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Canine Parvovirus (26 Jan 2000)

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Classification and Epidemiology
Two distinct parvoviruses (CPV), are now known to infect dogs - the pathogenic CPV-2, which was recognized as a new disease of dogs and wild canines in 1978, and the "minute virus of canines" (MVC, CPV-1) reported by Binn in 1970. MVC, a completely different parvovirus, had not been associated with natural disease until 1992. MVC may cause pneumonia, myocarditis and enteritis in young pups, or transplacental infections in pregnant dams, with embryo resorptions and fetal death. Confirmed infections have been reported in the USA, Sweden, Germany, and, more recently in Italy. Only about 30 cases have been reported.

Canine parvovirus (CPV, CPV-2) and feline panleukopenia virus (FPV) are very closely related and are important pathogens of their respective hosts, the dog and cat. CPV-2 infects dogs and other Canidae such as wolves, coyotes, South American dogs and Asiatic raccoon dogs, but not cats. FPV and the FPV-like viruses infect both large and small cats, as well as mink, raccoons, and possibly foxes, but not dogs. However, the clear separation of a cat virus infecting only cats (FPV) and a dog virus infecting only dogs (CPV-2) is no longer certain as the original dog virus, CPV-2 was transitory, and replaced in nature by so-called 'new antigenic types' (CPV-2a and CPV-2b) that infect or replicate in, and are transmitted between, dogs and cats. FPV has long been known as the cause of disease in cats, raccoons and certain related carnivores, but CPV is a genuine newly emerged virus which was probably derived from a close relative of FPV during the 1970s and has, since 1978, established itself in dog populations throughout the world. Amino acid (AA) sequences which comprise the surface proteins of the viral capsid are the primary determinants of the host range of parvoviruses, and only a few AA differences between CPV and FPV determine the ability of each virus to replicate in dogs, cats or their cultured cells. Although CPV and FPV isolates are >98% identical in their DNA sequences, the viruses can be readily distinguished by antigenic typing with monoclonal antibodies. The determinants of host range differences among the various parvoviruses are complex. All members of the group comprising CPV/FPV replicate in feline cells in tissue culture, but only isolates from dogs replicate in cultured canine cells. Their in vivo host ranges also differ, since FPV isolates replicate efficiently only in cats, whereas CPV isolates show variable replication in cats or feline cell cultures, depending on the strain of CPV. The original CPV-2 isolates do not replicate in cats, but the variants of CPV-2, designated CPV-2a and CPV-2b, replicate efficiently in cats. In addition, CPV-2a and CPV-2b have been isolated from cats in Japan, Germany and the USA which had natural parvovirus disease indistinguishable from panleukopenia. CPV appears to have been present initially in Europe and it subsequently spread throughout the world in 1978-1979 in a period of about 6 months. As noted, the origin of the original virus is not known, although it most likely was derived from a closely related virus of other carnivore species - cats, mink, raccoons, Asiatic raccoon dogs, or foxes. It was then replaced between 1979 and 1984 by the two distinct antigenic variants. Derivation from an FPV vaccine strain in tissue culture was suggested as one possibility, but subsequent studies did not reveal any support for that hypothesis, and derivation from a virus in nature, e.g., a wild carnivore such as the European red fox (Vulpes vulpes) appears more likely.

The extension of the in vivo host range to cats and dogs has important epidemiological consequences. Any dog with parvovirus infection also is a potential carrier of the virus to susceptible (non-vaccinated) cats.
Parovirus disease in cats is mainly caused by FPV, however CPV-2a or -2b viruses have been isolated from approximately 5% of samples submitted for feline panleukopenia diagnosis, indicating that some parvovirus infected cats may also transmit CPV to susceptible dogs. This finding should be recognized by veterinarians who treat both cats and dogs. Another unexpected finding from retrospective studies of tissues from large cats, e.g., cheetahs and tigers, was the occurrence of parvoviral disease in zoos in the USA, Southern Africa and Germany, where it was found that the cats were diagnosed as infected with CPV-2a or -2b; only 30% were found infected by FPV. This may indicate a higher susceptibility of large cats to CPV, a situation which is similar to that with canine distemper virus, which also has been shown to be the cause serious or fatal infections of large cats.

**Pathogenesis**

CPV replicates in several lymphoid tissues and the intestinal epithelium of dogs, and FPV replicates in the corresponding tissues in the cat; however, there are differences in the extent of viral growth in tissues of the two species. The pathogenesis of infections by CPV and FPV in dogs and cats are very similar. The route of entry and initial sites of virus replication are cells of the nasal- and oral-pharynx, including the tonsils and other lymphoid tissues. Animals can be experimentally infected by most parenteral routes; however, the oral route is the most common natural route of infection. Virus spreads systemically via a viremia, and it is found after 1 - 3 days in the tonsils, retropharyngeal lymph nodes, thymus and mesenteric lymph nodes. By 3 days post-infection, virus also can be recovered from the intestinal-associated lymphoid tissues (Peyer's patches). It is important to recognize that infection of the crypt cells of the intestinal epithelium occurs after the viremic phase, and it is not derived directly from ingested virus in the gut lumen. Circulating neutralizing antibodies, therefore, are able to minimize the extent of infection of the intestinal epithelium, but they do not prevent infection unless antibody levels are high. This phenomenon has relevance to vaccination since inactivated vaccines may prevent disease for several months, but they do not prevent actual infection, except for a few post-vaccination weeks. Cytokines may play an important role in the pathogenesis of CPV/FPV infections, however studies have not been reported.

**Clinical Signs and Pathology**

Clinical signs of CPV are well known, and only briefly reviewed here since they have been reviewed in several publications. Disease is often asymptomatic in older dogs or in pups that receive a low virus dose since the severity of infection is highly dose related. For example, a pup may acquire infection by CPV in a contaminated kennel, dog show, or veterinary clinic and experience only mild, or no illness. However, virus amplified in the intestine of that pup would be shed in large amounts to littermates or other susceptible dogs in contact. In contrast to the marked panleukopenia seen in cats infected with FPV, a relative lymphopenia, not panleukopenia, is often observed in dogs infected with CPV. Lymphocyte numbers decline, but there is little effect on eosinophil, basophil, monocyte, or red cell numbers. Interestingly, in experimental studies of cats with a CPV-2b isolate, the virus caused only a slight leukopenia but there was a marked lymphopenia, similar to the pattern seen in CPV infection of dogs. Infection of the lymphoid tissues with CPV results in lymphocytolysis, cellular depletion and, subsequently, tissue regeneration in surviving animals. Virus replication and cell destruction in lymphoid tissues occur primarily in areas of dividing cells, including the germinal centers of lymph nodes (Fig. 1) and the thymus cortex. In clinically infected dogs, dehydration is severe and early treatment with electrolyte solutions is essential. Profound weight loss also is characteristic of CPV infection and the architecture of the small intestine is not restored to normal for 2 - 3 post-infection weeks, at which time weight losses return to normal. Certain breeds, e.g., Doberman Pinschers, Rottweilers and English Springer Spaniels are reported to be at higher risk of severe disease. Parovivirus disease may be exacerbated by concurrent infections with Giardia, hookworms, other enteric organisms or canine coronavirus.

![Figure 1. CPV viral antigen in mesenteric lymph node 4 days after oral-nasal infection (Immunofluorescence microscopy).](https://www.ivis.org)
3 and 5 days after infection (Fig. 2). The degree and the severity of the infection are in part determined by the rate of turn-over of the intestinal epithelial cells. The severity of clinical disease probably reflects the extent of damage the virus produces to the small intestine. During the intestinal phase of the infection, virus is excreted in large amounts in the feces (Fig. 3). Virus is commonly shed from post-infection days 3 - 9, with peak titers occurring at the time, or prior to, the onset of clinical signs. It is important to note that a carrier state has not been demonstrated.

![Figure 2](https://www.ivis.org).

Figure 2. CPV viral antigen primarily in crypt areas of small intestinal (ilium) epithelium (Immunofluorescence microscopy). To view this image in full size go to the IVIS website at www.ivis.org.

![Figure 3](https://www.ivis.org).

Figure 3. Parvoviral particles in the feces of infected dog. Field case. (Electron photomicrograph x30,000). To view this image in full size go to the IVIS website at www.ivis.org.

Infection of neonatal pups, unlike that in older animals, is characterized by infection of the developing heart in puppies (Fig. 4). In contrast to the infection of pups, kittens which become infected either in utero, or shortly after birth, experience viral replication in cells of the external germinal epithelium of the cerebellum, resulting in cerebella hypoplasia. CPV infection of neonatal pups can result in death from myocarditis, generally between 3 - 8 weeks of age, but deaths may occur up to 16 weeks of age or, rarely, longer. The age-dependence of the myocardial and cerebellar infections of cats is due to the active cell division in those tissues, but only in very young animals. Neither myocarditis in kittens, nor cerebellar lesions in puppies, have been reported with parvovirus infections. Neonatal infections also can result in generalized infection with lesions in several tissues. Unlike CPV infection in dogs, in utero infections of cats with FPV or Arctic foxes with blue fox FPV, may result in fetal death and resorption, abortion or neonatal death.

![Figure 4](https://www.ivis.org).

Figure 4. Heart from puppy which died of parvoviral myocarditis. Note the necrotic (light) areas in myocardium. To view this image in full size go to the IVIS website at www.ivis.org.

### Diagnosis

Several laboratory tests have been developed and are available for specific viral diagnosis. Where facilities are available, rapid diagnosis can be made by electron microscopy (EM) of fecal material from cases with typical signs of disease. The virus also can be isolated in several feline and canine cell lines such as canine and feline kidney cells, but isolation is seldom used in practice since cell cultures are required and at least 1 week for results is required. Fecal hemagglutination-hemagglutination inhibition (HA-HI) tests have provided a simple and rapid method for detecting virus in fecal and tissue samples and are employed by several diagnostic laboratories in the USA, however the HA test is less sensitive than EM or enzyme-linked immunoassays (ELISA). Several species' erythrocytes, e.g., pig, rhesus monkey or cat red cells, have been used. For specificity, a second HA test is done, using 10% fecal extracts from suspect cases, but with prior addition of specific immune serum, or monoclonal antibodies, to the extracts. Tests based on ELISA are commercially available and are based on an antigen-antibody reactions with specific monoclonal antibodies fixed on plastic, nitrocellulose membranes, latex or gold particles. The tests are rapid and relatively cheap, and can be
performed in any veterinary practice or clinic. The specificity of the tests relate to the antibodies used in the test. A problem in the past was an unacceptably high percentage of false positive results. Stringent quality control of each antigen lot appears critical. In general, about 103 particles per gram feces can be detected by electron microscopy or ELISA. Serological tests have limited value for diagnosis since high titers are usually present at the onset of clinical illness. However ELISA tests may detect specific IgM antibodies, which occur early in infection, but disappear after 2 - 3 weeks post-infection. Recently a semi-quantitative "Immunocomb Test" (Galed BioLabs, Israel) has been developed and has been made available commercially. That test can be performed by clinics or diagnostic laboratories and detects antibodies to CPV, where titers are reported to correlate well with HI test results. About 10-fold higher sensitivity can be achieved by using the polymerase chain reaction (PCR), but this assay is available only in a few laboratories and has been mainly used for research.

**Therapy**

The restoration of the electrolyte and fluid balance is the most important goal of therapy. Antibiotic treatment to reduce or prevent secondary bacterial infections are recommended. During the early phase of the disease the application of hyper-immune serum may help to reduce the virus load and render the infection less dramatic. Such treatment, used experimentally, has been shown to reduce mortality and shorten the length of the disease; however, the hyper-immune sera is difficult to obtain.

**Immunization**

Effective vaccines are available for the prevention of CPV-2 infection. Both modified live and inactivated parvovirus vaccines have been shown to immunize fully susceptible (seronegative) pups. Attenuated strains of CPV have been derived by repeated passage of the viruses in cell culture. The attenuating mutations in those viruses are not known, but the vaccine viruses are shed at much lower titers in the feces, suggesting that the absence of enteritis results from decreased viral replication in the intestine. Experimentally, live virus vaccines have been shown to protect for at least 3 years, or longer. Inactivated vaccines, however, provide only a limited duration of immunity to infection, although dogs may be protected against disease for several months. For parvovirus prophylaxis, MLV vaccines have proved to be much more effective than inactivated vaccines. This has led to the virtual removal of inactivated vaccines from the German market MLV vaccines have been shown to be safe, and neither vaccine-induced diseases, reversion to virulence or the involvement of vaccine viruses in the generation of 'new viruses' have been confirmed.

There is a strong correlation between HI or serum neutralizing (SN) antibody titers and resistance to infection with CPV. The HI test has been useful to measure antibodies which correlate with immunity. Titers >1:40 or 1:80, as determined by HI tests, are considered protective. The highest rate of infection is reported in pups older than 6 weeks of age. As with other infectious diseases of dogs, puppies from immune bitches are protected for the first weeks of life by maternal antibodies which are acquired via the colostrum. Successful immunization with most vaccines can be accomplished with a high degree of confidence only in seronegative pups, or in pups with very low antibody titers. Maternal antibodies are acquired during the initial 2 - 3 days of life and then decline, with an average half-life of about 9 - 10 days. Passively acquired antibody titers below 40 - 80 are not considered protective against infection, but they commonly interfere with immunization. There is a ‘critical period’ (‘window of vulnerability’), where maternal antibodies are no longer present in sufficient quantity to confer protection. Nevertheless, they may neutralize the vaccine virus, thereby preventing immunization, which is a major problem in achieving successful immunization of pups before 12 weeks of age (Fig. 5). In pups from dams which had been infected with virulent parvovirus, maternal antibody interference with vaccination may last as long as 18 - 20 weeks, but >90% of pups from vaccinated populations respond to vaccines at 12 weeks of age. Little is known about cellular immunity in CPV infection, but neutralizing antibodies are known to correlate with protection, and the determination of antibodies therefore allows an assessment of protective immunity.

![Figure 5. "Critical period" for vaccination against CPV due to the persistence of maternal antibodies. Titers below 1:40 are variably protective, but may interfere with vaccination.](http://www.ivis.org)
Vaccination of dogs is generally performed using multivalent vaccines which contain canine distemper virus, canine parvovirus, canine adenovirus, leptospira bacterin, and inactivated rabies virus. Monovalent CPV vaccines are also available, some of them containing very high titers (up to 10^7 TCID50) and are widely advertised for the initial vaccination of puppies. The most common practice in Germany is to vaccinate dogs at 8 weeks of age against CDV, CAV, CPV, and leptospirosis. This schedule is completed by another vaccination at 12 weeks, using CDV, CAV, CPV, leptospira and rabies vaccines. In kennels that have experienced parvovirus problems, vaccination is recommended at 6 weeks of age with a CPV monovalent vaccine.

Both of the schedules, noted above, were tested recently in a study that employed 400 puppies from 60 litters and vaccines from four manufacturers. In that study, about 60% of all puppies seroconverted after a single vaccination, either at 6 weeks of age with a CPV monovalent vaccine, or at 8 weeks of age with a multivalent vaccine. After completion of the immunization series at 12 of age weeks, when all pups had received at two or three inoculations depending on the vaccination schedule used, nearly 10% of the puppies still had not seroconverted. The principal reason for the non-responders was the persistence of interfering levels of maternal antibodies. None of the vaccines tested were capable of breaking through a maternal antibody titer of 1:160 or higher, regardless whether the vaccines were "high titer vaccines" or not. The distribution of maternal antibody titers in pups within a litter was very homogenous, and 97% of the puppies had a maximal titer differences of one 2-fold dilution step, when compared to littermates. In contrast, the decline of maternal antibody titers was not as uniform as expected and serology was not sufficiently accurate to be used as the basis for the estimation of the best time point to achieve successful immunization.

Based on the study above, the following general vaccination schedule is recommended:

1. Vaccination at 6 weeks of age with a CPV monovalent vaccine.
2. Vaccination at 8 weeks of age with a multivalent vaccine containing CPV, CDV, CAV, and leptospira bacterin.
3. Vaccination at 12 weeks of age with a multivalent vaccine containing CPV, CDV, CAV, leptospira bacterin, and rabies virus antigen.
4. Vaccination at 15 or 16 weeks with a multivalent vaccine containing CPV, CDV, CAV, leptospira bacterin and rabies virus antigen.

If it is necessary to develop an individual vaccination schedule, determination of the antibody titer of one or two pups in the litter could be determined at 5 or 6 weeks of age; then, vaccination of the litter may be the calculated on the basis of that titer, using an estimated antibody ½-life of 9.5 days. Vaccination is most likely to be successful when the maternal antibody titer has declined to less than 1:10. Titers below 1:40 are variably protective, but they may interfere with vaccination.

**Public Health**

Neither CPV nor FPV have been implicated in human disease.

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