Scientific Report

EFFICACY OF A HALF-DOSE CANINE PARVOVIRUS AND DISTEMPER VACCINE IN SMALL ADULT DOGS: A PILOT STUDY

W. Jean Dodds, DVM
Hemopet, 11561 Salinaz Avenue, Garden Grove, CA 92843; Phone: 714-891-2022, ext. 115; Fax: 714-891-2123;
E-mail: info@hemopet.org

ABBREVIATONS

CAV-2 – canine adenovirus-2 CDV – canine distemper vaccine CPV – canine parvovirus vaccine DOI – duration of immunity
DPV – canine distemper and parvovirus vaccine ELISA – enzyme-linked immunosorbent assay FPV – feline panleukopenia virus

FCV – feline calicivirus FHV – feline herpesvirus
HI – hemaglutination inhibition MLV – modifi live virus
OD – optical density
SN – serum neutralization
VAAE – vaccine-associated adverse events

ABSTRACT

Small adult dogs between 3 and 9 years of age, participated in a clinical research study to determine whether giving them just a half-dose of a bivalent canine distemper and parvovirus vaccine (DPV) generated a protective serum antibody titer response 1 and 6 months later in comparison to pre-vaccination titer levels. None of these dogs had received a vaccination for at least 3 years, and all were healthy. The half-dose vaccine generated increased serum vaccine antibody titers for all of the dogs studied. Results varied quantitatively when titers measured on the undiluted serum were compared to endpoint titers determined on the same samples when the serum was serially diluted. The median titer and endpoint titer levels had a sustained increase in all dogs at 6 months post-vaccination. Results confi that receiving a half-dose of bivalent DPV was effi for this study cohort. Further investigations could address a larger number of smaller breed canines.

INTRODUCTION

Background: Vaccination has been and remains the single most important reason why most pet owners bring their pets to

veterinarians for an annual or more often “wellness visit” (1–8). Despite evidence indicating that annual vaccinations are not necessary for previously immunized pets, many practitioners are reluctant to change their current vaccination programs. This is likely because they rarely are taught applied clinical immunology and may not understand the principles of vaccinal immunity (that portion of immunity conveyed by vaccines) (1–3, 9). Clearly, the accumulated evidence indicates that vaccination protocols should no longer be considered as a “one size fi all” program (10).

(CPV) vaccines can be reduced to 50%, but not more, for small breed and small mixed breed type dogs, based on body weight, and still convey full duration of immunity (1–4). This applies to puppies and older dogs of small breeds and breed types that weigh 12 pounds or less as adults. Serum vaccine antibody titers have also been performed 3 or more weeks

after vaccination. As reported for dogs given a full dose of vaccine (11), greater than 95% of the dogs given a full or a half half dose mounted what is considered to be protective antibody titers to both CDV and CPV (1). To the author's knowledge, there are no parallel published data on half-dose vaccines given to cats (12–14).

It makes little immunological sense to vaccinate toy- and giant-breed puppies and adult dogs, to exemplify the 2 size extremes, with the same dose of vaccine. These products are stated to provide a sufficient excess of antigen for the average-sized animal so they are likely to be either too much for the toy breeds or too little for the giant breeds (2). Although the minimum immunizing doses have been established (2, 5–7), the optimum dosages required for disease protection have yet to be determined. Researchers are still uncertain as to whether these dosages should be based on body mass (2, 6). It apparently depends to some extent upon whether the vaccine is of modified live virus (MLV) attenuated origin or killed inactivated viral origin because of the differing immunogenic principles involved (2, 5, 6, 9). According to some experts, killed, inactivated vaccines should be adjusted for body mass, and yet even today, rabies vaccine — the most potent of all such vaccines — is required by law to be given at a full dose to dogs of all sizes (2, 3). More field evidence and clinical data are still needed today on this important issue.

Similarly, the administration of identical vaccine dosages for animals in all age groups is questionable (2, 3, 6, 13). The combination of certain specific viral antigens such as CDV with canine adenovirus-2 (CAV-2) (for cross-protection against infectious canine hepatitis virus) and/or with CPV has been shown to influence the immune system by reducing lymphocyte numbers and responsiveness (9) and causing thymic depletion (2, 3).

What is the potential effect of those findings on vaccine dosage or age of vaccination, given the wide divergence of size among dog breeds? Why has this been largely ignored by the research and clinical veterinary communities 25 years later? In humans, questions of the vaccine dosage necessary to elicit full protection in infants rather than adults have been addressed for hepatitis B vaccine (15). The investigation was made for economic reasons to determine whether the standard dosage could be split and still afford protection for more than one infant (to reduce

costs of vaccinating children in socioecomically deprived countries). One fifth of the adult dose of hepatitis B vaccine was found to protect infants vaccinated during the first 6 months of life (15).

Tragically, a similar principle was applied to vaccinating children with a 10- to 50- fold higher titered measles virus vaccine in an attempt to overcome maternal immunity. Increased infant mortality resulted, especially in girls, who succumbed to other infections because their immune systems became suppressed (2).

In one study, adult household pets having adequate to very good serum antibody titers to one or more of CDV, CPV and CAV-2 were given an additional polyvalent booster vaccination (7). Two months later, serum antibody titers to these 3 viruses were measured again. Whereas titers to CDV and CAV-2 showed a signifi increase, those for CPV did not (7), raising the question of whether these dogs were already well-immunized against CPV, or if some other immunological mechanism was being invoked. Regardless, the existing CPV antibody titers indicated

study was to see if the simultaneous administration of leptospirosis vaccination had any infl upon the serum antibody titers elicited 11– 13 months later. Additionally, this multivariant study examined 3 different adult age and body weight groups. Some confl results were obtained: signifi lower CPV antibody titers were found in dogs vaccinated with leptospirosis versus those not given leptospirosis vaccine for 2 of the vaccines given to the 2-yr old age group and for 1 vaccine given to the 7-yr and greater age group, but no signifi differences were seen at the 3–6 yr-old ages (6). No signifi differences were seen for CPV titers of any group with respect to body weight. For CDV, no differences were seen for any of the age groups, although a signifi lower CDV titer was seen in those receiving leptospirosis vaccines in the medium weight group but for only 1 vaccine product.

Results for CAV-2 titers also were lower in the leptospirosis vaccine group but for only 1 vaccine product in the 2-yr age group and also in the small dog size group (6).

What do the results of this complex multivariant study reveal? Solid conclusions are difficult to make, except that adding a leptospirosis bacterin to the polyvalent MLV vaccines reduced the subsequent serum antibody titers primarily against CPV. Does this reduction in antibody titer level leave these dogs susceptible to CPV disease? Probably not, as vaccine protection against the CPV, CDV and CAV-2 "core" vaccine antigens is known to be influenced by the age of the animal, with older animals being less susceptible to these viral diseases (11, 13). However, separating leptospirosis vaccines from the rest of the "core" may be the most reliable way to ensure that adequate "core" vaccine immunity is sustained.

Study Objective: The purpose of the current study was to document the serum antibody titer responses from administering a half-dose of a bivalent CDV and CPV (a) to small breed adult dogs that had not been vaccinated in at least 3 years.

METHODS

Eligible small adult dogs betwen 3 and 9 years of age were recruited by posting an announcement on the author's web site (b) and by e-mail to holistic veterinarians and small breed pet owner clients that are entered into the author's

company electronic Laboratory Information System (c).

Participating veterinarians were given an Instruction Sheet **(Figure 1)** and Informed Consent Form to be completed at the time of enrollment and signed by the dog owner **(Figure 2)**.

Prior to receiving a half (1/2 - dose of the bivalent DPV vaccine (a), a pre-vaccination whole blood sample (3–5 ml) was collected by the participating veterinary clinic and allowed to clot by placing it into a plain red-top glass tube (d). The clotted sample was centrifuged, and the separated serum was decanted and placed into a labeled, empty glass or plastic tube for shipment, by fi class or priority mail in a small padded box, to the author's laboratory (c).

Upon receipt at the laboratory, the serum samples were stored at 4°C until assayed in batches. Serum antibody titers were measured for CDV and CPV using previously established enzyme-linked immunosorbent assay (ELISA) methodology, and optical density (OD) readings were obtained with a spectrophotometer (e) (10). The ELISA assay methods used for CDV and CPV have been shown to have high diagnostic accuracy in comparison to the

reference standard assays of serum neutralization (SN) and hemagglutination inhibition (HI) (16).

The participating veterinarians and dog owners had blood from the same dogs collected and processed as described above at 4 weeks and 6 months after each dog had received a half-dose of DPV vaccine. The samples were labeled as 4 weeks Post-DPV and 6 months Post-DPV, and shipped to the author's laboratory.

All 13 samples were assayed at each of the 3 sampling times for CDV and CPV titers; these were measured on the undiluted serum and then in serial dilutions until the endpoint titer was reached. At the 6-month time point, 5 of the samples were inadvertently discarded before being assayed.

RESULTS

The pilot study enrolled 13 adult dogs that weighed 12 pounds or less and had not received any routine booster vaccines for at least 3 years. Two dogs were rejected because they were over 10 years of age, and another 3 were ineligible as they had received booster vaccinations less than 3 years prior.

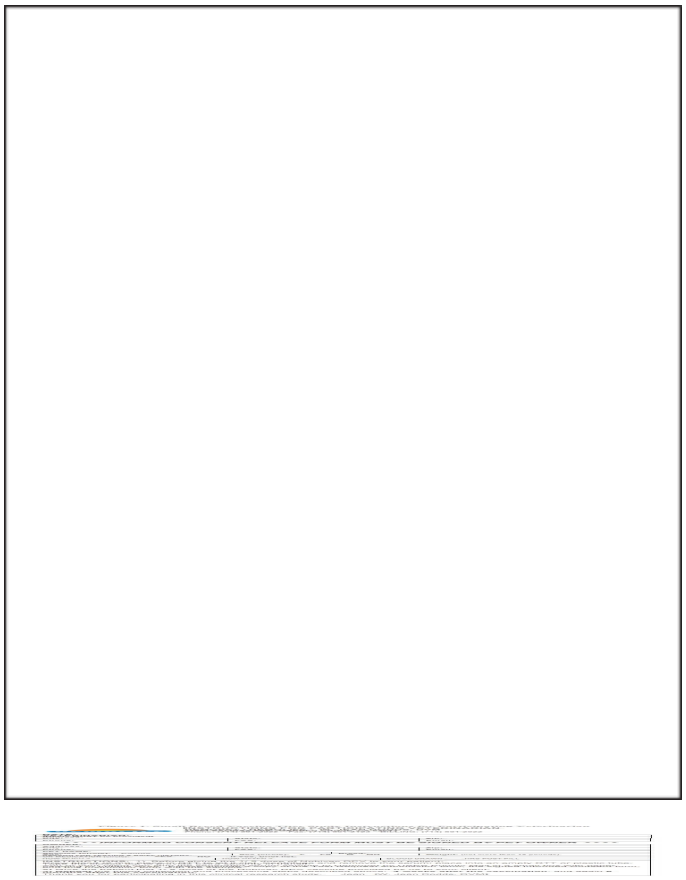


Figure 1: Instruction Sheet

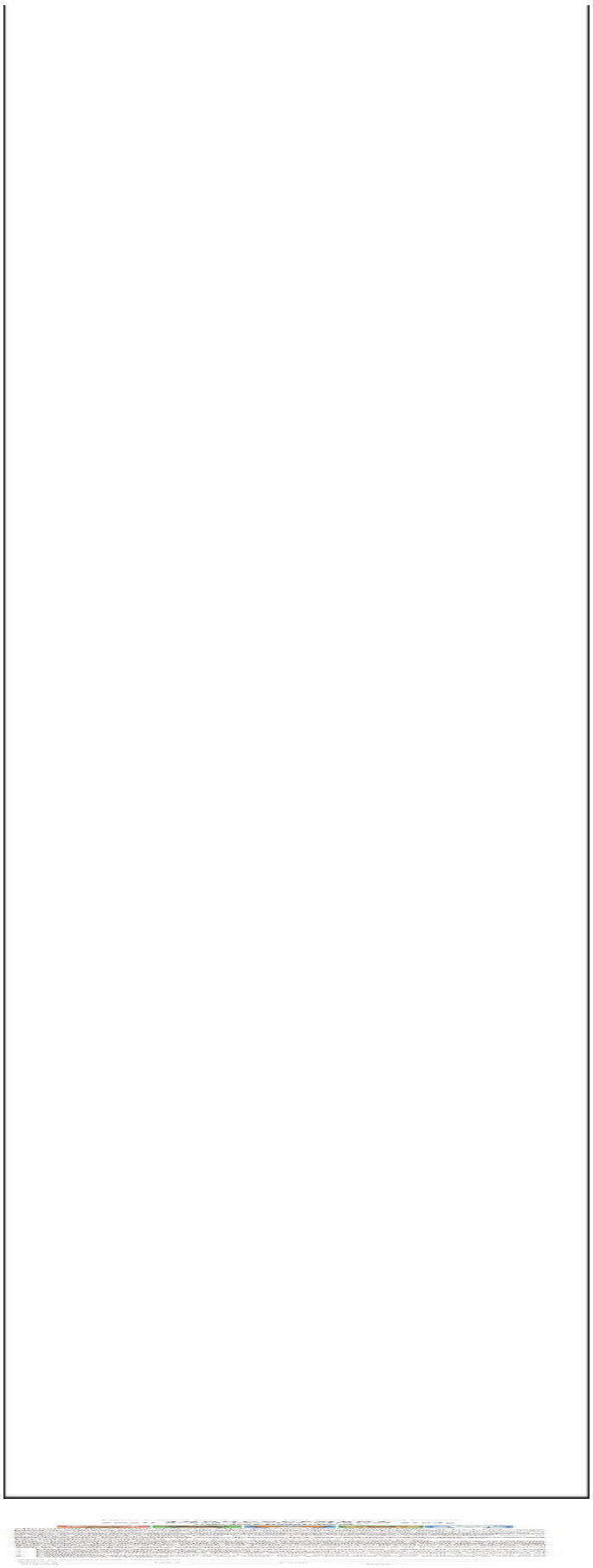


Figure 2: Informed Consent Form

drawn at 6 months but these were inadvertently discarded.

Titers on Undiluted Serum **(Figures 3a and 3b; Table 1)** Results indicated that all 13 dogs (not vaccinated for at least 3 years), had measurable serum antibody titers to both CPV and CDV.

Canine Parvovirus (CPV)

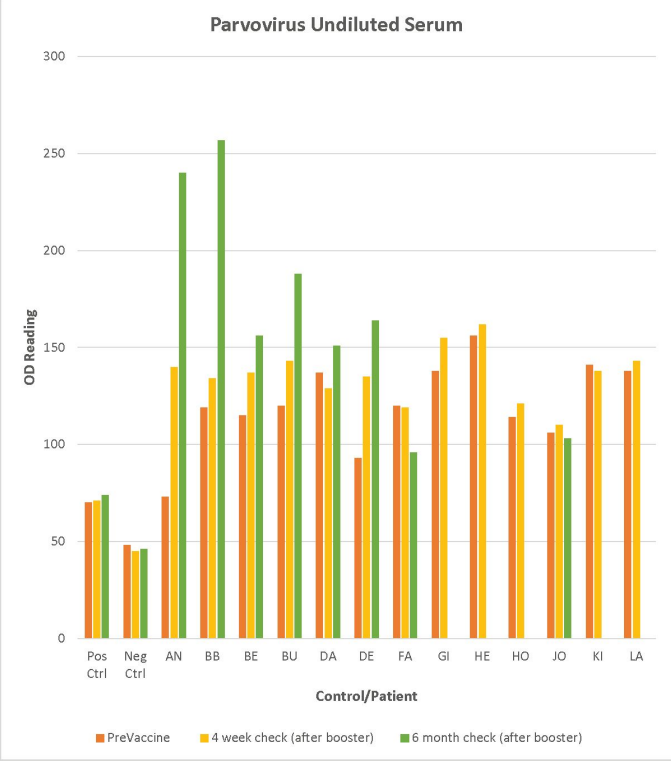
Pre-Vaccination The pre-vaccination titers for CPV were all above the positive control with 12 of 13 being well above that OD level, when measured on the undiluted serum samples **(Figure 3a)**. The median titer level was 125 (range 73–125) **(Table 1)**.

4 Weeks Post -1/2 - Dose Vaccination Four weeks after receiving the 1/2 dose of DPV vaccine, CPV titers rose in 9 of the 13 dogs and stayed essentially the same in the other 4 dogs, whose

Table 1. AHVMF Small Breed Half-Dose Vaccine Study for CPV & CDV Titers *

Serum Titers	Pre-Vaccine Titers n =13	4 Week Post-Vaccine Titers n =13	6 Months Post-Vaccine Titers n = 8
CPV, Undiluted	125 ± 22 (73–156)	136 ± 14 (110–162)	169 ± 58 (96–257)
CPV, Endpoint Dilution	116 ± 87 (32–256)	94 ± 65 (32–256)	240 ± 183 (64–512)
CDV, Undiluted	89 ± 31 (55–143)	148 ± 33 (106–199)	148 ± 71 (110–257)
CDV, Endpoint Dilution	21 ± 26 (2–64)	80 ± 38 (32–128)	97 ± 87 (8–256)

* Median ± SD and Ranges



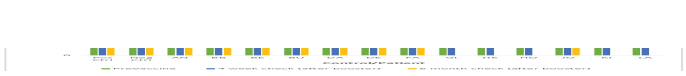


Figure 3a: **Small Breed Vaccine Study**
Serum Vaccine Titers for CPV on Undiluted Serum.

Figure 3b: **Small Breed Vaccine Study**
Serum Vaccine Titers for CDV on Undiluted Serum.

pre-booster titers were already high or very high **(Figure 3a)**. The median titer level was 136 (range 110–162) **(Table 1)**.

Results of the fi serum CPV titers measured on undiluted serum at 6 months after the 1/2 dose vaccination showed the following **(Figure 3a)**:

6 Months Post- 1/2 - Dose Vaccination Six of the 8 dogs showed a rise in CPV OD from the 4-weeks sample. The other 2 dogs had lower 6-month OD titers for CPV, although one of these dogs had essentially the same high titer level at all 3 time points **(Figure 3a)**. The median titer level was 169 (range 96–257) **(Table 1)**.

Canine Distemper Virus (CDV)

Pre-Vaccination The pre-vaccination titers for CDV were lower than those of CPV relative to the positive control OD; 2 of these were just below the positive control but above the negative control OD, and another 6 samples were at or slightly above the positive control OD. Thus, only 5 dogs had high pre-vaccination CDV titers **(Figure 3b)**. The median titer was 89 (range 55–143) **(Table 1)**.

4 Weeks Post-1/2 -Dose Vaccination For CDV titers, 11 of 13 dogs had signifi boosted titers after vaccination, and the other 2 dogs had slightly lower post-vaccination titers but their pre-vaccination titer levels were already high or very high **(Figure 3b)**. The median titer level was 148 (range 106–199) **(Table 1)**.

Results of the fi serum CDV titers measured on undiluted serum at 6 months after the 1/2 -dose vaccination showed the following **(Figure 3b)**:

6 Months Post-1/2 - Dose Vaccination For CDV, 3 of the 8 dogs had higher OD titers at 6 months than at 4 weeks post- vaccination. The other 5 had lower OD titer readings than at 4 weeks, and were still high except for one dog. The median titer level was also

Canine Parvovirus (CPV)

Pre-Vaccination The pre-vaccination endpoint titers for CPV were all above the positive control with 12 of 13 being well above that OD level, when measured on the diluted serum

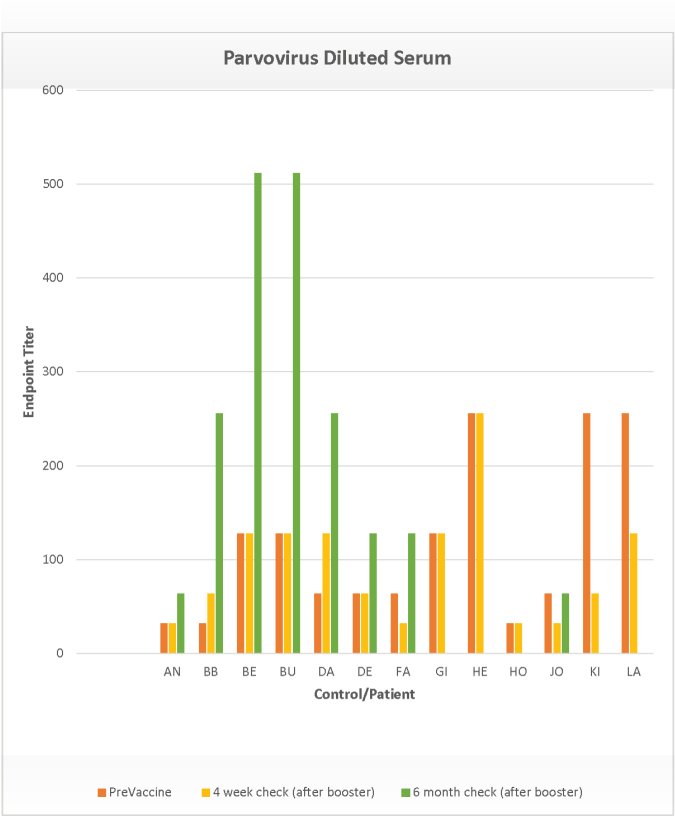


Figure 4a: **Small Breed Vaccine Study**
Serum Vaccine Endpoint Titers for CPV on Diluted Serum

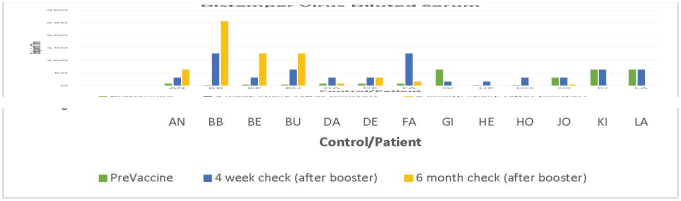


Figure 4b: **Small Breed Vaccine Study**
Serum Vaccine Endpoint Titers for CDV on Diluted

samples **(Figure 4a)**. The median endpoint titer level was 116 (range 32–256) **(Table 1)**.

4 Weeks Post-1/2 - Dose Vaccination Two of 13 dogs had boosted endpoint titers levels at 4 weeks, with a high titer level of 1:256 **(Figure 4a)**. The median endpoint titer level was 94 (range 32–256) **(Table 1)**.

6 Months Post-1/2 - Dose Vaccination For CPV, 7 of the 8 dogs had boosted endpoint titers levels at 6 months with endpoint titer dilutions as high as 1:512. Seven of the 13 dogs had essentially the same endpoint titer levels at 4 weeks as they had pre-vaccination, with the highest level at 1:256. The other 4 of 13 dogs had lower endpoint titer levels at 4 weeks than they had prior to the 1/2 - dose vaccination. The median titer level was 240 (range 64–512) **(Table 1)**.

Canine Distemper Virus (CDV)
Pre-Vaccination The pre-vaccination endpoint titers for CDV were lower than those of CPV relative to the positive control OD; 2 of these were just below the positive control but above the negative control OD, and another 6 samples were at or slightly above the positive control OD. Only 3 dogs had higher pre-vaccination CDV endpoint titers **(Figure 4b)**.The median endpoint titer level was 21 (range 2–64) **(Table 1)**.

4 Weeks Post-1/2 -Dose Vaccination For CDV titers, 9 of

median endpoint titer level was 80 (range 32–128) (Table 1).

6 Months Post-1/2 -Dose Vaccination For CDV, 4 of 8 dogs had markedly boosted endpoint titer levels at 6 months, with the highest level at 1:256 (Figure 4b). The median endpoint titer level was 97 (range 8–256) (Table 1).

DISCUSSION

The rationale for the present study was prompted by the fact that adverse reactions to vaccines, also called vaccine- associated adverse events (VAAE), can still cause serious illness, suffering, and death (2, 3, 15, 17–23). They remain relatively rare, however, based upon the published human and veterinary literature and personal clinical experience (2, 3, 15, 17–23).

Viral vaccines are intended to provide an immune response

similar in duration to that following a natural infection. These anti-viral adaptive immune responses typically result in the development of sterilizing immunity that not only prevents clinical disease but also prevents infection; and the duration of immunity (DOI) generated here is often lifelong. In contrast to viruses, adaptive immunity to bacteria, fungi or parasites develops more slowly with a generally shorter DOI; and development of sterilizing immunity is less common. Older dogs and cats rarely die from vaccine-preventable infectious diseases, especially when they have been vaccinated and immunized as young adults (5, 11, 18, 19). Young animals, however, can still become seriously ill and die from these infectious diseases, most often because vaccines were given too early in life when the presence of their residual maternally derived antibody partially neutralized the effects of the vaccine, leaving the youngster inadequately protected.

Studies in dogs (18) and cats (19) assessed the DOI in previously vaccinated pets that had not received a booster vaccination in as long as 9 years. When the dogs were challenged with CDV, CPV, and CAV-2 and the cats were challenged with feline panleukopenia virus (FPV), feline calicivirus (FCV) and feline herpesvirus (FHV), both species resisted infection and/or disease. Thus, even a single dose of these MLV canine or feline “core” vaccines, when administered at 16 weeks or older, should provide long-term immunity in a very high percentage of animals, while also increasing the overall herd (population) immunity (18, 19).

But factors associated with the age and weight of pet animals being vaccinated are also important, not only for affording protection against these diseases, but also for helping to assure the well-being of those vaccinated.

The risk of a VAAE in this large canine study population was inversely related to the dog’s weight, such that for dogs weighing
< 10 kg, the actual VAAE rate was underestimated (18). This weight-response relationship was previously suggested by a study in which dogs of toy breeds had signifi more suspected VAAEs than other dogs, although body weight was not reported (18). Vaccines, in contrast to virtually all veterinary pharmaceuticals, are prescribed on a one-dose-fi all basis, rather than by body weight (2, 5, 11, 20). Even when adjusted for body weight, there was a nearly linear increase in VAAE rate when the number of vaccine antigens given simultaneously was increased (18). This suggests that vaccine components other than the primary antigen may contribute to

adverse events (14–19). In a published study (9), 8 of 18 dogs that developed immediate-type allergic reactions had high concentrations of specifi serum IgE against the vaccines, and 7 also had specifi IgE antibodies against fetal calf serum (9, 11, 12, 14–16).

Parallel data were documented by these same investigators 2 years later for cats (19), where the risk of VAAE significantly increased as the number of vaccines administered per office visit increased. The risk was greatest for cats about 1 year of age, and overall risk was greater for young adult neutered versus sexually intact cats (19). The most commonly diagnosed VAAE was lethargy with or without fever. The authors concluded that veterinarians should incorporate these findings into risk communications and limit the number of vaccinations administered concurrently to cats (19).

For these special cases, appropriate alternatives to current vaccine practices include (10, 11, 13, 16, 20–22):

- measuring serum antibody titers;
- avoidance of unnecessary vaccines or over vaccinating;
- caution in vaccinating sick or febrile individuals;
- tailoring a specifi minimal vaccination protocol for dogs and cats of breeds or families known to be at increased risk for adverse reactions;
- starting the vaccination series later, such as at 8–10 weeks of age when the immune system is more able to handle antigenic challenge;
- alerting the caregiver to pay particular attention to the puppy and kitten behavior and overall health after the second or subsequent boosters; and
- avoiding revaccination of individuals already experiencing a signifi adverse event. Littermates of affected puppies and kittens should be closely monitored after receiving additional vaccines in a series, as they too are potentially at higher risk.

Canine Vaccine Adverse Events (18)

- retrospective cohort study; 1.25 million dogs vaccinated at 360 veterinary hospitals
- 38 adverse events per 10,000 dogs vaccinated
- inversely related to dog weight
- vaccines prescribed on a 1-dose-fi basis, rather than by body weight.
- increased for dogs up to 2 yr of age, then declined
- greater for neutered versus sexually intact dogs
- increased as number of vaccines given together increased
- increased after the 3rd or 4th vaccination
- genetic predisposition to adverse events documented

Feline Vaccine Adverse Events (19)

- retrospective cohort study; 0.5 million cats vaccinated at 329 veterinary hospitals
- 51.6 adverse events per 10,000 cats vaccinated
- inversely related to cat weight
- increased for cats about 1 yr of age
- greater for neutered versus sexually intact cats
- increased as number of vaccines given together increased
- lethargy with or without fever was most common sign

Serologic Vaccine Titer Testing

Some veterinarians have challenged the validity of using vaccine titer testing to assess the immunologic status of animals against the common, clinically important infectious diseases (10–12).

Research has shown that once an animal's titer stabilizes, it is likely to remain constant for many years. Properly immunized animals have sterilizing immunity that not only prevents clinical disease but also prevents infection, and only the presence of antibody can prevent infection (10–14, 16, 24–27). As stated by eminent expert Dr. Ronald Schultz in discussing the value of vaccine titer testing, these tests "show that an animal with a positive test has sterilizing immunity and should be protected from infection. If that animal were vaccinated it would not respond with a signifi increase in antibody titer, but may develop a hypersensitivity to vaccine components (e.g. fetal calf serum). Furthermore, the animal doesn't need to be revaccinated and should not be revaccinated since the vaccine could cause an adverse reaction (hypersensitivity disorder). You should avoid vaccinating animals that are already protected. It is often said that the antibody level detected is 'only a snapshot in time'. That's simply not true; it is more a 'motion picture that plays for years'" (10).

Furthermore, protection as indicated by a positive titer result is not likely to suddenly drop-off unless an animal develops a medical problem such as cancer or receives high or prolonged doses of immunosuppressive drugs. Viral vaccines prompt an immune response that lasts much longer than that elicited by classic antigen. Lack of distinction between the 2 kinds of responses may be why practitioners think titers can suddenly disappear (10, 14, 16).

But, not all vaccines produce sterilizing immunity (3, 10, 13). Those that do include: CDV, CPV, and CAV-2 in the dog, and FPV in the cat. Examples of vaccines that produced non- sterile immunity would be leptospirosis, bordetella, rabies virus, FCV and FHV — the latter two being upper respiratory viruses of cats. While non-sterile immunity may not protect the animal from infection, it should keep the infection from progressing to severe clinical disease (3, 10, 25).

Therefore, interpreting titers correctly depends upon the disease in question. Some titers must reach a certain level to indicate immunity, but with other agents like those that

produce sterile immunity, the presence of any measurable antibody shows protection (10, 11, 20, 24). The positive titer test result is fairly straightforward, but a negative titer test result is more diffi to interpret, because a negative titer is not the same thing as a zero titer and it does not necessarily mean that animal is unprotected. A negative result usually means the titer has failed to reach the threshold of providing sterile immunity. This is an important distinction, because for the clinically important CDV and CPV of dogs, and FPV of cats, a zero antibody titer indicates that the animal is not protected against CPV and may not be protected against CDV or FPV (10–14, 24–27).

Finally, a decade of experience with vaccine titer testing reveals the following: Published studies in refereed journals show that 90–98% of dogs and cats that have been properly vaccinated develop good measurable antibody titers to the infectious agent measured (10–13, 24–27). So, in contrast to the concerns of some practitioners (4, 6, 7), using vaccine titer testing as a means to assess vaccine-induced protection will likely result in the animal avoiding needless and unwise booster vaccinations.

The author's study, evaluated 1441 dogs for CPV antibody titer and 1379 dogs for CDV antibody titer (11). Of these, 95.1 % were judged to have adequate CPV titers, and nearly all (97.6
%) had adequate CDV titers. Vaccine histories were available for 444 dogs (CPV) and 433 dogs (CDV). Only 43 dogs had been vaccinated within the previous year, with the majority of dogs (268 or 60%) having received a booster

(27) were published a decade ago by researchers at a major pharmaceutical company (f), and found a sustained DOI of at least 3 years in both dogs and cats, raising the question of why the veterinary profession at large has not followed suit.

When an adequate immune memory has already been established, there is little reason to introduce unnecessary antigen, adjuvant, and preservatives by administering booster vaccines. By titering triennially or more often, if needed, one can assess whether a given animal's humoral immune response has fallen below levels of adequate immune memory. In that event, an appropriate vaccine booster can be administered (20–24).

CONCLUSIONS

This study addressed whether small breed adult dogs, vaccinated at least 3 years previously, could be adequately immunized and protected by receiving less than a full dose of a bivalent DPV vaccine. A half-dose of this vaccine was given and generated increased serum vaccine antibody titers for all of the dogs studied. Results varied quantitatively when titers measured on the undiluted serum (standard method) were compared to endpoint titers determined on the same samples when the serum was serially diluted. The median

titer and endpoint titer levels had a sustained increase in all dogs at 6 months post-vaccination. As the presence of measurable CPV and CDV serum antibody titers refl immunity to these viruses, and given that vaccines are known to cause adverse events, especially in smaller dogs, results of this study confi that receiving a half-dose of bivalent DPV vaccine was effi for this study cohort. Further investigations could address a larger number of smaller canines.

ENDNOTES

a. Nobivac DPV; Merck Animal Health, Madison, NJ.

b. *www. hemopet.org*; Garden Grove, CA.

c. *www.hemolife.org*; Garden Grove, CA.

d. Vacutainer, RTT; Becton-Dickinson, East Rutherford, NJ.

e. TiterChek; Zoetis US, Florham Park, NJ.

f. Pfi Animal Health, Kalamazoo, MI.

REFERENCES

1. Dodds WJ. Complementary and alternative veterinary medicine: the immune system. Clin Tech Sm An Pract. 2012;17(1):58–63.
2. Dodds WJ. Vaccine-related issues. In: Complementary and Alternative Veterinary Medicine (eds: Allen M. Schoen and Susan G. Wynn). Mosby-Year Book, St. Louis, MO, 1997:pp. 701–712.
3. Dodds WJ. More bumps on the vaccine road. Adv Vet Med. 1999;41:715–732.
4. Hustead DR, Carpenter T, Sawyer DC, et al. Vaccination issues of concern to practitioners. J Am Vet Med Assoc. 1999;214:1000–1002.
5. Schultz RD. Current and future canine and feline vaccination programs. Vet Med. 1998;93:233–254.
6. Taguchi M, Namikawa K, Maruo T, et al. Antibodies to parvovirus, distemper virus and adenovirus conferred to household dogs using commercial combination vaccines containing Leptospira bacterin. Vet Rec. 2010;167:931–934.
7. Taguchi M, Namikawa K, Maruo T, et al. Booster effect of canine distemper, canine parvovirus infection and infectious canine hepatitis combination vaccine in domesticated adult dogs. Microbiol Immunol. 2012;56:579–582.
8. Smith CA. Are we vaccinating too much? J Am Vet Med Assoc. 1995;207:421–425.
9. Phillips TR, Jensen JL, Rubino MJ, Yang WC, et al. Effects on vaccines on the canine immune system. Can J Vet Res. 1989;53:154–160.
10. Schultz RD, Ford RB, Olsen J, Scott F. Titer testing and vaccination: a new look at traditional practices. Vet Med. 2002;97:1–13

12. Lappin MR, Andrews J, Simpson D, et al. Use of serologic tests to predict resistance to feline herpesvirus 1, feline calicivirus, and feline parvovirus infection in cats. J Am Vet Med Assoc. 2002;220:38–42.

13. Schultz RD, Thiel B, Mukhtar E, et al. Age and long-term protective immunity in dogs and cats. J Comp Pathol. 2010;142 Suppl 1:S102–S108.

14. Scott FW, Geissinger CM. Long-term immunity in cats vaccinated with an inactivated trivalent vaccine. Am J Vet Res. 1999;60:652–658.

15. Moyes CD, Milne A. Should the dose of hepatitis B vaccine be reduced in newborn babies? Lancet 1988;20:415.

16. Gray LK, Crawford PC, Levy JK, Dubovi EJ. Comparison of two assays for detection of antibodies against canine parvovirus and canine distemper virus in dogs admitted to a Florida animal shelter. J Am Vet Med Assoc. 2012;240:1084–1087.

17. Hogenesch H, Azcona-Olivera J, Scott-Moncreiff C, et al. Vaccine- induced autoimmunity in the dog. Adv Vet Med. 1999;41:733–744.

18 Moore GE, Guptill, LF, Ward, WP, et al. Adverse events diagnosed within three days of vaccine administration in dogs. J Am Vet Med Assoc. 2005;227:1102–1108.

19. Moore GE, DeSantis-Kerr AC, Guptill LF, et al. Adverse events after vaccine administration in cats: 2,560 cases (2002–2005). J Am Vet Med Assoc. 2007;231: 94–100.

20. Dodds WJ. Vaccination protocols for dogs predisposed to vaccine reactions. J Am An Hosp Assoc. 2001;38: 1–4.

21. Vascellari M, Melchiotti E, Bozza MA et al. Fibrosarcomas at presumed sites of injection in dogs: characteristics and comparison with non-vaccination site fi and feline post-vaccinal fi J Vet Med. 2003;50(6):286–291.

22. Scott-Moncrieff JC, Azcona-Olivera J, Glickman NW, et al. Evaluation of antithyroglobulin antibodies after routine vaccination in pet and research dogs. J Am Vet Med Assoc. 2002;221:515–521.

23. Tizard I. Risks associated with use of live vaccines. J Am Vet Med Assoc. 1990;196:1851–1858.

24. Moore GE, Glickman LT. A perspective on vaccine guidelines and titer tests for dogs. J Am Vet Med Assoc. 2004; 24:200–203.

25. Tizard I, Ni Y. Use of serologic testing to assess immune status of companion animals. J Am Vet Med Assoc. 1998;213:54–60.

26. Mouzin DE, Lorenzen M J, Haworth, et al. Duration of serologic response to fi viral antigens in dogs. J Am Vet Med Assoc. 2004;224:55–60.

27. Mouzin DE, Lorenzen M J, Haworth, et al. Duration of serologic response to three viral antigens in cats. J Am Vet Med Assoc. 2004;224:61–66.