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Three-Year Duration of Immunity in Dogs Vaccinated with a Canarypox-Vectored Recombinant Canine Distemper Virus Vaccine*

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CLINICAL RELEVANCE

Two studies evaluated the duration of serologic response to the recombinant canarypox-vectored canine distemper virus vaccine (Recombitek, Merial). Serologic duration of immunity was shown to be at least 36 months. Thus, Recombitek provides protection when administered less frequently than recommended by the manufacturer's label. After the initial vaccination protocol of two or more doses administered approximately 4 weeks apart, with the last dose given at 12 to 16 weeks of age or older, and revaccination at 1 year of age, Recombitek can confidently be readministered every 3 years with assurance of protection in immunocompetent dogs. This allows the vaccine to be administered in accordance with the recommendations of the American Animal Hospital Association Canine Vaccine Task Force and others.

INTRODUCTION

Canine distemper, caused by canine distemper virus (CDV), is a highly contagious disease with worldwide distribution.¹ Before vaccines were developed, CDV caused more canine deaths in the United States than any other infectious disease.¹ Modified-live virus (MLV) vaccines to prevent canine distemper have been available commercially since the late 1950s. These vaccines have been highly effective, and canine distemper is now rarely seen in well-cared-for pet dogs in the United States.

However, the disease remains prevalent among dogs in shelters, primarily because of the large number of unvaccinated dogs present. Such dogs either are already infected on arrival or become infected in the shelter before being vaccinated.² Canine distemper is also present in susceptible wildlife species, such as raccoons.^{3,4} In countries where CDV vaccination is less prevalent than in the United States, canine distemper remains one of the major infectious diseases of dogs.^{1,4} We estimate that approximately 45% of all dogs in the United

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States have been vaccinated against CDV at least once.⁵

Vaccination is a significant component of a comprehensive pet health program and offers the only means by which to protect dogs from CDV.^{6,7} MLV-CDV vaccines have proved efficacious when administered to dogs beginning at 6 to 8 weeks of age; two to three doses administered at least 2 to 4 weeks apart are required, with the last dose given at 12 to 16 weeks of age. Although annual revaccination has been common during the past 25 years, studies have shown the duration of immunity (DOI) for MLV vaccines to be many years, potentially up to the life of the dog.^{4,6} Earlier studies using MLV-CDV vaccines have shown that they induce protection against challenge for a minimum of 7 to 9 years.⁶ This is similar to the DOI for vaccines of the morbilliviruses closely related

Snyder Hill strains caused disease and death in this species, which is more susceptible to CDV than dogs.⁴ When MLV-CDV vaccines were first developed, postvaccinal CDV signs, especially postvaccinal encephalitis, were not uncommon. This was most likely the result of a poorly attenuated vaccine and/or vaccination of immunocompromised pups.^{1,4} Although now rare, postvaccinal encephalitis does occur, most likely in dogs that are unable to effectively respond immunologically to the CDV immunodeterminants hemagglutinin (HA) and fusion (F) membrane protein antigens.⁴

In rCDV vaccines, genes coding for the HA and F membrane proteins, which are found on the surface of CDV, are inserted into specific sites of the genome of the canarypox vector.⁸⁻¹⁰ When injected into dogs, the canarypox-vectored rCDV vaccine enters susceptible cells. The

Canine distemper remains prevalent among dogs in shelters.

to CDV (e.g., measles of human beings, rinderpest of cattle) in which immunity is believed to persist for a lifetime.¹

Two types of commercial CDV vaccines are currently available, the MLV-CDV vaccine and the canarypox recombinant CDV (rCDV) vaccine (Recombitek, Merial). MLV-CDV vaccines contain the Rockborn, modified Snyder Hill, or Onderstepoort strain of CDV. It has been a commonly held belief among veterinary vaccinologists that the vaccines incorporating the Rockborn and Snyder Hill strains of CDV are more effective, but also more virulent, than those using the Onderstepoort strain, which was adapted to grow in embryonated eggs.⁴

This belief was upheld when it was shown that MLV-CDV vaccines containing the Onderstepoort strain could be safely administered to ferrets, while those using the Rockborn or

genes coding for the CDV HA and F proteins are translated, with resulting expression of these proteins. Subsequently, the HA and F proteins are presented, both exogenously and endogenously, by antigen-presenting cells, resulting in T and B lymphocyte responses. Because there is no productive replication of the vector virus and only specific CDV genes are expressed, it is not possible for the rCDV vaccine to produce CDV in the target vaccinee. Additionally, it has been demonstrated that vaccination with one recombinant form of canarypox does not interfere with development of immunity in response to the same or a different recombinant vaccine using the same canarypox vector.¹¹

The DOI in dogs surviving a natural infection with virulent CDV is generally considered to be life-long.^{4,6} Seven years after natural infection with CDV, dogs remained resistant to

virulent CDV intracranial challenge.¹² Dogs vaccinated with a variety of MLV vaccines and then challenged intravenously were resistant to infection up to 7 to 9 years after vaccination.⁶ The protective immunity of dogs to vaccination or infection can also be assessed by demonstrating the presence of serum antibody. There is an excellent correlation between serum viral-neutralizing (SVN) antibody and protection from disease.^{1,4,13,14} Challenge studies in pups suggest that a CDV SVN antibody titer of 1:20 or higher protects against a virulent CDV challenge.^{6,13,14} The long-lived SVN antibody titers produced by immunization have spurred questions regarding the practice of annual revaccination and have led to the development of vaccination guidelines, such as

become customary to use serology as a means of assessing susceptibility to these diseases.^{4,6}

In challenge and antibody studies, results have shown that the canarypox rCDV vaccine provides a level of protection similar to that of the MLV-CDV vaccine, is extremely safe, and stimulates immunity in the face of passive maternal antibody.^{21,22} The purpose of this study was to demonstrate that commercially available canarypox-vectored rCDV vaccine provides 3 or more years' DOI in dogs maintained in a CDV-free environment as well as in pet dogs in conventional environments.

■ MATERIALS AND METHODS

Two separate and distinct serologic studies were performed. Institutional Animal Care and

It is not possible for the rCDV vaccine to produce CDV in the target vaccinate.

those published by the American Animal Hospital Association (AAHA).^{7,15} These guidelines were developed based on disease risk, duration of serologic response to vaccination and/or challenge, vaccination interval, and adverse event risk. The guidelines seek to minimize unnecessary risks associated with vaccination-induced adverse events such as immune-mediated diseases (e.g., anaphylaxis, autoimmune reactions)¹⁶⁻¹⁸ and immunosuppression.¹⁹ Although the USDA Center for Veterinary Biologics states that the role of serologic titers in disease prevention has not been established, the research and industrial communities rely on such data as an indicator of susceptibility to disease.²⁰ Because it has been demonstrated that serologic titers for many viral diseases, most notably CDV, canine parvovirus type 2, and canine adenovirus type 1 in dogs, directly correlate with protection and because challenge studies are both expensive and time-consuming, it has

Use Committee approval was obtained before conducting Study 1, which included 58 beagle pups housed in a CDV-free environment. Unvaccinated sentinel pups are present in this environment and are monitored to ensure the facility is free of CDV and several other canine pathogens. All pups selected for Study 1 were determined to be antibody negative for CDV via serum virus neutralization assay²³ 1 to 2 weeks before beginning the rCDV vaccination series. Pups from multiple litters were randomly separated into four groups. All groups were vaccinated with two doses of Recombitek approximately 4 weeks apart according to the manufacturer's label recommendations. All pups were 12 to 13 weeks of age at the first vaccination and 15 to 17 weeks at the second administration. Group 1 was subsequently revaccinated at 1 year of age, as recommended by the AAHA CanineVaccine Task Force; Group 2 was revaccinated at 6 months of age; and the

other two groups were not revaccinated. Sera collected from all dogs 30 to 42 months after the final vaccination were assayed for the presence of virus-neutralizing CDV antibody.²³

Study 2 included 239 client-owned dogs of various breeds seen for routine care at veterinary clinics throughout the United States; all dogs had been previously vaccinated with Recombitek. Clinics selected to participate in Study 2 used rCDV vaccine exclusively. The interval since vaccination for dogs in this study, which was determined through medical record examination, ranged from 10 to 67 months. Sera collected from these dogs were also tested for CDV antibody via serum virus-neutralization assay.²³ For both Study 1 and Study 2, serology technicians were blinded to study details and assayed these sera as part of ongoing routine testing.

■ RESULTS

Mean \log_2 antibody titers for beagle dogs maintained in a CDV-free environment (Study 1) are shown graphically in Figure 1. Mean \log_2 antibody titers for client-owned dogs (Study 2) are shown graphically in Figure 2.

Study 1 demonstrated that rCDV vaccine induced mean \log_2 SVN titers of:

- 7.3 in Group 1 ($n = 15$) that persisted for at least 37 months
- 8.5 in Group 2 ($n = 18$) that persisted for at least 42 months
- 7.25 in Group 3 ($n = 12$) that persisted for at least 36 months
- 6.5 in Group 4 ($n = 13$) that persisted for at least 30 months

No dog in this study had an SVN antibody titer considered to be negative.

Study 2 demonstrated that rCDV vaccine induced mean \log_2 SVN titers of:

- 8.6 in a group of 85 pet dogs vaccinated 10 to 14 months previously

- 8.7 in a group of 72 pet dogs vaccinated 15 to 26 months previously
- 8.6 in a group of 33 pet dogs vaccinated 27 to 32 months previously
- 8.6 in a group of 49 pet dogs vaccinated 33 to 67 months previously

One dog in the 11- to 14-month group and one in the 27- to 32-month group did not have detectable SVN antibody against CDV.

As a point of reference, a mean \log_2 value of 8 is a titer of 256.

■ DISCUSSION

The results of these studies demonstrate that vaccination with commercial vaccines containing a canarypox-vectored rCDV vaccine consistently induced serologic responses that persisted at least 36 months both in beagle dogs maintained in a CDV-free environment and in client-owned dogs.

Multiple studies using MLV-CDV vaccines have demonstrated similar findings.^{6,20} Prydie²⁴ reported protective CDV SVN titers in 57 of 64 dogs (89%) held in isolation for up to 6 years after vaccination at 9 to 12 weeks of age. Auby and colleagues²⁵ also demonstrated protective CDV antibody titers in five dogs isolated for 30 months after administration of the second vaccine. Olson and associates²⁶ reported the persistence of CDV antibody in 30 dogs vaccinated at least once, with 22 of 30 dogs (73%) maintaining antibody for up to 10 years in a CDV-free environment. Schultz⁶ has demonstrated CDV vaccinal immunity lasting for at least 7 to 9 years based on challenge studies involving many dogs and as long as 11 years in a study in which a few dogs were challenged beyond 9 years.

The present study confirms that rCDV vaccine administered according to the manufacturer's recommendations induces CDV antibody titers that are maintained for a minimum of 3 years, both in dogs housed in a CDV-free environment and in pet dogs. It is important to note that in the pres-

ent study, rCDV vaccine was efficacious and induced a similar DOI in a homogeneous population of dogs housed in the same highly controlled environment, as well as in an extremely heterogeneous group of dogs with diverse lifestyles and housed in various environments. Although none of the pet dogs in Study 2 were reported to have had clinical canine distemper, their environment may have included CDV, and thus natural revaccination may have occurred in some dogs. Of the 239 client-owned dogs included in the study, two did not respond to the rCDV vaccine and remained serologically negative. We can infer that these dogs remained seronegative owing to “clean” home environments in which natural challenge with CDV did not occur, or they may represent the small percentage of dogs that are incapable of responding serologically to CDV. Information gathered from pet dogs living in their owners’ homes is crucial to understanding the actual benefits of this vaccine in its intended use. Because SVN antibody correlates strongly with protection from CDV-induced disease, these studies clearly show that the minimum DOI for rCDV vaccine is 36 months.^{4,6,11–14}

CONCLUSION

This study demonstrates that the serologic DOI for rCDV vaccine is at least 36 months. Thus, revaccination with rCDV provides protection even when the vaccine is ad-

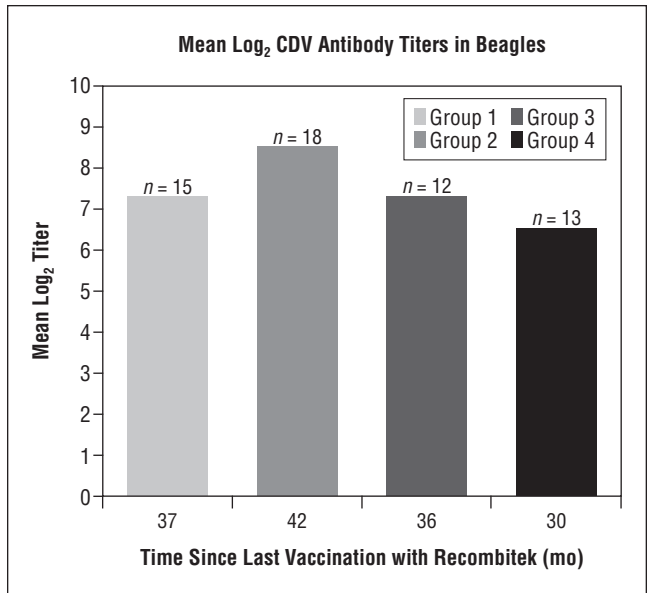


Figure 1. Mean \log_2 canine distemper virus (CDV) antibody titers in beagles that received Recombitek.

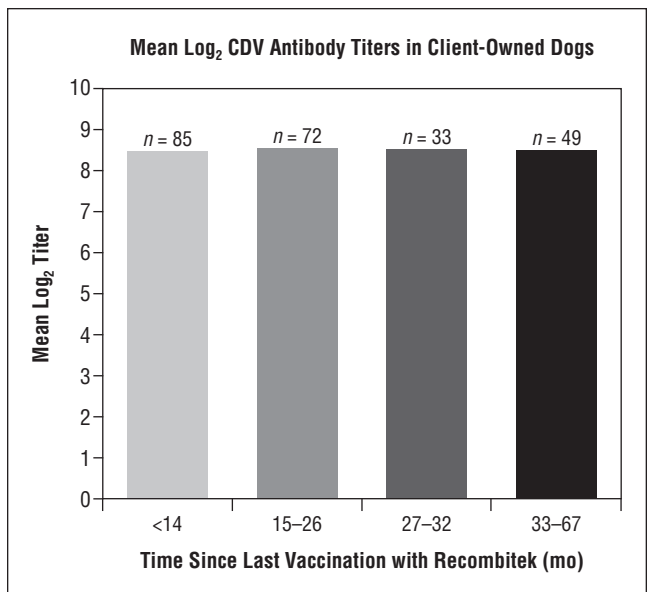


Figure 2. Mean \log_2 canine distemper virus (CDV) antibody titers in client-owned dogs that received Recombitek.

ministered to adult dogs less frequently than the manufacturer's label recommendations. These results show that like MLV-CDV vaccines, the rCDV vaccine can be used in a vaccination program such as the one recommended by the AAHA Canine Vaccine Task Force; that is, subsequent to the puppy vaccination sequence, the dog should be revaccinated at 1 year of age and then no more often than every 3 years. Recombitek can confidently be administered every 3 years, with assured protection from CDV disease.

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