

What about using the rCDV vaccine when boosting an animal previously vaccinated with a conventional MLV-CDV?

In two (2) separate studies conducted at the University of Wisconsin-Madison using multiple distemper vaccines on the market, it has been shown that RECOMBITEK® (rCDV) vaccine is more likely to significantly boost the antibody immune response, regardless of whether the dog was originally vaccinated with a MLV vaccine or the rCDV vaccine. This is a real advantage with the new vaccination schedule where vaccination for core vaccines will be done not more often than every 3 years.

What studies have been and are being conducted on the DOI for the distemper vaccines, both conventional and recombinant?

I recently completed a preliminary study using a small number of dogs that demonstrated the DOI for rCDV is at least 2.5 years. These dogs when challenged intranasally with CDV showed no clinical signs of disease and all of the dogs developed anamnestic antibody response within 3 days of challenge, demonstrating immunologic memory. Based on my results of 2.5 years, it is highly likely that the rCDV product will have a DOI of 3 years or more. I currently have many more dogs on DOI studies to prove this belief.

In a larger study, in which serologic data was collected on more than 50 RECOMBITEK® vaccinated dogs (in a CDV-free environment), it was shown that immunologic memory persists for up to 3 years. Challenge studies are already planned to follow-up this study.

Currently, a total of 65 dogs are involved in DOI studies using RECOMBITEK® C6. The dogs were divided into 4 groups vaccinated in September 2002, January 2003, August 2003, and July 2004. The dogs in these groups will be challenged with CDV, CPV-2 and CAV-1 in September 2004, January 2005, and August 2005 to obtain DOI data at time points ranging from 6 months to 3 years. Based on my experimental study results to date, I anticipate that a 3 year DOI will be easily achieved.

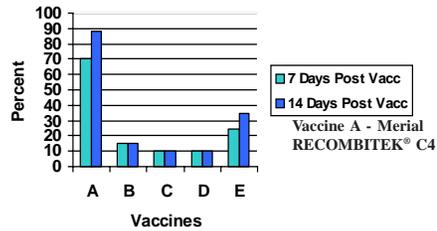
What conclusions are you able to draw from the study results you have now on the recombinant distemper vaccines?

Based on my recent experimental results with RECOMBITEK® rCDV vaccines, I can now make the following recommendations:

1. The rCDV product can **and should** be used in shelters, kennels, breeding colonies and puppy facilities.
2. The rCDV products should be the product of choice to revaccinate dogs to stimulate the anamnestic response.
3. The rCDV product is **the only** vaccine that should be used when vaccinating wild and exotic species against CDV.
4. The rCDV product can be used in the delayed interval vaccination programs like the one recommended by the AAHA with assurance of 3 years immunization.

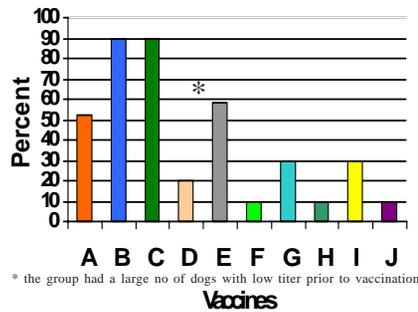
**Study 1
rCDV Booster Vaccination**

Percentage of Dogs with Significant Antibody Response to CDV



**Study 2
rCDV Booster Vaccination**

Percentage of Dogs with Significant Antibody Response to CDV 7 Days Post-Booster Vaccination with CDV



* the group had a large no of dogs with low titer prior to vaccination

Vaccine A - Merial PUREVAX® Ferret Distemper
Vaccine B - RECOMBITEK® C6
Vaccine C - RECOMBITEK® C4

Canine Distemper & Vaccination

Questions and Answers on the use of Recombinant Canine Distemper Vaccine Within the 2003 Canine Vaccine Guidelines and Compared to Conventional MLV-CDV vaccines

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A tenured professor at University of Wisconsin-Madison's School of Veterinary Medicine, Dr. Schultz's diverse background includes the teaching of Agriculture and Life Sciences, Microbiology & Immunology, and Environmental Toxicology.

Dr. Schultz holds a Doctorate in Microbiology and Immunology from Pennsylvania State University and held teaching, research and clinical positions at Cornell and Auburn Universities prior to the University of Wisconsin. He served as the first President of the American Association of Veterinary Immunologists, and has authored some 200 articles in peer-reviewed journals, edited several books and holds a number of registered patents.

Through extensive research programs, Dr. Schultz continually contributes to the fields of clinical immunology, immunopathology associated with viral diseases, immunomodulators, vaccinology and zoonotic diseases.

Introduction

While the safety of the recombinant canine distemper vaccine (rCDV) is well established, the efficacy of this product was not sufficiently addressed in the American Animal Hospital Association (AAHA) 2003 Canine Vaccine Guidelines. The simple fact is that the research needed to make appropriate duration of immunity (DOI) and efficacy determinations was not completed in time for AAHA Canine Vaccine Task Force considerations and review. Recently, Dr. Ronald D. Schultz, whose pioneering research spans over two decades, shared the results of some recently completed studies and several ongoing studies in an attempt to answer questions about the efficacy of the recombinant distemper vaccine during presentations at the 2004 ACVIM convention in Minneapolis, Minnesota, and AVMA convention in Philadelphia, Pennsylvania. Following are some of the key questions and answers addressed by Dr. Schultz in his research at the University of Wisconsin-Madison and presented at these national veterinary conventions.

Why is vaccination for distemper so important?

Infection with canine distemper virus (CDV) causes significant morbidity in unprotected animals and is associated with high rates of mortality from respiratory, gastrointestinal and neurological abnormalities. Depending upon which strain of virus has infected a dog, neurological disease can manifest as acute, subacute or chronic encephalomyelitis. Furthermore, there is minimal geographic difference in CDV distribution, and it is highly contagious.

What were the original AAHA 2003 Canine Vaccine Guidelines and Recommendations for vaccination against distemper?

The AAHA 2003 Canine Vaccine Guidelines stated that all puppies should be vaccinated with a CDV vaccine. If a conventional modified live canine distemper virus (MLV-CDV) vaccine was used, puppies (≤ 16 wks of age) should receive 1 dose at 6-8 weeks, 9-11 weeks, and 12-14 weeks of age. They should receive a booster vaccination at 1 year, and subsequently be revaccinated once every 3 (three) years. If the puppy is >16 weeks of age at the time of initial vaccination, 1 dose is protective for 1 year. They should be revaccinated at 1 year then subsequently revaccinated once every 3 years.

Since information was lacking, the 2003 AAHA Canine Vaccine Guidelines went on to state, if a recombinant (canarypox-vectored) CDV (rCDV) was used, puppies (≤ 16 weeks of age) should receive 1 dose at 6-8 weeks, 9-11 weeks and 12-14 weeks of age. A dose ≥ 4 weeks after the last dose in this series will significantly increase the likelihood of sterile immunity with this product. Puppies >16 weeks of age should receive 2 doses, 2-4 weeks apart. All dogs should then receive a booster at 1 year, and annually thereafter.

The guidelines also stated that a vaccination program that included MLV-CDV for initial vaccination followed by booster vaccinations with recombinant canine distemper virus vaccine provided excellent protection and protection was also conferred with revaccination using rCDV every 3 years.

Why was the recombinant distemper vaccine differentiated from the other major distemper vaccines in the AAHA 2003 Canine Vaccine Guidelines and Recommendations?

In the original Minimum Protective Dose studies with rCDV antibody titers were low or there were no titers. It was believed that recombinant distemper vaccine did not routinely provide sterile immunity (a serum antibody level at which no viral replication occurs) and a longer period of the time was necessary to protect immunologically naive dogs. Therefore rCDV was not recommended where CDV was a serious threat for puppies (e.g. shelters, kennels, puppy/pet stores). In addition, the DOI for rCDV has not been tested beyond 1 year, therefore annual revaccination was recommended.

Why consider an alternative CDV vaccine?

A considered advantage of virus-vectored vaccines, like rCDV (RECOMBITEK[®]), is the unparalleled safety. Adverse reactions such as post-vaccinal encephalitis which have long been associated with conventional MLV-CDV vaccines are not possible with rCDV. It is estimated that post-vaccinal encephalitis occurs in 1 of 10,000 doses given of the Rockborn and Snyder Hill MLV-CDV strains, and in 1 of 50,000 doses given for the MLV-CDV Onderstepoort and Lederle strains (Schultz et al - unpublished). Modified live CDV vaccines also create a transient immuno suppression for up to 9 days when combined with canine adenovirus 1 or 2 (CAV). With rCDV such immunosuppression does not occur. Furthermore, MLV-CDV vaccine virus infects lymphocytes of the central and peripheral lymphoid tissues, posing a possible concern in an animal with genetic predisposition to immune-mediated and/or immunodeficiency disorders. Again, this is not an issue with rCDV as the vaccine elicits an immune response without utilizing the complete distemper virus.

Virus-vectored vaccines like RECOMBITEK[®] are designed to work around such safety issues. This type of vaccine combines the efficacy of modified live vaccines with the safety of killed ones, by including only the genetic material that codes for the protective antigen(s). The recombinant canine distemper virus vaccine cannot cause the disease it was designed to prevent since it includes only a small fraction of the disease-causing organism. Virus-vectored vaccines require no adjuvant cannot revert to virulence and are potentially less dangerous to immunosuppressed or malnourished animals that are modified live vaccine.

In addition to this excellent safety profile, my recent studies comparing RECOMBITEK[®] to the other major distemper vaccine brands vaccine show that rCDV is as efficacious, if not more so, than the conventional MLV-CDV vaccines. Because virus-vectored vaccines attempt to replicate after administration, they provide both a cell-mediated and humoral immune response like the current MLV-CDV vaccines. These studies further demonstrates that rCDV immunize puppies at an earlier age than conventional MLV-CDV vaccines even when Passively Acquired Maternal Antibody (PMA) is present. In another study, recombinant canine distemper vaccine greatly enhanced (boosted) the immune response of actively immunized dogs. So aspects of rCDV originally considered to be weaknesses by the members of the AAHA Vaccine Guideline Committee actually turned out to be unparalleled strengths of rCDV.

Why was rCDV not previously recommended for use against distemper in shelter situations?

The original studies on rCDV suggested that the vaccine did not routinely provide sterile immunity and may take longer to protect immunologically naive dogs. My recently completed studies on rCDV suggested otherwise. Puppies were fully protected from clinical distemper with just 1 dose of rCDV and 2 doses gave a very high antibody titer when compared to the conventional MLV-CDV vaccines.

Can puppies vaccinated with 1 dose of rCDV be protected against distemper?

In my study at the University of Wisconsin-Madison, designed to mimic an animal shelter environment, I wanted to find the answer to the question, "Will puppies vaccinated with 1 dose of RECOMBITEK[®] C6 (recombinant canine distemper, adenovirus type 2, parainfluenza, parvovirus vaccine, with *Leptospira canicola*, *L. icterohaemorrhagiae* bacterin) 4 hours prior to being palced in a room with CDV-infected/diseased dogs be protected against disease?"

The answer was "YES"

All of the RECOMBITEK[®] vaccinated puppies (12 weeks old and CDV antibody negative) were protected from development of clinical distemper. They remained healthy for 4 weeks post-challenge, at which time they were placed in another study.

Although 2 and even 3 doses of rCDV were the original recommendations made in the AAHA 2003 Canine Vaccine Guideline in my study designed to test the efficacy of a single dose of rCDV protection was provided even against a challenge as soon as 4 hours after vaccination.

How does rCDV compare to conventional MLV-CDV vaccine in the face of passive maternal antibody?

Studies recently concluded demonstrates that rCDV is more likely to provide active immunization in the face of PMA than the conventional MLV vaccines. Thus, more puppies were immunized at an earlier age with the rCDV vaccines.

In one study conducted to evaluate the effect of PMA on vaccination with rCDV, several groups of puppies were administered two vaccinations (initial and second vaccinations) with rCDV vaccine. Passive antibody titer was measured at the time of first vaccination and CDV titer was measured again 14 days after second vaccination. CDV Virus Neutralizing Titers persisted even in the face of high passive antibody titers.

In another study, eight (8) groups of puppies received two doses of various CDV vaccines, both conventional MLV, DNA experimental, and rCDV. The percentage of puppies with significant antibody response was much higher in the rCDV vaccinated puppies than in those vaccinated with the leading conventional CDV vaccines or the DNA experimental product.

Challenge Studies of Pups with PMA* that Were Vaccinated with Various Vaccines

Vaccines	Morbidity	Mortality
A (rCDV-Ferret 1:3)	3/9 - 33%	2/9 - 22%
B (RECOMBITEK C4)	2/9 - 22%	2/9 - 22%
C (Naked DNA)	2/9 - 22%	2/9 - 22%
D (CDV/MV)	2/9 - 22%	1/9 - 11%
E (MLV)	6/9 - 66%	6/9 - 66%
F (Saline)	8/9 - 88%	7/9 - 77%

*PMA titers identical among groups-pups vaccinated 2 times at 4 week interval. Challenged 4 weeks after 2nd dose

In addition, other challenge studies of puppies with PMA that were vaccinated with various vaccines revealed that the RECOMBITEK[®] products resulted in significantly less morbidity and mortality when compared to conventional MLV-CDV vaccines and saline control. Morbidity and mortality in the MLV group was more than twice that of the RECOMBITEK[®] groups.