Three-Year Duration of Immunity in Dogs Following Vaccination Against Canine Adenovirus Type-1, Canine Parvovirus, and Canine Distemper Virus*

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CLINICAL RELEVANCE

A challenge-of-immunity study was conducted to demonstrate immunity in dogs 3 years after their second vaccination with a new multivalent, modified-live vaccine containing canine adenovirus type-2, canine parvovirus (CPV), and canine distemper virus (CDV). Twenty-three seronegative pups were vaccinated at 7 and 11 weeks of age. Eighteen seronegative pups, randomized into groups of six dogs, served as challenge controls. Dogs were kept in strict isolation for 3 years following the last vaccination and then challenged sequentially with virulent canine adenovirus type-1 (CAV-1), CPV, and CDV. For each viral challenge, a separate group of six control dogs was also challenged. Clinical signs of CAV-1, CPV, and CDV infections were prevented in 100% of vaccinated dogs, demonstrating that the multivalent, modified-live test vaccine provided protection against virulent CAV-1, CPV, and CDV challenge in dogs 7 weeks of age or older for a minimum of 3 years following second vaccination.

INTRODUCTION

During the past 35 years, infectious canine diseases have been effectively controlled through traditional puppy vaccination protocols followed by annual revaccination of adult dogs. Historically, when doubt existed regarding the need for revaccination, clinicians generally opted to revaccinate on the premise of providing the dog with maximum protection.[1] In recent years, this practice has come into

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question, largely as a result of concerns about potential adverse reactions to vaccines and the limited scientific evidence supporting traditional vaccination protocols.[1–3] A number of investigators and immunologists have presented immunologic and serologic evidence suggesting that vaccine-induced immunity lasts longer than 1 year.[1,4–9] The American Veterinary Medical Association (AVMA) Council on Biologic and Therapeutic Agents (COBTA) has recommended that veterinarians take an active role in determining the most appropriate vaccination protocols based on individual patient needs.[1]

A significant development in the vaccine protocol debate occurred when the American Animal Hospital Association (AAHA) Canine Vaccine Task Force published its *2003 Canine Vaccine Guidelines and Recommendations*. These guidelines defined core (routine for most dogs) and noncore (recommended based only on specific need) vaccine antigens and recommended adoption of triennial vaccination protocols when using certain core vaccines, including canine distemper virus (CDV), canine adenovirus type-2 (CAV-2), and canine parvovirus (CPV).[10]

The questioning of long-established annual protocols and publication of the AAHA guidelines have generated confusion and unease within the veterinary community as to what is and should be the standard of practice related to vaccination protocols to best meet patient needs. Though there is much debate about whether 1- or 3-year vaccination protocols should be the standard, there does appear to be consensus in peer-reviewed literature regarding the pressing needs for additional vaccine information from experts and for more scientific evidence, particularly challenge-of-immunity data, to evaluate extended duration of immunity (longer than 1 year) following vaccination.[3,11–14]

The objective of the present study was to use real-time, challenge-of-immunity testing methodologies to demonstrate duration of immunity of at least 3 years in dogs following second vaccination with a new multivalent, modified-live CDV, CAV-2, and CPV vaccine.

MATERIALS AND METHODS

Dogs

The 41 antibody-profile–defined beagles used in this study were bred specifically for study purposes by a commercial supplier. Identification of each dog was ensured through the use of individual permanent ear tattoos, each marked with a unique alphanumeric sequence.

To prevent any passage of maternal antibody protection to dogs used in this study, their dams had been housed in highly secure barrier-isolation (ABSL2) facilities since birth and maintained free of vaccination against bacterial or viral pathogens, including CAV-2, CPV, and CDV. Similarly, the study dogs were neither vaccinated against nor exposed to any of these pathogens; like their dams, they were housed in strict isolation in highly secure ABSL2 facilities. Prevaccination serology test results confirmed that the pups were seronegative to the above pathogens as determined by serum neutralization (SN) titer tests (1:2 or less). Dogs were fed standard growth or maintenance dog food rations, and water was avail-

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able ad libitum. Dogs remained sexually intact—neither spayed nor neutered.

Study dogs were randomly assigned to treatment and control groups, which were maintained uniformly based on age and gender. Dogs were segregated in separate facilities based on gender. Injuries and deaths occurring after vaccination and before challenge were documented and reported with study data submitted to the USDA.

Average pup age was 7.1 weeks (50 days) at time of initial vaccination and 11.1 weeks (78 days) at time of second vaccination. Following vaccination, the general health of each pup was observed and recorded daily. Veterinarian-supervised care and treatment for non–study-related health concerns were provided to all dogs throughout the 3-year (39-month) study period. Test animals seriously compromised as a result of non–study-related medical or physical reasons were removed from the study until recovery or were euthanized.

Test Vaccine

The new modified-live virus test vaccine (Continuum DAPP, Intervet) includes the three components in Continuum DAP as well as canine parainfluenza virus. The vaccine contained the following attenuated strains, which are found in Continuum DAP:

- Manhattan strain of CAV-2 (which confers cross-protection against canine infectious hepatitis caused by CAV type-1 (CAV-1) without the adverse reactions associated with CAV-1, such as corneal edema)[15]
- High-titer patented CPV STRAIN 154 (Intervet, US Patent No. 4,810,494) of canine origin
- High-titer Onderstepoort strain of CDV

Viral vaccine components were formulated at maximum virus passage level from the master seed virus (MSV). The serial was formulated at minimum production titers, lyophilized in one-dose vials, and stored at 4°C until use. This vaccine was presented in a desiccated form with sterile diluent provided for reconstitution.

Vaccination Protocol

At 7 and 11 weeks of age, 23 of the seronegative pups were given a 1-ml dose of the multivalent vaccine (rehydrated with 1 ml of sterile diluent) SC in the scruff of the neck.

Serologic Assays

CAV-2, CPV, and CDV antibody levels were established in each test dog before vaccinations at 7 and 11 weeks of age. A blood sample from each dog was evaluated for antibodies using SN testing methodology. Similarly, following second vaccination, blood samples from vaccinates and control dogs were evaluated quarterly throughout the 36-month evaluation isolation period for SN titers for antibodies against CAV-2 and CDV and hemagglutination inhibition (HI) titers for antibodies against CPV.

Test animals were held in strict isolation for 36 months following vaccination.

Challenge Protocol

This challenge-efficacy study was performed in compliance with the 9 CFR §§ 113.317, 113.306, and 113.305 specifications required to obtain a vaccine license and 3-year duration-of-immunity claim from the USDA.[16]

Test animals were held in strict isolation for 3 years (36 months) following vaccination. After this postvaccination isolation period, the dogs were challenged sequentially, first with virulent CAV-1 (Mirandola strain, intravenous challenge), second with CPV (CPV type-2b field isolate, oral/nasal challenge), and third with CDV (Snyder Hill strain, intracranial challenge). National Veterinary Services Laboratories (NVSL) challenge strains obtained from the Center for Veterinary Biologicals–Laboratory (CVB-L) were used. These challenges occurred at 37, 38, and 39 months after vaccination, respectively. For each individual virus challenge, a new group of six age-matched, nonvaccinated control dogs was also challenged. Unlike the vaccinate group, each control group was exposed to only one of the challenge organisms. Immediately before each challenge, blood samples were drawn from each dog and evaluated using SN or HI testing methods to determine serologic status at the time of challenge.

In addition, before CAV-1 challenge, all vaccinates and the six controls assigned to the specific challenge subgroup were transferred from isolation to challenge facilities. Any remaining control subgroups stayed at the production facilities until needed for their respective challenge test.

Daily clinical examinations were performed on all dogs beginning 4 days before each challenge and during the postchallenge observation period as mandated by 9 CFR guidelines. Clinical signs for the particular challenge virus infections were recorded daily. In our reported clinical observations following all three viral challenges, pyrexia was defined as temperatures of 103.4°F or higher (as defined for CPV challenges in 9 CFR § 113.317).[16]

Statistical Analysis

Chi-square analysis was used to determine significant differences in disease incidence between vaccinated test dogs and nonvaccinated control dogs following CAV-1, CPV, and CDV challenges. Disease criteria evaluated included clinical signs, lymphopenia, and viral shedding. Differences in data analyzed by statistical methods were considered significant at $P \leq .05$.

RESULTS

Serologic Tests

All dogs were seronegative for CAV-2, CPV, and CDV on the day of initial vaccination as demonstrated by SN titer evaluation. Following second vaccination, serum antibody titers were measured quarterly and all dogs responded serologically to CAV-2, CPV, and CDV antigens, demonstrating that the multivalent vaccine elicited strong initial antibody responses. Geometric mean titers (GMTs) remained at high levels throughout the postvaccination isolation period (Table 1). At 36 months after vaccination, GMTs were 1:357 for CAV-2, 1:237 for CPV, and 1:193 for CDV.

Following second vaccination, all dogs responded serologically to CAV-2, CPV, and CDV antigens.

CAV-1 Challenge

Severe clinical signs of CAV-1, including depression, diarrhea, increased water consumption, anorexia, corneal opacity, and vomiting, were seen in five (83%) of the six control dogs (Table 2). The remaining control dog died before developing clinical signs. Three (50%) of

TABLE 1. Geometric Mean Titers in Dogs Following Second Vaccination with CAV-2, CPV, and CDV

Virus Fraction (Assay)	*Prevaccination*	*Months after Vaccination*									
		1	*3*	*6*	*9*	*12*	*21*	*24*	*30*	*33*	*36*
CAV-2 (SN)	<2	89	153	964	497	672	368	379	332	256	357
CPV (HI)	<10	567	680	1,444	395	640	350	257	192	151	237
CDV (SN)	<2	402	781	195	110	241	201	48	144	100	193

HI = hemagglutination inhibition titers; SN = serum neutralization titer test.

the six control dogs died following CAV-1 challenge. Conversely, clinical signs of CAV-1 infection were prevented in 100% of the vaccinated dogs.

Note: Protection against CAV-1 is obtained from the cross-protection provided by CAV-2 vaccines. Because CAV-2 vaccines have been shown to have less potential to induce adverse responses, only vaccines containing CAV-2 are recommended for use.[1,16] For the CAV-2 component of this vaccine, a 3-year duration of immunity is supported by data demonstrating a robust serologic response to CAV-2 throughout the 36-month postvaccination period and strong cross-protection (100%) against heterologous CAV-1 challenge in dogs.

CPV Challenge

Following CPV-2b challenge, all six control dogs showed lymphopenia and severe clinical signs of CPV, including depression, diarrhea, dehydration, anorexia, vomiting, and pyrexia, lasting for 3 to 11 consecutive days (Table 3). Two (33%) of the six control dogs died following challenge.

Fecal samples were evaluated for presence of CPV using standard hemagglutination (HA) methods. Dogs with a viral HA titer at a level of 1:64 or higher in a 1:5 dilution of feces were considered to be infected and shedding virulent CPV. All of the control dogs excreted virulent CPV in their feces. In contrast, no vaccinates excreted virus. Eight of the 22 vaccinated dogs had unrelated, infrequent clinical signs of short duration (2 days or less). Although clinical signs resulting from CPV-2b infections characteristically appear 4 to 5 days after challenge, isolated occurrences of diarrhea or vomiting were reported as early as 1 day after challenge in some of the vaccinated dogs, which is inconsistent with CPV infection. Clinical signs required to confirm the presence of CPV infection were prevented in 100% of the vaccinated dogs.

CDV Challenge

Three control groups were used to evaluate the severity of CDV challenge. These three groups included the six age-matched controls challenged with the full challenge dose, an additional five seronegative 10- to 12-week-old pups challenged with the full challenge dose, and another five seronegative 10- to 12-week-old pups challenged with one-tenth of the challenge dose. The two groups of 10- to 12-week-old pups were included to verify the severity of the CDV challenge. Severe clinical signs of CDV, including depression, dehydration, salivation, apprehension, diarrhea, anorexia, inability to rise, pyrexia, tremor, and vomiting, were seen in 100% of the control dogs in all groups (Table 4). Two (33%) of the age-matched control dogs, five (100%) of the 10- to 12-week-old pups

TABLE 2. Clinical Signs and Death in Dogs Following CAV-1 Challenge

	No. of Dogs				
Test Group	*Total*	*Clinical Signs*[a]	*Temperature ≥ 103.4°F*	*Deaths*	***Total No. of Ill Dogs***
Vaccinates	23	0	0	0	0[b]
Controls	6	5	4	3	6

[a]Depression, diarrhea, increased water consumption, anorexia, corneal opacity, and vomiting.
[b]One vaccinated dog died 3 days after challenge due to physical injury.

TABLE 3. Clinical Signs and Death in Dogs Following CPV-2b Challenge

Test Group	*No. of Dogs*	*Positive Virus Isolation*	*Lymphopenia (≥50% Baseline Value)*	*Clinical Signs*[a] *(No. of Days Sick)*	*Deaths*
Vaccinates	22	0	0	8 (≤2)	0
Controls	6	6	6	6 (3–11)	2

[a]Depression, diarrhea, dehydration, anorexia, vomiting, and pyrexia.

challenged with the full challenge dose, and four (80%) of the 10- to 12-week-old pups challenged with one-tenth of the challenge dose died following challenge. Clinical signs and death resulting from CDV infection were prevented in 100% of the vaccinated dogs.

Statistical Evaluation

Significant differences (P = .001 for CAV-1 and CDV challenges; P = .005 for CPV challenge) were seen between vaccinated test dogs and nonvaccinated control dogs in clinical signs manifested following CAV-1, CPV, and CDV challenges (1 day or more after challenge). Similarly, significant differences (P = .001) were also seen between vaccinated and control dogs in viral shedding titers and incidence of lymphopenia following CPV challenge.

DISCUSSION

Results of this study demonstrated that this new multivalent, modified-live test vaccine provided protection against virulent CAV-1, CPV, and CDV challenges in dogs 7 weeks of age or older for a minimum of 3 years following second vaccination. These findings are significant when examined in the context of current scientific thought and recommendations from advisory groups related to vaccination protocols.

AVMA has stated that some vaccines provide duration of immunity beyond 1 year, and AAHA has recommended triennial revaccination with some core antigens.[1,10] These recommendations were published as guidelines, not standards, and without definitive challenge-of-immunity data to support extension of current annual vaccination protocols (other than for the rabies antigen).[17] In fact, scientific data providing evidence of long-term duration of immunity as a result of vaccination are limited.[11] Most estimates of the duration of immunity induced by vaccines have been based on the persistence of serum antibodies, although serologic evidence alone may not be conclusive for

certain antigens.[11] Antibody titers are correlated with protection against CAV-1, CPV, and CDV, among others, and there has been serologic evidence that titers for these antigens persist for extended periods.[1,2–9,18]

TABLE 4. Clinical Signs and Death in Dogs Following CDV Challenge

	No. of Dogs			
Test Group	*Total*	*Clinical Signs*[a]	*Deaths*	***% Dead***
Vaccinates	22	0	0	0
Adult controls	6	6	2	33
Puppy controls	5	5	5	100
Puppy controls (diluted challenge)[b]	5	5	4	80

[a]Depression, dehydration, salivation, apprehension, diarrhea, anorexia, inability to rise, pyrexia, tremor, and vomiting.
[b]Diluted challenge was 1:10 dose of standard challenge.

Alternatives to challenge studies, such as analyses of serologic data, are generally not acceptable for establishing the efficacy of a vaccine.[11] Such data can be considered only when reasonable evidence exists that the serologic test is indicative of protection.[11] For example, one group of investigators found serologic evidence of long-lived immunity to CPV and CDV in vaccinated dogs but pointed out that deviations from annual revaccination should be justified only on the basis of scientific evidence. The group recommended continuation of annual revaccination against CPV on the basis of serologic evidence alone, which indicated that fewer than its target of 90% of test animals had protective titers.[5]

In the absence of challenge-of-immunity data, serologic data have inherent limitations. There has been little standardization of serologic testing methodology to allow easy, consistent interpretation of results between or among laboratories.[11] Variations exist within and among laboratories, and there is a lack of validated sensitivity, specificity, and confidence intervals; thus, an investigator could send aliquots of one sample to five different clinical laboratories and receive five different results. Furthermore, serologic results do not appear to be a sensitive indicator of immune response for some diseases or vaccines in cats and dogs. It also is difficult to interpret titers that provide less than sterile immunity but still protect from disease challenge.[7,11] These limitations have lead COBTA and others to conclude that serologic testing is generally unreliable.[1,11]

Significant differences in clinical signs, viral shedding titers, and incidence of lymphopenia were seen between vaccinated and control dogs.

Additional scientific studies, particularly challenge tests, have been called for by many in the veterinary profession to help determine vaccine duration of immunity.[1,3,13] There is evidence published in peer-reviewed journals to indicate that data from studies involving a single killed or modified-live virus vaccine cannot always be used to predict the immune responses or degree of protection after challenge expo-

sure induced by other similar vaccines, even when they contain the same antigens.[7] Vaccines vary tremendously in postvaccination duration of immunity based on route of administration, immunizing strains and antigen content, potency, MSV, production method, adjuvant used (if any), level of attenuation, and whether the vaccine contains killed or modified-live virus.[10,11,17]

A need for challenge-efficacy data and vaccine labeling that includes both minimum and maximum duration-of-immunity information has been identified.[2,3] Furthermore, while serologic evidence suggests that some vaccines may offer extended protection, giving a vaccine less frequently than a label directs presents a risk to practitioners.[3,7] If veterinarians elect to use revaccination intervals other than those indicated on a vaccine label, advisors have recommended they should do so on the basis of the preventive medicine needs of individual patients and sound immunologic principles accompanied by adequate informed consent from the client and documentation by the veterinarian.[7]

In light of these shortcomings of serologic testing alone, challenge data are considered to be the gold standard when assessing immunity in dogs.[1,11,18] The significance of this study is that the results provide real-time challenge-of-immunity data to demonstrate extended (3-year) duration of immunity in the face of CAV-1, CPV, and CDV challenge. The data are also specific for a vaccine labeled in accordance with 9 CFR to attain 3-year duration of immunity following vaccination with three antigens recommended by AAHA to be part of a core program with triennial revaccination. In accordance with 9 CFR, the study design met—and in some cases exceeded—the use of the required minimum of 25 test animals (20 vaccinates and five controls for each specific challenge). In addition, the requirements were met for at least four of five (80%) of the controls showing severe clinical signs of canine hepatitis following CAV-1 challenge, at least 80% of controls showing three of four criteria for CPV infection following CPV challenge, and at least 80% mortality following CDV challenge. To our knowledge, this is the first time that a nonrabies vaccine has received a 3-year duration-of-immunity label approval from USDA in full accordance with 9 CFR standards.

These study results provide scientific evidence supporting the triennial revaccination guidelines recommended by AAHA. The challenge for veterinarians is how to implement the guidelines in their practices. COBTA has concluded that inadequate data exist to scientifically determine a single, one-size-fits-all vaccination protocol for dogs and cats. Experts agree that variations exist among patients, their lifestyles, and their relative disease risks, as well as among individual vaccines. Thus, the best approach is to evaluate each dog's risk factors and tailor vaccination to the specific needs of the patient rather than to a routine protocol.[1,11] COBTA, AAHA, and others suggest that veterinarians focus on a core vaccination program using their experience in their geographic area, patient and client profiles, and the best current scientific data to determine the appropriate

The results provide real-time challenge-of-immunity data to demonstrate extended duration of immunity in the face of CAV-1, CPV, and CDV challenge.

vaccination protocol for each patient.[1,2,10] One technique that may be of use to clinicians is to develop a health-risk profile for each patient, including risk of exposure and infection, and estimated consequence of infection.[19] Individual health risk is determined by three factors:

- Host factors (e.g., age, stress, concurrent illness, heredity)
- Environmental factors (e.g., population density, geographic area, cleaning techniques and floor plan in housing, temperature, humidity, exposure to other animals)
- Pathogen-related factors (i.e., virulence, dose, and mutation, often related to population density and rate of virus replication)

Choosing whether to vaccinate should be a medical decision based on the needs of each patient, entailing the same considerations and reasoning skills required when selecting appropriate medical treatment or a specific surgical procedure.[2] For further guidance about how to implement a 3-year vaccination protocol, clinicians may refer to the complete AAHA *2003 Canine Vaccine Guidelines and Recommendations* (including full text of guidelines, recommendations, and supporting literature), available to AAHA members on the organization's Web site (www.aahanet.org).

CONCLUSIONS

Using real-time, challenge-of-immunity methodologies, study results met or exceeded 9 CFR requirements to demonstrate that this new multivalent, modified-live test vaccine provided protection against virulent CAV-1, CPV, and CDV challenges in dogs 7 weeks of age or older for a minimum of 3 years following second vaccination. The findings provide scientific support via gold standard challenge data to support veterinarians who would like to implement recent recommendations by AAHA for triennial CAV-2, CPV, and CDV revaccination protocols in adult dogs.

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