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Review Article

Circulation and Presentation of Canine Distemper Virus Among Various fox Species

Key words

canine distemper virus;
fox;
Vulpes vulpes;
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Abstract: Canine distemper virus (CDV) is a highly contagious and often fatal virus that affects members of the Canidae family. Foxes are susceptible to CDV, and outbreaks among fox populations have been reported in several species. The symptoms of distemper in foxes are similar to those in domestic dogs. Foxes may contract the virus directly from infected animals or via exposure to a contaminated environment. Among domestic animals' dogs are often a source of infection for domestic and wildlife populations, while among wildlife primary sources are other wildlife through direct contact or vectors such as insects. This review comprehensively discusses the virus itself, its pathology, clinical signs, diagnostic methods, treatment options, preventive measures, and its impact on fox populations. Wildlife veterinarians and researchers monitor and study the impact of diseases like distemper on fox populations. Understanding the spread and prevalence of such diseases is crucial for wildlife conservation efforts.

Introduction

Canine Distemper Virus (CDV) is a pathogen causing significant morbidity and mortality in both domestic and wild carnivores (1). This virus is predominantly associated with dogs, which are largely responsible for its spread into wildlife populations that had not been previously exposed (2).

CDV's impact is a major concern for the conservation and health of wild species (3). In recent decades, this highly infectious disease has contributed to the decline of some wild carnivore populations due to its susceptibility to the virus (4). Factors facilitating the spread of CDV include a wide host spectrum, genetic variability, uncontrolled animal movement, environmental changes, and habitat reduction (5, 6).

Treatment options for CDV are limited, with vaccination being the primary preventative measure (6). Diagnosing CDV based solely on clinical signs can be challenging, as it shares respiratory, neurological, and gastrointestinal symptoms with other diseases like rabies, parvovirus, toxoplasmosis, and feline panleukopenia (4).

The prevalence of Canine Distemper Virus (CDV) in wildlife has been explored in a limited number of studies, most of which focus on symptomatic or dead animals (7). Among all wild carnivores, foxes are notably affected by CDV.

The Canidae family is divided into two tribes: the Canini tribe, which includes dogs, wolves, jackals, and coyotes, and the Vulpini tribe, which consists of foxes (8). Foxes, small to medium-sized omnivorous mammals (9, 10), are characterized by their upright triangular ears, pointed snouts, and long bushy tails (11, 12). They inhabit every continent except Antarctica and comprise 12 species (13, 14). Some fox species, such as the *Vulpes vulpes necator*, *Vulpes bengalensis*, and *Vulpes chama* are classified as vulnerable or critically endangered (15). Foxes are highly adaptable predators, with species like *Vulpes vulpes* often found in urban areas that benefit from readily available food and shelter (16).

This review comprehensively discusses the virus itself, its pathology, clinical signs, diagnostic methods, treatment options, preventive measures, and its impact on different foxes species populations.

Canine Distemper Virus Structure

Negative-sense single-stranded RNA virus having a diameter of about 100-250nm (4, 17). It belongs to the genus Morbillivirus of the family Paramyxoviridae (4, 17). It possesses a helical nucleocapsid (N) surrounded by a lipoprotein envelop structure (17). The RNA genome consists of six genes that code for a single envelope-associated protein – matrix (M), two glycoproteins (hemagglutinin(H), fusion protein (F)), and two transcriptase-associated proteins (phosphoprotein (P), large protein (L) (4, 5) (Figure 1).

The haemagglutinin (H) protein is responsible for the first virus-host cell interaction and initial virus entry into a host (4). Due to its higher genetic and antigenic variation than other viral genes, the H gene is a pivotal target for investigating the genetic and antigenic diversity of the Canine Distemper Virus. Studies have revealed significant genetic diversity in the H gene, identifying various geographically distinct genotypes such as Asia-1, Asia-2, Europe-1, Arctic, America-1, America-2, Wildlife, Arctic-Like, and others. This diversity has made the H gene the primary focus of molecular epidemiological studies on CDV. Researchers have identified seven major lineages based on the genetic relationships among complete H gene sequences of different CDV strains. These lineages include America-1, America-2-5, Arctic-like, Asia-1-4, Asia-2, Europe-1, Europe-Wildlife, Caspian, Asia 4–6, Rockborn-like, India-1/Asia-5, Asia-6, South Africa, East Africa, and South America-2-3 (4, 17-19).

Host Range

In recent years, CDV has been detected in various hosts beyond canids (17). It is regarded as a multi-host and globally distributed pathogen (20). Among the vertebrate groups where CDV has been reported are included: Canidae (dogs, wolves, fox, dingo, African dogs), Ailuridae (red panda), Mephitidae (skunks), Mustelidae (ferrets, minks, otters, badgers), Procyonidae (raccoons), Ursidae (giant pandas), Felidae (lions, tigers, and leopards), Hyaenidae (hyenas), Viverridae (binturongs and civet), non-human primats (*Macaca mulatta*, *Macaca fascicularis*, *Macaca fuscata*), Tayassuidae (*Pecari tajacu*), and marine mammals (seals, dolphins, porpoises) (8, 20, 21).

Table 1 and Figure 2 describe the geographical distribution of CDV reports available to the moment of the writing of this manuscript, across 15 different fox species all around the world.

Pathogenesis and transmission routes

CDV is known for its high contagiousness and rapid transmission among susceptible hosts (4). The virus causes

Table 1: Fox species and countries where the CDV has been reported

Specie	Country	Reference
Red foxes (*Vulpes vulpes*)	USA	(11, 22–27)
	Norway	(20)
	Italy	(6, 7, 18, 21, 28, 29)
	Spain	(5, 30, 31)
	Portugal	(2)
	Croatia	(7)
	Germany	(7, 9, 9, 32, 32–35)
	Denmark	(7, 16, 36)
	Switzerland	(7)
	Greece	(37)
	Austria	(38)
	Slovenia	(38)
	Czech Republic	(19)
	Belgium	(39)
	Luxembourg	(10)
Desert foxes (*Vulpes macrotis arsipus*)	USA	(40)
Grey foxes (*Urocyon cinereoargenteus*)	USA	(11, 22–24, 26, 41–45)
South American gray fox (*Lycalopex griseus*)	Brazil	(46, 47)
	Argentina	(48)
Culpeo (*Dusicyon culpaeus*)	Argentina	(48)
Darwin's foxes (*Lycalopex fulvipes*)	Chile	(49)
Fennec foxes (*Vulpes zerda*)	Sudan	(8)
Island fox (*Urocyon littoralis catalinae*)	California USA	(50, 51)
Artic fox (*Vulpes lagopus*)	Norway	(20, 25)
	USA	(52)
Crab-eating fox (*Cerdocyon thous*)	Brazil	(53–55)
	Colombia	(56)
	Argentina	(57)
Pampas fox (*Lycalopex gymnocercus*)	Brazil	(53, 58)
hoary fox (*Lycalopex vetulus*)	Brazil	(3, 54)
swift foxes (*Vulpes velox*)	USA	(59)
Indian foxes (*Vulpes bengalensis*)	India	(60)
Bat-eared foxes (*Otocyon megalotis*)	Africa	(61)

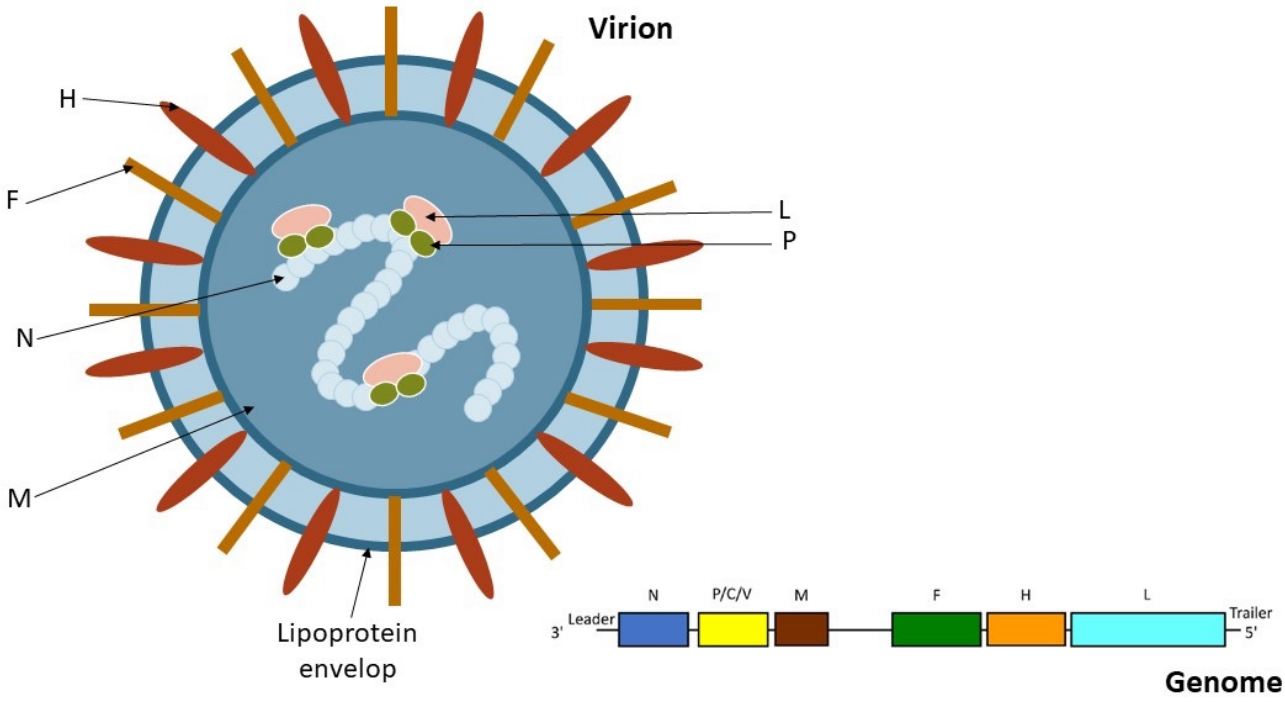

Figure 1: Structure of the Virion and Genome of Canine Distemper Virus (F- fusion protein, M-Matrix protein, P- phosphoprotein, L – large protein, H – hemagglutinin protein, N – nucleocapsid). (Adapted from 4).

Figure 2: Distribution worldwide of fox species where CDV was reported. (Author: Andreia Garcês)

an acute, highly immunizing infection, which requires dense host populations for its long-term persistence (18, 26, 62). CVD is resistant to cold temperatures but is rapidly inactivated by factors such as ultraviolet light, oxidizing agents, detergents, heat, lipid solvents, or dissection (4, 30). At room temperature (around 25°C), its viability is limited, lasting only between 20 minutes to 3 hours when in contact with tissue or exudates (4).

The transmission of CDV occurs through direct contact or aerosolized fluids such as oral and respiratory secretions (including coughing, sneezing, licking, and biting), ocular

fluids, urine, faeces, and blood. It can also spread through shared contaminated food and water during the acute phase of infection (4, 21, 26). The host can shed the virus for 60–90 days post-infection (26). In domestic dogs, transplacental infection has been observed (21). CDV can also be transmitted via fomites at room temperature or lower for several hours (63). In wildlife, infections can occur throughout the year, but there is often a peak in cases during spring and summer, correlating with higher susceptibility in juveniles (63).

The virus often enters the host via the respiratory tract, primarily affecting the epithelial cells of both the respiratory and gastrointestinal tracts. Its initial replication takes place within these mucosal epithelial cells (20, 26) (Figure 3a).

The virus then spreads within the respiratory and gastrointestinal tissues and continues replicating. This leads to the development of respiratory and gastrointestinal clinical signs, as illustrated in Figure 3b. Rapidly, the virus spreads to regional lymph nodes (lymphotropism) (17), multiplies within macrophages and then enters the bloodstream, disseminating throughout the various organs and tissues of the body (25, 26) (Figure 3c). The virus can potentially affect immune cells during viremia, resulting in immunosuppression. It can also cross the blood-brain barrier, subsequently infecting neurons and glial cells. This invasion into the central nervous system leads to the development of neurological signs (3, 4, 28) (Figure 3d). Then, the virus is released by the apical surface of epithelial cells through aerosol and contaminates other animals (Figure 2e). CDV demonstrates extended persistence in tissues such as neurons, urothelium, foot pads, and uvea. In healthy animals that develop antibodies, the virus is typically cleared approximately 14 days following infection. However, even if the animal recovers, it can continue to shed the virus in its urine for 60–90 days (42).

Clinical signs

The severity of the infection is influenced by various factors, including the host's immune status, age, and the virulence of the strain (21). Approximately 50-70% of dog infections are subclinical, presenting non-specific symptoms or mild, self-limiting respiratory signs (21). Similarly, such subclinical infections are likely to occur in wild hosts, such as foxes. The clinical signs in foxes are very similar to other members of the Canidae family (31).

The clinical manifestations of CDV infection include neurological, respiratory, and gastrointestinal signs (4, 5, 17). There are two main clinical forms: acute systemic and chronic nervous (4, 21). Early signs, such as listlessness, loss of appetite and fever, are often overlooked (4). The acute systemic phase, occurring 2-3 weeks post-infection, presents clinical signs such as fever, anorexia, rash, coughing, dyspnoea, dehydration, mucopurulent oculonasal discharge, optic neuritis, dermal manifestations including pustular dermatitis (distemper exanthema), chorioretinitis, rhinitis, uveitis, hyperkeratosis of the nose, foot pads and eyelids, vomiting, conjunctivitis, depression, jaundice, and

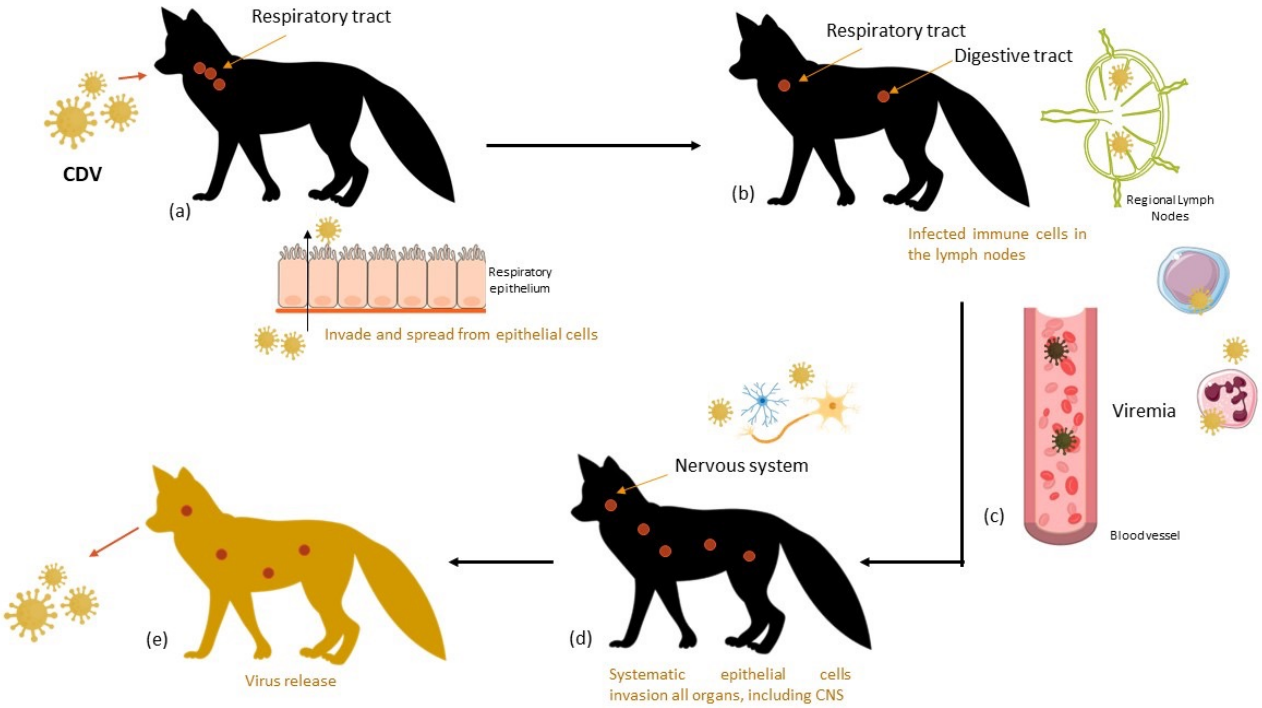

Figure 3a-3d: Pathogenesis of Canine Distemper Virus. (Author: Andreia Garcês)

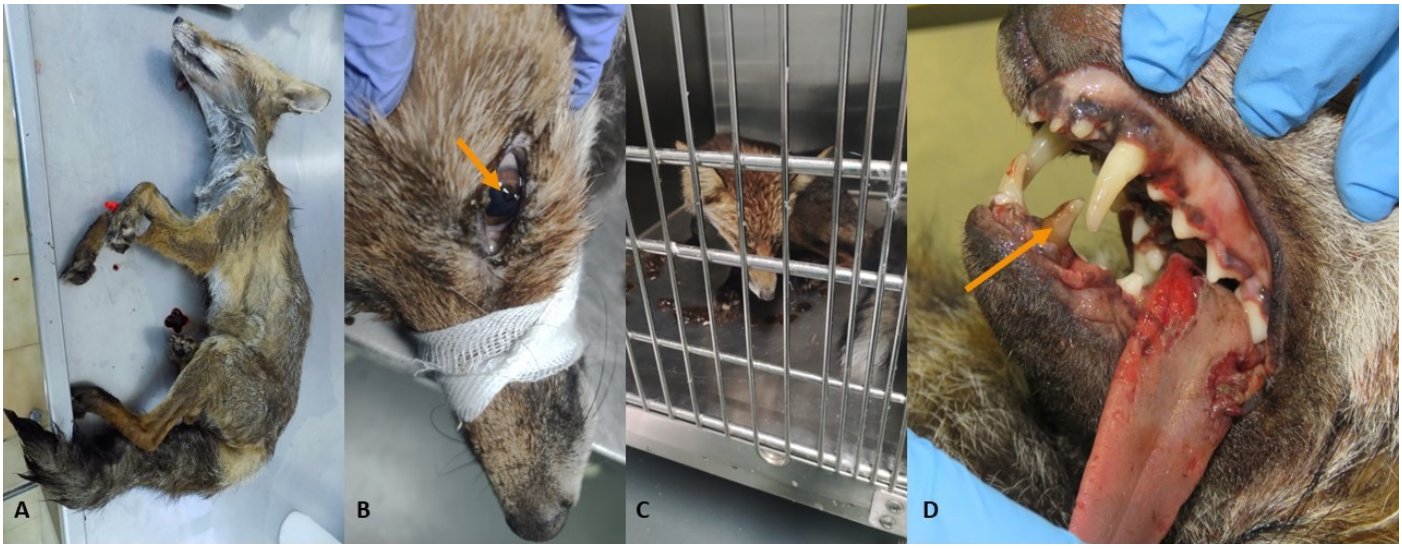

Figure 4: *Vulpes vulpes* emaciated (A), ulceration of the cornea (B), diarrhoea (C), enamel hypoplasia (D). (Author: Andreia Garcês/Isabel Pires)

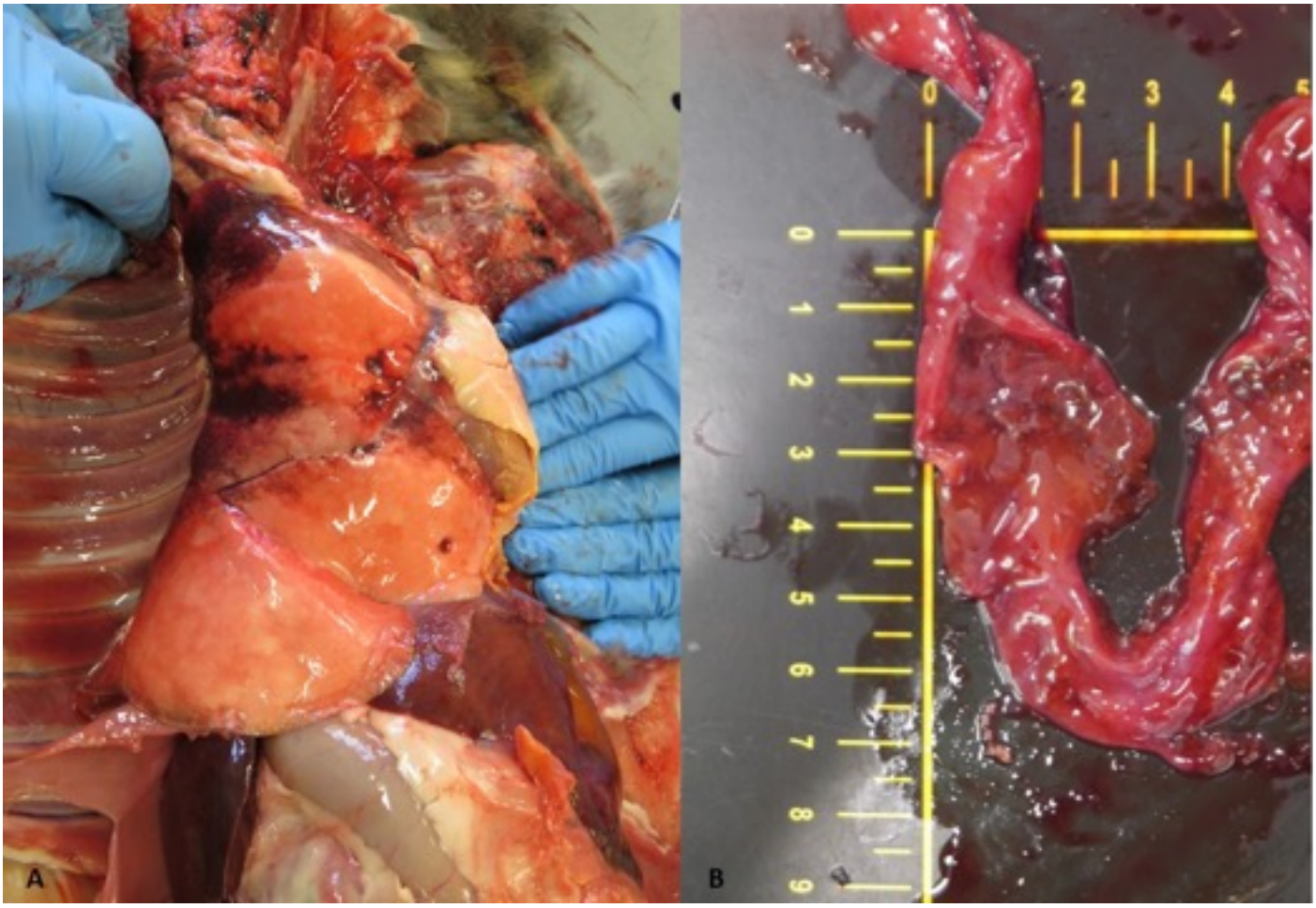

Figure 5: *Vulpes vulpes* pneumonia (A) where the lungs were incompletely deflated, diffusely and mildly oedematous, and the right cranial and middle lobes had multifocal to coalescing, dark red, consolidated area. Enteritis (B). (Author: Andreia Garcês/Isabel Pires)

diarrhoea (4). During this phase, the virus can be found in all body secretions (4, 42) (Figure 4).

The neurological phase typically arises 2-3 weeks after the initial infection, with acute and chronic presentations. The progression and variety of signs depend on the affected brain region. These include abnormal behavior, diminished fear of humans, seizures, hyperesthesia, cervical rigidity, paresis or paralysis, tetraparesis with sensory ataxia, chewing gum-like mouth movements, incoordination, as well as cerebellar and vestibular signs, cycling motions, and blindness (4). Approximately 20 days post-infection,

inflammation, reduced myelin synthesis (demyelination), and metabolic dysfunction often result in the death of the animal within 2 to 4 weeks (42). Additionally, the compromised immune state post-CDV infection frequently exacerbates clinical signs due to secondary bacterial infections of the skin and respiratory tract (4).

CDV can affect tooth buds and ameloblast in very young animals, leading to enamel hypoplasia, juvenile cellulitis and bone lesions (4, 64).

In terms of clinical pathology, CDV infection may result in various hematological and biochemical changes, including lymphopenia, thrombocytopenia, regenerative anemia, reduced albumin levels, and increased concentrations of alpha- and gamma-globulins (64).

Post-mortem findings

During a necropsy, samples collected for examination should include the spleen, tonsil, lymph node, stomach, kidney, lung, duodenum, urinary bladder, and brain (63). The most significant gross lesions observed in cases of Canine Distemper Virus infection are pneumonia, depletion of lymphopoietic organs, hyperkeratosis of the nose, foot pads, and eyelids, emaciation and dehydration (Figure 5) (64).

Microscopic examination often reveals the presence of eosinophilic intracytoplasmic inclusion bodies, which are more common, and intranuclear inclusion bodies, particularly in the central nervous system, urinary bladder, and bronchial epithelium (4, 5). It is also possible to observe perivascular lymphoplasmacytic infiltration in areas of demyelination and neuronal degeneration of the CNS, lymphohistiocytic polioencephalitis, diffuse interstitial pneumonia, broncho interstitial pneumonia, pustular dermatitis. Syncytial giant cells in the lungs and CNS white matter, anterior uvea, and lymph nodes may also be present (65) (Figure 6).

Canine Distemper Virus and Fox Populations

CDV poses significant risks to fox populations, with outbreaks leading to illness and high mortality rates, especially among young or immunocompromised individuals. The severity of the disease can vary among individuals and populations (4, 66). For instance, the Island fox population (*Urocyon littoralis*) on Santa Catalina Island, California, USA, has been experiencing a decline since 1999. Research indicates that CDV is partly to blame for this decline, likely due to the introduction of raccoons (50, 51).

Outbreaks of CDV can significantly influence the dynamics of fox populations. In certain instances, the virus may lead to fluctuations in population size, characterized by increased mortality rates during outbreaks. The degree to which CDV impacts these populations can vary, depending on factors like the density of the fox population, the presence of additional stressors, and the availability of susceptible individuals(17, 32, 34).

Fox populations may have developed some level of coexistence with CDV over time (67). Fox populations may have developed immune responses that provide some level of resistance to CDV (68). Through natural selection, individuals with genetic variations that confer greater immunity to the virus may be more likely to survive and reproduce, leading to the prevalence of these traits within the population over time (35, 69). Also, through passive

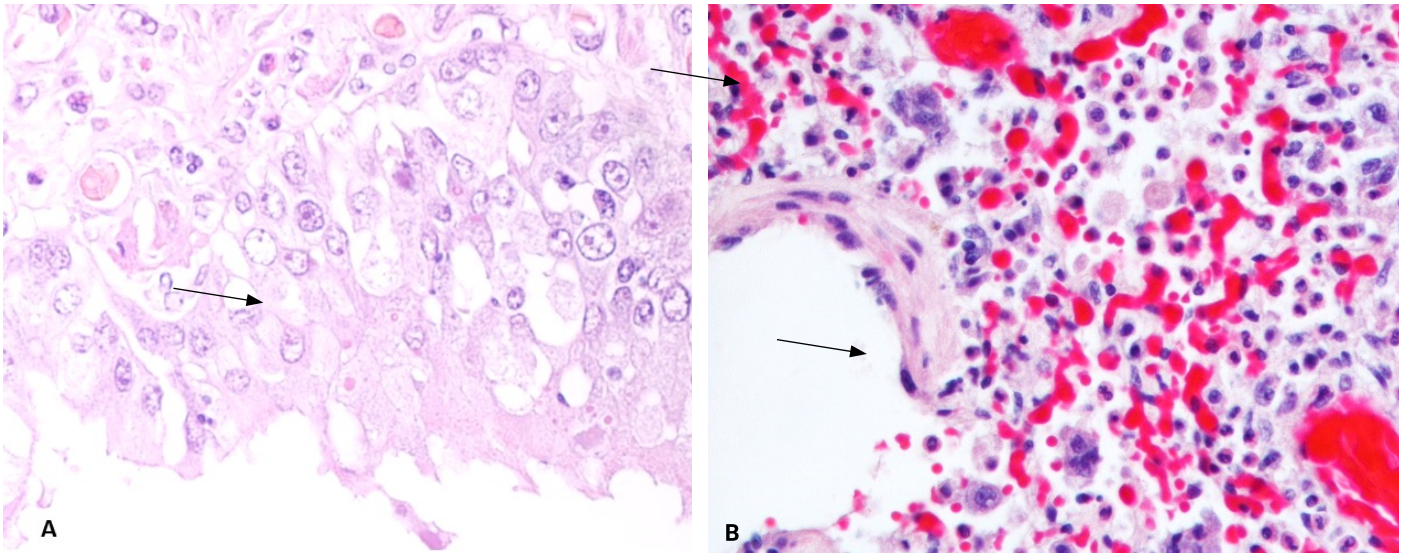

Figure 6: CDV infected *Vulpes vulpes* (A) eosinophilic inclusions in bronchial epithelium, H&E, 400x, (B) Lung syncytial cells, H&E, 200x. (Author: Isabel Pires)

immunity maternal antibodies could provide protection to fox pups during the critical early stages of life when they are most vulnerable to infections like CDV (70). Foxes might exhibit behaviors that reduce their risk of contracting CDV or limit the spread of the virus within their populations. For example, foxes could alter their social behavior to minimize direct contact with infected individuals, reducing the likelihood of transmission (71).

Diagnosis, treatment, and prevention

The diagnosis of CDV infection based only on clinical signs can lead to a false diagnosis since the clinical signs are similar to other diseases (64). *Ante-mortem* diagnosis can be achieved using methods like immunofluorescence assay (IFA), serological tests, cell culture, or reverse transcription–polymerase chain reaction (RT-PCR) (63). *Post-mortem* diagnosis can be done by observing CDV inclusion bodies in various organs (4).

To enhance the accuracy of serological results for canine distemper virus (CDV) in foxes using ELISA tests, it's imperative to consider potential adaptations of cut-off values tailored specifically for this species (72). This entails analyzing a robust dataset of serum samples collected from healthy fox populations to establish species-specific cut-off values. Additionally, accounting for geographic variation in CDV prevalence and antibody levels among fox populations is crucial, necessitating adjustments based on regional disease dynamics (5). Age-related differences in immune response should also be taken into account, potentially warranting age-specific cut-off values to accurately assess serological status across different age groups (73). Longitudinal monitoring of antibody levels in fox populations can provide insights into temporal trends, facilitating refinement of cut-off values over time. Furthermore, validation studies comparing the performance of alternative cut-off values in terms of sensitivity and specificity are essential to identify the optimal threshold for accurate detection of CDV antibodies in foxes (74). By integrating these potential adaptations and employing rigorous quality control measures, such as standardization of laboratory protocols and proficiency testing, we can improve the reliability of serological testing and enhance our understanding of CDV prevalence and dynamics in wild fox populations (51, 75).

Unfortunately, there is no specific antiviral treatment for CDV infection in foxes or any other species (4, 66). Treatment for CDV in foxes primarily focuses on supportive care to manage symptoms and complications associated with the disease. All infected animals should be isolated from other susceptible hosts. Symptomatic treatment, that includes fluid therapy, respiratory control, nutritional support (vitamin A supplementation can be added), temperature control, and control of secondary infections can be applied. Early intervention can improve the chances of a more favourable outcome (42, 76). In cases where the CDV infection is severe, causing irreversible damage or suffering that cannot be alleviated by treatment, euthanasia may be considered to prevent further distress to the animal (50, 64).

Preventing CDV infection in foxes primarily involves implementing measures to reduce exposure to the virus and promoting immunity through vaccination (58, 62). Vaccination is the most effective strategy against CDV infection. Various vaccines have been developed, eliciting differing responses across species. Vaccines are available for domestic dogs and can indirectly benefit fox populations by reducing the circulation of the virus in the environment (70). Vaccination programs for domestic dogs should be comprehensive and include regular boosters to maintain immunity. Additionally, efforts should be made to vaccinate captive fox populations, such as those in rehabilitation centers or wildlife parks, where feasible (12, 32, 76). Avian cell-adapted CDV vaccines have proven highly effective in fennec and red and grey foxes. The canarypox-vectored vaccine has also been effective in fennec foxes (4). These vaccines can be administered via parenteral, intranasal, and intraduodenal routes. It is necessary to monitor continuously and study genetic and antigenic drift in circulating CDV strains to ensure the effectiveness of the vaccine in preventing infection (17).

Minimizing contact between foxes and other animals, particularly domestic dogs, reduces the risk of transmission (4, 58, 62). This may involve implementing measures to deter foxes from entering areas frequented by dogs or managing waste and food sources to reduce attraction (4, 38). Minimizing environmental contamination through proper disposal of carcasses and contaminated materials, as well as regular cleaning and disinfection of areas frequented by foxes, can help reduce the risk of transmission (38).

Regular surveillance and monitoring of foxes and other wildlife populations can provide valuable data on disease prevalence, including CDV, and help identify outbreaks or emerging threats (42, 76). This may involve collecting biological samples (e.g., blood, tissue, faeces) for laboratory testing, conducting necropsies on deceased animals to determine the cause of death, and implementing disease surveillance programs in collaboration with wildlife management agencies, research institutions, and conservation organizations (33, 47).

Conclusions

CDV infection poses a significant concern for wildlife conservation, particularly for endangered or threatened canid species. Outbreaks of the disease can exacerbate the threats to already vulnerable populations. It is crucial to understand the dynamics of CDV within fox populations, as this knowledge is vital for both wildlife management

and the health of domestic animals. This understanding underscores the interconnectedness of ecosystems and the potential impact of infectious diseases on wildlife populations. Efforts towards wildlife conservation may involve monitoring for disease outbreaks, implementing vaccination programs, studying population dynamics, and exploring interactions between domestic and wild canid populations.

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Kroženje in predstavitev virusa pasje kuge med različnimi vrstami lisic

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Izvleček: Virus pasje kuge (CDV) je zelo nalezljiv in pogosto smrtonosen virus, ki prizadene pripadnike družine Canidae. Lisice so dovzetne za CDV, o izbruhih v populacijah lisic pa so poročali pri več vrstah. Simptomi kuge pri lisicah so podobni tistim pri domačih psih. Lisice se lahko z virusom okužijo neposredno od okuženih živali ali z izpostavljenostjo okuženemu okolju. Med domačimi živalmi so psi pogosto vir okužbe za domače in divje živalske populacije, med divjimi živalmi pa so glavni vir okužbe druge divje živali prek neposrednega stika ali prenašalcev, kot so žuželke. Ta pregled izčrpno obravnava virus, njegovo patologijo, klinične znake, diagnostične metode, možnosti zdravljenja, preventivne ukrepe in njegov vpliv na populacije lisic. Veterinarji in raziskovalci prostoživečih živali spremljajo in preučujejo vpliv različnih bolezni, kot je kuga, na populacije lisic. Razumevanje prenosa in razširjenosti teh bolezni je ključno pri prizadevanjih za ohranjanje prostoživečih živali.

Ključne besede: virus pasje kuge; lisica; *Vulpes vulpes*; Canidae; virus; obolevnost