a link for exchange of

pathogens among livestock, wildlife, and humans.^{113–115} An International Expert Meeting on Dog Population Management was held in Banna, Italy, in March 2011 as a joint effort between the Food and Agricultural Organization of the United Nations and the World Society for the Protection of Animals with technical support from the World Health Organization, to address the challenges of domestic and stray dog population management throughout the world.¹¹⁶ Regular domestic animal health care is not universally available in developing nations or even in remote areas of developed countries. This hinders development of effective disease detection and preventative veterinary medicine programs.¹¹⁵ Lack of vaccination to achieve herd immunity, uncontrolled reproduction of domestic dogs, and free-roaming dogs, they are whether owned, abandoned, or feral, are major roadblocks to preventing further spread of CDV to all susceptible species.^{72,73,117,118}

Studying the demographic characteristics of dog populations in urban and rural areas is critical for understanding the epidemiology of canine infectious diseases and to make decisions in planning and implementing dog population management schemes to control zoonotic diseases and diseases that are of conservation interest such as CDV.^{72,117,118} Three recent prospective studies of large felids in Brazil, Iberian lynx in Andalusia, Spain, and wolves in the remote north coastal mainland and islands of British Columbia, Canada, suggest that unvaccinated dogs in towns and small settlements do pose a significant risk; seroprevalence for CDV exposure in these animals is high.^{72,73,119} Additional prospective studies of disease in threatened and endangered species and dog populations that reside in transecting areas of urban populations, towns or settlements, and wilderness areas are needed to provide baseline health and serologic information. The heterogeneity of CDV genotypes that have been isolated in restricted geographical areas within the United States, Europe, and elsewhere are postulated as being the result of intense, legal, or uncontrolled trade and travel of domestic dogs and uncontrolled movement receptive wild species.^{10,12,120} Recent reports of European Wildlife and EdoMex genotypes isolated from North American dogs that have not traveled outside the United States underscore the need to gather additional sequence information to elucidate the epidemiologic patterns of CDV on a local and global scale.¹⁰ Characterization of circulating CVD genotypes in domestic dogs and wildlife within a discrete territory over a protracted timeline would also further our understanding of how the virus spreads and evolves within and between species. Reliable information about transmission of CDV among domestic and wild carnivores should enable more effective management of the disease.⁷⁶

SUMMARY

Canine distemper is a highly contagious disease of domestic dogs that also infects multiple wildlife hosts, some that serve as secondary or amplifying reservoirs of the virus. Transmission of CDV among dogs and other susceptible hosts continues to present many challenges in the United States and worldwide. Control of distemper in dog populations requires a strong commitment by many constituencies. CDV is the most significant viral threat to the extinction of endangered carnivores, eclipsing rabies. Effective vaccines for distemper are available to control CDV in domestic dogs, although the vaccine strains that are used in commercial vaccines have not changed in the past 60 years. Client education about the serious consequences of CDV to both their pet dogs and to wildlife is the critical first step to curtail the spread of CDV, followed by reducing reproduction rates of dogs and abandonment of pets. It is important for veterinarians, dog owners, animal control officers, wildlife wardens, and quarantine officers to understand that canine distemper can cross continents

during the transportation of dogs. A major challenge in diagnostic testing is differentiating infection due to attenuated vaccine virus from infection caused by wild-type virus so that recently CDV-vaccinated dogs are not unnecessarily euthanized where outbreaks of distemper occur, particularly in animal shelters. Because canine distemper is an RNA virus, a potential for emergence of antigenic variants exists, particularly in situations where wildlife that are infected with a strain of CDV that has adapted to that host spills back to domestic dogs. Introduction of novel canine distemper viruses in improperly vaccinated dog populations with insufficient immunity can cause new outbreaks of CDV. Increased surveillance of CDV in dog and wildlife populations to identify new genotypes and trace movement of strains within and between species will broaden our epidemiologic knowledge base and advise the veterinary profession and biologics industry as to the need for changes to vaccine strains to protect domestic dogs.

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