# Report of the American Animal Hospital Association (AAHA) Canine Vaccine Task Force: 2003 Canine Vaccine Guidelines, Recommendations, and Supporting Literature

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## Introduction

Few in veterinary practice today can recall a time when serious infectious diseases were not preventable by the administration of safe immunizations. With the exception of the canine parvovirus (CPV) pandemic in the late 1970s, widespread morbidity and mortality due to life-threatening diseases have largely been preventable in recent years. Even when CPV erupted on the scene, the rapid response by researchers and biologics (vaccine) manufacturers allowed our profession to curtail the terrible losses of dogs to this disease. It is therefore safe to say that no single achievement has had greater impact on the lives and well-being of our patients, our clients, and our ability to prevent infectious diseases than the development and ongoing improvements in companion animal vaccines.

The evolution of biologics represents a continuum of advances encompassing efficacy, safety, and usage. Early vaccines did not enjoy the same safety and efficacy profiles of currently available products, often resulting in adverse reactions or short durations of immunity (DOI). The resulting recommendations for revaccination reflected these product limitations, and most of the widely accepted recommendations for revaccination were based on a "better safe than sorry" approach because the diseases these vaccines were designed to prevent were widespread and devastating. While the evolution of scientific knowledge has resulted in tremendous

improvements in the field of vaccinology, the ultimate goal of combining 100% efficacy and 100% safety into the same vaccine product is not a reality at this time. Although it is possible to develop a vaccine that is virtually free of all adverse side effects, it would likely be a poor stimulant of immunity or produce a short DOI. Conversely, vaccines can be produced that provide higher percentages of long-term immunity but would exact a price of unacceptable adverse events. Therefore, current knowledge supports the statement that no vaccine is always safe, no vaccine is always protective, and no vaccine is always indicated. However, the information that this statement is based on is in a constant state of flux; hence, the historical and current debate on appropriate vaccine use.

While significant efforts have been expended and realized with respect to vaccine efficacy and safety, their impact on product use (specifically vaccine protocols) has largely been ignored until recently; this despite early recommendations for less frequent revaccination. In 1978, "an ideal vaccination program" was recommended where dogs and cats would be vaccinated as puppies and kittens and then revaccinated at 1 year of age and every third year thereafter.[1] In 1998, the American Association of Feline Practitioners (AAFP) debated and subsequently endorsed this same recommendation for feline core vaccines; the AAFP recommendations were updated in 2000.[2] Also in 1998, recommendations from a group of canine vaccine experts were published.[3] They recommended revaccination with canine core vaccines no more than once every 3 years following initial booster revaccination at 1 year of age. This proposed vaccination program, and various iterations thereof, has been adopted to varying degrees by a growing part of the profession, but misunderstandings, misinformation, and the conservative nature of the profession have slowed adoption of these protocols advocating decreased frequency of revaccination.

In 2002, the American Veterinary Medical Association (AVMA) updated their vaccine guidelines[4] after recognizing that traditional guidelines were not compatible with the recommendations of a growing number of veterinary practitioners and experts in the fields of vaccinology and infectious diseases. Although many of these experts support triennial vaccination against core diseases, there is a relative paucity of published scientific documentation to indicate that every 3 years is any more rational than every 2 years or any less rational than every 7 years. For that reason, the AVMA and AAHA guidelines intentionally allow room for individual veterinarians to apply them. Information (including discussions on core/noncore vaccines, immunology, DOI, vaccine production and licensing, adverse event reporting, and potential practice impact and opportunity) is provided in this report for veterinarians to review and use as they develop a vaccine program for their practices and their individual patients.

Many diseases we immunize against are ubiquitous. Many are serious and some even life threatening. Some are of limited demographic concern given the exposure risk for each patient. These factors have all been considered in developing the AAHA Canine Vaccine Guidelines and Recommendations. In the end, each veterinarian must do what he or she determines to be in the best interest of the patient. Vaccination of individual animals produces not only individual immunity but also population or herd immunity. Since we have no readily available and reliable way to determine if each patient has developed an adequate immune response, we encourage the practice philosophy of vaccinating more patients while vaccinating each patient no more than needed.

## Task Force Recommendations Regarding the Selection and Use of Canine Vaccine Antigens

Decisions on vaccine selection and use require a balance among disease incidence and severity, vaccine efficacy (including DOI) and safety, and the health, welfare, and lifestyle of the individual animal. When taking all these variables into account, it becomes apparent that a blanket or generic statement encompassing the use of all vaccine products is impossible to make. However, based on the growing body of knowledge in the areas of vaccinology and immunology, general vaccine guidelines are appropriate and useful as a foundation upon which to make specific recommendations for individual patients. The 2003 AAHA Canine Vaccine Guidelines and Recommendations are discussed in the following sections as well as presented in an easy-to-reference table format [Table 1]. These guidelines are based on current knowledge with respect to disease incidence and severity and vaccine efficacy.

### Vaccine Selection: Core (Recommended), Noncore (Optional), and Not Generally Recommended Canine Vaccines

Recommended or **"core"** vaccines are those that the committee believes should be administered to all puppies (dogs ≤6 months of age) or dogs with an unknown vaccination history. The diseases involved have significant morbidity and mortality and are widely distributed. The committee believes this group of vaccines comprises canine distemper virus (CDV), CPV, canine adenovirus-2 (CAV-2), and rabies virus.

Optional or **"noncore"** vaccines are those that the committee believes should be considered only in special circumstances because their use is more dependent on the exposure risk of the individual animal. Issues of geographic distribution and lifestyle should be considered before administering these vaccines. In addition, the diseases involved are generally self-limiting or respond readily to treatment. The committee believes this group of vaccines comprises distemper-measles virus (D-MV), canine parainfluenza virus (CPIV), *Leptospira spp.*, *Bordetella bronchiseptica*, and *Borrelia burgdorferi*.

Vaccines identified as **"not generally recommended"** are those that the committee believes have little or no indication. The diseases involved are either of little clinical significance or respond readily to treatment. In addition, the

## Table 1

### AAHA 2003 Canine Vaccination Guidelines and Recommendations*

| Vaccine[†] | Initial Puppy Vaccination[‡] (≤16 weeks) | Initial Adult Vaccination (>16 weeks) | Revaccination (Booster) Recommendations | Overall Comments and Recommendations |
|---|---|---|---|---|
| Canine Distemper Virus (CDV) (MLV) | Administer one dose at 6-8 wks, 9-11 wks, and 12-14 wks of age. | One dose is protective. | Annually (manufacturer)<br><br>After a booster at 1 yr, revaccination once every 3 yrs is considered protective. | *Highly Recommended:* Despite annual booster recommendations, adult dogs challenged 7 yrs (Rockborn Strain) and 5 yrs (Onderstepoort Strain) following MLV vaccination were protected (DOI).§ Usually combined with CDV and CPV vaccinations.<br><br>A booster vaccination interval of 3 yrs among adult dogs is protective and reasonable. |
| **r**Canine Distemper Virus (**r**CDV) (recombinant) | Administer one dose at 6-8 wks, 9-11 wks, and 12-14 wks of age.<br><br>A dose ≥4 wks after the last dose in this series will significantly increase the likelihood of sterile immunity\ with this product. | Two doses, 2-4 wks apart. | Annually (manufacturer)<br><br>After a booster at 1 yr, annual revaccination is recommended. | *Recommended:* As a suitable alternative to the MLV-CDV and may be used interchangeably with the MLV-CDV vaccine.<br><br>Does not routinely provide sterile immunity and may take longer to protect immunologically naive dogs. Therefore, not recommended where CDV is a serious threat for puppies (e.g., shelters, kennels, puppy/pet stores).<br><br>Minimum demonstrated DOI for **r**CDV is 1 yr. Therefore, at present, annual revaccination is recommended. A vaccination program that includes MLV-CDV vaccine for the initial vaccination followed by booster vaccinations with **r**CDV would provide excellent protection; revaccination with **r**CDV every 3 yrs would be reasonable in this scenario. |

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**Table 1 (cont'd)**

AAHA 2003 Canine Vaccination Guidelines and Recommendations*

| Vaccine[†] | Initial Puppy Vaccination[‡] (≤16 weeks) | Initial Adult Vaccination (>16 weeks) | Revaccination (Booster) Recommendations | Overall Comments and Recommendations |
|---|---|---|---|---|
| Canine Parvovirus (CPV-2) (MLV) | Administer one dose at 6-8 wks, 9-11 wks, and 12-14 wks of age. | Two doses, 3-4 wks apart. One dose is protective and acceptable. | Annually (manufacturer) After a booster at 1 yr, revaccination every 3 yrs is considered protective. | *Highly Recommended:* Although annual boosters are recommended by vaccine manufacturers, studies have shown protection against challenge (DOI) up to 7 yrs postvaccination with MLV vaccine. Products with CPV-2 regardless of genotype (i.e., CPV-2, 2a, or 2b) all provide excellent protection against field isolates. |
| Canine Parvovirus (CPV-2) (killed) | Administer one dose at 6-8 wks, 9-11 wks, 12-14 wks, and 15-17 wks of age. | Two doses, 2-4 wks apart, is recommended. | Annually (manufacturer) Annual vaccination recommended until DOI studies show longer than 1 yr of protection with the killed product. When puppy is vaccinated with MLV and revaccinated at 1 yr with MLV, killed product could be used as booster ≥3 yrs. | *Recommended:* As a suitable alternative to the MLV canine parvovirus vaccine in low-risk environment. Not recommended for animals at high risk for parvovirus (e.g., shelters, kennels, puppy/pet stores). Killed parvovirus products are susceptible to maternal antibody interference in puppies as old as 16-18 wks of age. |
| Canine Adenovirus-2 (CAV-2) (MLV, killed, or MLV-topical) | Administer one dose at 6-8 wks, 9-11 wks, and 12-14 wks of age. | One dose (if using MLV) Two doses, 2-4 wks apart (if using killed) | Annually (manufacturer) Upon completion of the initial series, and following a booster at 1 yr, revaccination once every 3 yrs is considered protective. | *Recommended:* Demonstrated cross protection against canine hepatitis (CAV-1) and CAV-2, one of the agents known to be associated with infectious tracheobronchitis. Adult dogs challenged 7 yrs following CAV-2 MLV vaccination have been found to be protected (DOI) against the more virulent CAV-1. |

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## Table 1 (cont'd)

### AAHA 2003 Canine Vaccination Guidelines and Recommendations*

| Vaccine[†] | Initial Puppy Vaccination[‡] (≤16 weeks) | Initial Adult Vaccination (>16 weeks) | Revaccination (Booster) Recommendations | Overall Comments and Recommendations |
|---|---|---|---|---|
| Canine Adenovirus-2 (continued) | | | | Usually combined with CDV and CPV vaccines; revaccination every 3 yrs would be protective and reasonable. |
| Rabies 1-year (killed) | Administer one dose as early as 3 mos of age. | Administer a single dose. | Annually. State, provincial, and/or local laws apply.<br><br>The 1-yr rabies vaccine may be used as a booster vaccine when dogs are required by statute to be vaccinated annually against rabies. | *Required:* State, provincial, and local statutes govern the frequency of administration for products labeled as "1-year rabies."<br><br>*Note:* The rabies (1-yr) vaccine is sometimes administered as the initial dose followed 1 yr later by administration of the rabies 3-yr vaccine. State, provincial, and local statutes may dictate otherwise.<br><br>One-yr rabies products should not be considered to cause fewer adverse reactions when given annually than 3-yr rabies products.<br><br>*Note:* Route of administration may not be optional—see product literature for details. |
| Rabies 3-year (killed) | Administer one dose as early as 3 mos of age.<br><br>*Note:* The 3-yr rabies vaccine may be used as an alternative to the 1-yr rabies vaccine for initial and subsequent doses. Local statutes apply. | Administer a single dose.<br><br>*Note:* The 3-yr rabies vaccine may be used as an alternative to the 1-yr rabies vaccine for initial and subsequent doses. Local statutes apply. | The second rabies vaccination is recommended 1 yr following administration of the initial dose regardless of the animal's age at the time the first dose was administered. | *Required:* State, provincial, and local statutes govern the frequency of administration for products labeled as rabies 3-yr—these statutes vary throughout the U.S. and Canada.<br><br>*Note:* The rabies 1-yr vaccine is sometimes administered as the |

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## Table 1 (cont'd)

### AAHA 2003 Canine Vaccination Guidelines and Recommendations*

| Vaccine[†] | Initial Puppy Vaccination[‡] (≤16 weeks) | Initial Adult Vaccination (>16 weeks) | Revaccination (Booster) Recommendations | Overall Comments and Recommendations |
|---|---|---|---|---|
| Rabies 3-year (continued) | | | Booster vaccines should be administered every 3 yrs. State, provincial, and/or local laws apply. | initial dose followed 1 yr later by administration of the rabies 3-yr vaccine. State, provincial, and local statutes may dictate otherwise.<br><br>Every effort should be made to change laws that require vaccination with this rabies product more often than every 3 yrs since annual vaccinations cannot be shown to increase efficacy and it is known to increase adverse events.<br><br>*Note:* Route of administration may not be optional—see product literature for details. |
| Distemper-Measles Virus (D-MV) (MLV) | One dose between 4 and 12 wks of age **only** (follow with one dose MLV-CDV or two doses **r**CDV vaccine after 12 wks of age). | Not indicated for use in dogs over 12 wks of age.<br><br>May produce maternal MV antibodies that would be passed to subsequent pups of female dogs resulting in blocking of puppy response to D-MV vaccination. | Revaccination is not recommended. D-MV vaccine would not cause any health problem in the recipient, but if used in a breeding female, puppies would acquire MV antibody and the protection offered by the MV would be lost. | *Optional (Not Recommended for Routine Use):* Intended to provide temporary protection in young puppies only. Indicated for use in households/kennels/ shelters where CDV is a recognized problem.<br><br>Do not administer to female dogs over 12 wks of age.<br><br>*Note:* Administer **IM** only—MV does not effectively immunize if administered subcutaneously. |
| Parainfluenza Virus (CPIV) (MLV or MLV-topical) | Administer one dose at 6-8 wks, 9-11 wks, and 12-14 wks of age. | One dose is adequate. | Annually (manufacturer)<br><br>Parenteral—Upon completion of the initial series, and following a booster at 1 yr, revaccination once every 3 yrs is considered protective (DOI). | *Recommended:* Parenteral vaccine is usually combined with CDV, CPV-2, and CAV vaccines.<br><br>Parenterally administered vaccine is less effective than topically (intranasal) administered vaccine. |

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## Table 1 (cont'd)

### AAHA 2003 Canine Vaccination Guidelines and Recommendations*

| Vaccine† | Initial Puppy Vaccination‡ (≤16 weeks) | Initial Adult Vaccination (>16 weeks) | Revaccination (Booster) Recommendations | Overall Comments and Recommendations |
|---|---|---|---|---|
| Parainfluenza Virus (continued) | | | Intranasal commonly given annually with *Bordetella bronchiseptica*. | Topical is in combination with *Bordetella* or *Bordetella* and CAV-2. DOI by challenge has been shown to be at least 1 yr (unpublished) for topical vaccine. |
| *Leptospira interrogans* (combined with serovars *canicola* and *icterohaemorrhagiae*) (killed bacterin) (Also available with serovars *grippotyphosa* and *pomona*) | Administer one dose at 12 wks and a second dose at 14-16 wks. Do not administer to dogs <12 wks of age for optimal response. | Two doses, 2-4 wks apart | Annually (manufacturer) Annually unless severe incidence of leptospirosis continues. In situations of significant high-risk exposure, administer a booster every 6 mos. Discontinue 6 mos booster when local or regional incidence problem is improved since this product carries high-risk for adverse vaccine events. | *Optional:* Disease prevalence is likely to vary for each serovar. Vaccine recommendations are therefore difficult to make due to the lack of information on prevalance of specific serovar infections in dogs in various geographic regions. Anecdotal reports from veterinarians and breeders suggest that the incidence of postvaccination reactions (acute anaphylaxis) in puppies (<12 wks of age) and small-breed dogs is high. Reactions are most severe in young (<9 wks of age) puppies. Routine use of the vaccine should be delayed until dogs are ≥9 wks of age. Older dogs are more likely to develop an optimal immune response than younger animals. Minimum DOI based on challenge studies has been shown to be approximately 1 yr for serovars *canicola* and *icterohaemorrhagiae*; however, efficacy of the products can be low (<75%). DOI for serovars *grippogyphosa* and *pomona* are assumed to be up to 1 yr. |
| *Bordetella bronchiseptica* (killed bacterin)— parenteral | Administer one dose at 6-8 wks and then at 10-12 wks of age. | Two doses, 2-4 wks apart | Annually (manufacturer) | *Optional (Recommended):* DOI is approximately 9 to 12 mos. There is no known advantage to |

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## Table 1 (cont'd)

### AAHA 2003 Canine Vaccination Guidelines and Recommendations*

| Vaccine† | Initial Puppy Vaccination‡ (≤16 weeks) | Initial Adult Vaccination (>16 weeks) | Revaccination (Booster) Recommendations | Overall Comments and Recommendations |
|---|---|---|---|---|
| *Bordetella bronchiseptica* (killed bacterin) (continued) | | | Annually or more often in very high-risk animals not protected by annual booster. | administering parenteral and intranasal *Bordetella bronchiseptica* vaccines simultaneously. |
| *Bordetella bronchiseptica* (live avirulent bacteria) + Parainfluenza Virus (MLV)-topical (intranasal) application | Administer a single dose as early as 3 wks of age (see product literature for specific age recommendations). For best results, if the product is used prior to 5-6 wks of age, it should be given again after 6 wks of age. | Not stipulated, although a single dose is recommended by the manufacturer. | Annually (manufacturer) If not vaccinated within the previous 6 mos, a booster is recommended 1 wk prior to known exposure (e.g., boarding, showing, etc.). | *Optional (Recommended):* For dogs housed in kennels, shelters, and prior to boarding in kennels. *Note:* Transient (3-10 days) coughing, sneezing, or nasal discharge occurs in a small percentage of vaccinates. Antimicrobial therapy may be indicated to manage postvaccination upper respiratory signs (persistent cough and nasal discharge). DOI is believed to be approximately 10 mos for *Bordetella bronchiseptica.* *Note:* Topically administered vaccines for canine infectious tracheobronchitis may provide a superior local immune response compared to parenterally administered vaccines. |
| *Bordetella bronchiseptica* (live avirulent bacteria) + CPIV (MLV) + CAV-2 (MLV)-topical (intranasal) application | Administer a single dose at ≥8 wks of age. Manufacturers' recommendations on the earliest age for administering the first dose varies and may be as early as 3-4 wks. Administering an intranasal vaccine to dogs this young is recommended only in situations where there is considerable risk of exposure and the vaccine can be | A single dose is recommended. | Annually (manufacturer) Same recommendation as for intranasal with CPIV. | *Optional (Recommended):* For dogs considered to be at risk of exposure to any of the pathogens listed. This product has not been shown to provide any benefit not achieved with the intranasal *Bordetella bronchiseptica* plus canine parainfluenza virus in dogs that are receiving CAV-2 parenterally. *Note:* Topically administered vaccines for canine infectious tracheobronchitis may |

**Table 1 (cont'd)**

AAHA 2003 Canine Vaccination Guidelines and Recommendations*

| Vaccine[†] | Initial Puppy Vaccination[‡] (≤16 weeks) | Initial Adult Vaccination (>16 weeks) | Revaccination (Booster) Recommendations | Overall Comments and Recommendations |
|---|---|---|---|---|
| *Bordetella bronchiseptica* (live avirulent bacteria) (continued) | administered 5 days prior to a known exposure. | | | provide a superior local immune response compared to parenterally administered vaccines. <br><br> DOIs as noted above for individual vaccines. |
| *Borrelia burgdorferi* (Lyme borreliosis) (killed whole bacterin) | Initial dose may be given at 9 or 12 wks of age (depending on manufacturer recommendations) and a second dose is required 2-4 wks later. | Two doses, 2-4 wks apart | Annually (manufacturer) <br><br> Revaccinate just prior to start of insect (tick) season | *Optional:* Generally recommended only for use in dogs with a known high risk of exposure; preferably dogs living or residing in endemic areas or regions where the risk of tick exposure is considered to be high. Minimum DOI based on challenge studies is 1 yr. |
| *Borrelia burgdorferi* (rLyme borreliosis) (recombinant-Outer Surface Protein A [OspA]) | Initial dose may be given at 9 wks of age with a second dose required 2-4 wks later. Optimal age for the initial dose is ≥3 mos, with a second dose 2-4 wks later. | Two doses, 2-4 wks apart | Annually (manufacturer) <br><br> Annually, just prior to start of insect (tick) season | *Optional:* Generally recommended only for use in dogs with a known high risk of exposure, preferably dogs living or residing in endemic areas or regions where the risk of tick exposure is considered to be high. <br><br> Most authoritative papers recommend the **r**Lyme borreliosis vaccine over the killed bacterin for reasons of safety (believed to be associated with fewer adverse reactions). <br><br> The minimum DOI for the recombinant vaccine is at least 1 yr, based on challenge. |

## Table 1 (cont'd)

### AAHA 2003 Canine Vaccination Guidelines and Recommendations*

| Vaccine[†] | Initial Puppy Vaccination[‡] (≤16 weeks) | Initial Adult Vaccination (>16 weeks) | Revaccination (Booster) Recommendations | Overall Comments and Recommendations |
|---|---|---|---|---|
| Canine Coronavirus (CCV) (killed and MLV) | Administer one dose every 2-4 wks of age until 12 wks of age (MLV and killed). Can begin as early as 6 wks of age with boosters every 2-3 wks with the final dose at 12 wks of age (killed). | One dose (if using MLV) (manufacturer) Two doses, 2-4 wks apart (if using killed) (manufacturer) (Not recommended in adult dogs as neither a need nor benefit has been demonstrated.) | Annually (manufacturer) Not recommended until this product is demonstrated to provide benefit not achieved with a vaccine combination that does not include CCV. | *Not Recommended:* Prevalence of clinical cases of confirmed CCV disease does not justify vaccination. Clinical disease rarely occurs but when seen is typically mild and self-limiting. It is recommended that animal shelters not utilize the CCV vaccine in routine vaccination programs due to additional costs incurred and the lack of defined benefit. Experience has shown no additional increase in infectious enteritis among adults or puppies subsequent to discontinuing the CCV vaccine. Neither the MLV vaccine nor the killed CCV vaccine has been shown to significantly reduce disease caused by a combination of CCV and CPV-2. Only CPV-2 vaccines have been shown to protect dogs against challenge when these two viruses are used. The DOI for the CCV vaccine cannot be determined. |
| *Giardia lamblia* (killed) | Initial dose may be given at 8 wks of age and a second dose should be given 2-4 wks later. | Two doses, 2-4 wks apart | Annually (manufacturer) Boosters not necessary in dogs ≥1 yr of age | *Not Recommended:* The vaccine may prevent oocyst shedding but does not prevent infection. Infection in puppies and kittens is often subclinical. Although giardiasis is the most common intestinal parasite among people in the U.S., the source of human infection is |

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## Table 1 (cont'd)

### AAHA 2003 Canine Vaccination Guidelines and Recommendations*

| Vaccine[†] | Initial Puppy Vaccination[‡] (≤16 weeks) | Initial Adult Vaccination (>16 weeks) | Revaccination (Booster) Recommendations | Overall Comments and Recommendations |
|---|---|---|---|---|
| *Giardia lamblia* (continued) | | | | contaminated water. Infections in dogs and cats are not likely to be zoonotic.<br><br>Because the vaccine does not prevent infection, a minimum DOI based on challenge is not reported. |
| Canine Adenovirus-1 (CAV-1) (MLV and killed) | Administer one dose at 6-8 wks, 9-11 wks, and 12-14 wks of age. | Killed vaccine: Two doses, 2-4 wks apart<br><br>MLV vaccine: One dose | Annually (manufacturer)<br><br>Upon completion of the intial series, and following a booster at 1 yr, revaccination once every 3 yrs is considered protective. | *Not Recommended:* Based on the low prevalence of infectious canine hepatitis in North America and the significant risk of "hepatitis blue-eye" reactions. CAV-2 vaccines will cross-protect against CAV-1 and are much safer. **Vaccines containing CAV-1 are not recommended.** |

* The AAHA 2003 Canine Vaccination Guidelines and Recommendations are provided to assist veterinarians in developing a vaccination protocol for use in clinical practice. They are **not** intended to represent vaccination standards for all dogs.
† MLV=modified live virus; **r**=recombinant
‡ Route of administration is SQ or IM unless otherwise noted by the manufacturer.
§ DOI=duration of immunity
\ Sterile immunity=complete prevention of infection

vaccines available against these diseases have not demonstrated clinical efficacy in the prevention of disease and may produce adverse events with limited benefit. The vaccines that the committee believes fall into this category are *Giardia spp.*, canine coronavirus (CCV), and canine adenovirus-1 (CAV-1).

## Vaccine Frequency of Use

All commercially available vaccine products have attendant vaccine protocols as defined by their manufacturers. These generally involve an initial (often puppy) series, followed by recommendations for revaccination (booster) at 1 year of age and annually (or less) thereafter. Regardless of product chosen, the current controversy over vaccination protocols centers on the traditional recommendation regarding revaccination schedules for dogs >1 year of age. The currently recommended vaccination schedules (with respect to frequency, not product choice) for dogs ≤1 year of age have not been questioned. Based on a growing body of information regarding immunology and product DOI in both animals and humans, the need for annual revaccination has been placed in doubt. Duration of immunity is the critical determining factor, but it defies simple definition, principally, because it is derived from a complex interplay between the host's immune response (see The Immune System as it Applies to Vaccination section) and the vaccine in question, and it is difficult to measure in an individual animal without direct challenge. Current scientific knowledge demonstrates that DOI varies among vaccines and is influenced by vaccine type (e.g., modified live virus [MLV], killed, or recombinant), route of administration, and antigen content and often extends for >1 year. This information is summarized in the following section on specific vaccine recommendations.

## Specific Vaccine Recommendations: Core Vaccines

**Canine Distemper Virus (CDV):** Infection with CDV causes significant morbidity in unprotected animals and is associated with high rates of mortality from respiratory, gastrointestinal, and neurological abnormalities; there is minimal geographic difference in its distribution. Therefore, all puppies should be vaccinated with a CDV vaccine, and boosters should be administered throughout the dog's life [Table 1]. Dogs with unknown vaccine histories should be considered at risk and vaccinated, and boosters should be administered throughout the dog's life [Table 1].

Challenge of immunity studies have shown that the minimum DOI for MLV-CDV vaccines derived from the Rockborn strain and the Onderstepoort strain are 7 and 5 years, respectively, and for the canarypox-vectored CDV vaccine, it is 1 year (not tested beyond 1 year). The minimum DOI for these same vaccines, using antibody titers at levels that provide sterilizing immunity, are 12 to 15 years for Rockborn and 9 years for Onderstepoort [Table 2]. The canarypox-vectored CDV vaccine does not provide sterilizing immunity in the majority of puppies receiving the required two doses of this vaccine. The recombinant vaccine does provide excellent immunity—infection occurs, but

anamnestic (memory) humoral and CMI responses develop and the challenged dog is protected from disease.

Therefore, following the initial vaccination series, revaccination every 3 years is considered protective for MLV-CDV vaccines and, due to the lack of information, revaccination every year for recombinant CDV vaccines is considered protective.

**Canine Parvovirus (CPV-2):** Infection with CPV-2 causes high morbidity and mortality in unprotected dogs primarily from gastrointestinal disease; the organism has worldwide distribution. Therefore, all puppies should be vaccinated with a CPV vaccine, and boosters should be administered throughout the dog's life [Table 1]. Dogs with unknown vaccine histories should be considered at risk and vaccinated, and boosters should be administered throughout the dog's life [Table 1].

Challenge studies have shown that the minimum DOI for MLV-CPV-2 vaccines is 7 years. The minimum DOI for these same vaccines based on serological data for sterilizing immunity is up to 10 years [Table 2].

Therefore, following the initial vaccination series, revaccination with an MLV-CPV-2 vaccine every 3 years is considered protective. However, if a killed CPV-2 is being used, due to lack of DOI information, annual revaccination is recommended unless it is used as a booster following an initial series with an MLV-CPV-2 vaccine. In this scenario, revaccination every 3 years is considered protective.

**Canine Adenovirus-2 (CAV-2):** Infection with CAV-2 causes a self-limiting respiratory disease in some infected dogs but produces an immune response that cross-protects against canine adenovirus-1 (CAV-1) infection, the etiology of canine infectious hepatitis, which has worldwide distribution. The CAV-1 vaccine has been associated with an unacceptable rate of serious adverse events (e.g., interstitial nephritis, anterior uveitis) and should not be administered; however, CAV-2 vaccines are safer. Therefore, all puppies should be vaccinated with a CAV-2 vaccine, and boosters should be administered throughout the dog's life [Table 1]. Dogs with unknown vaccine histories should be considered at risk and vaccinated, and boosters should be administered throughout the dog's life [Table 1].

The minimum DOI for CAV-1 and CAV-2 vaccines, based on challenge immunity for CAV-1, is 7 years. The minimum DOI based on antibody titers is at least 9 years [Table 2].

Therefore, following the initial vaccination series, revaccination every 3 years is considered protective.

**Rabies Virus (RV):** Infection with RV causes a fatal neurological disease, and infected dogs are a potential source for human infection, resulting in state and provincial laws mandating RV vaccination. Therefore, all puppies should be vaccinated with an RV vaccine, and boosters should be administered throughout the dog's life [Table 1]. Booster revaccination should be administered 12 months following

## Table 2

### Estimated Minimum Duration of Immunity (DOI) of Select Commercially Available Canine Vaccine Antigens

| Vaccine* | Estimated Minimum DOI† | Estimate of Relative Efficacy‡ (%) |
|---|---|---|
| **Core** | | |
| Canine Distemper (MLV) | ≥7 yr[27-29] | >90 |
| **r**Canine Distemper (R) | ≥1 yr | >90 |
| Canine Parvovirus-2 (MLV) | ≥7 yr[27-29] | >90 |
| Canine Adenovirus-2 (MLV) | ≥7 yr[27-29] | >90 |
| Rabies Virus (K) | ≥3 yr[27-29] | >85 |
| | | |
| **Noncore** | | |
| Canine Coronavirus (K or MLV) | NA[37,38]§ | NA |
| Canine Parainfluenza (MLV) | ≥3 yr[27-29] | >80 |
| *Bordetella bronchiseptica* (ML)\ | ≤1 yr[27-29]¶ | ≤70 |
| *Leptospira canicola* (K) | ≤1 yr¶ | ≤50 |
| *L. grippotyphosa* (K) | ≤1 yr# | NA |
| *L. icterohaemorrhagiae* (K) | ≤1 yr¶ | ≤75 |
| *L. pomona* (K) | ≤1 yr# | NA |
| *Borrelia burgdorferi* (K) | 1 yr[27-29] | ≤75 |
| *B. burgdorferi* OspA (R) | 1 yr | ≥75 |
| *Giardia lamblia* (K) | ≤1 yr# | NA |

\* MLV=modified live virus; K=killed; R=recombinant
† Experimental challenge studies and/or serological studies have been performed. Field experiences during outbreaks confirm experimental challenge studies; NA=not available
‡ Based primarily on observational, not controlled studies; however, when controlled studies were performed, efficacy was sometimes correlated with challenge and at other times with serology.
§ This infectious agent cannot be shown experimentally to cause significant disease; therefore, it is not possible to determine DOI or efficacy. Observations and studies to demonstrate the efficacy and/or need for the vaccine suggests the vaccine is not effective and therefore not needed.
\ This is a ML (avirulent) bacteria.
¶ Based on field experience and observations from outbreak studies and clinical records. Reliable experimental or controlled studies are often not available. Serological data for *Leptospira spp.* suggest vaccines have ≤6 mos DOI.
# Information from company data and limited experimental and field observations due to the fact these vaccines were recently licensed (products available for ≤3 yrs).

initial vaccine and then as required by local, state, or provincial law. Dogs with unknown vaccine histories should be considered at risk and vaccinated, an initial booster should be administered 12 months later, and boosters should be administered throughout the dog's life [Table 1].

The minimum DOI for killed rabies vaccine based on challenge studies is 3 years; based on antibody titers, it is considered to be up to 7 years [Table 2].

### Specific Vaccine Recommendations: Optional Vaccines

**Distemper-Measles Virus (D-MV) Combination Vaccine:**
When the D-MV vaccine is given to a puppy between 6 and 12 weeks of age, the measles component of the vaccine cross-protects against CDV and is not inactivated by maternal antibodies directed at CDV. Protection occurs within 72 hours of vaccination; however, the vaccine is not effective <4 weeks of age. Puppies vaccinated with a D-MV vaccine should be vaccinated at 3- to 4-week intervals using CDV vaccines until the immunization series is completed [Table 1]. The D-MV vaccine is not indicated for use in dogs >12 weeks of age, especially female dogs destined as breeding stock, as it may result in the production of maternal antibodies to MV that would be passed on to future puppies negating vaccine efficacy. The D-MV vaccine may play a role in the prevention and control of CDV in high-risk settings such as shelters.

**Canine Parainfluenza Virus (CPV):** Canine parainfluenza virus is one cause of the "kennel cough" syndrome, an infection in susceptible, unprotected dogs causing a mild, self-limiting upper respiratory disease; the agent rarely causes life-threatening disease in otherwise healthy dogs.

Parenteral CPIV vaccines do not block infection but only lessen clinical disease, and vaccines produce only a short DOI. This vaccine antigen is generally administered along with CDV, CPV-2, and CAV-2. Since these three vaccines are recommended, the CPIV vaccine is considered optional but recommended [Table 1].

The minimum DOI for CPIV is difficult to determine by challenge studies, and serum antibody titers correlate poorly with protection, but the duration of serum antibody without vaccination was up to 3 years [Table 2]. Therefore, the value of revaccinating dogs annually with CPIV cannot be demonstrated; however, it is often combined with *B. bronchiseptica* vaccines in dogs considered susceptible.

**Leptospira spp.:** Infection with *Leptospira spp.* can cause clinical disease in some unprotected dogs. The organism can infect both dogs and humans; therefore, infected dogs can serve as a source for human infection (i.e., zoonosis) via contaminated urine. There are multiple *Leptospira* serovars and minimal cross-protection is induced by individual serovars, especially those defined to be the etiology of recent leptospirosis outbreaks in specific geographic regions.[a,5] Currently available vaccines do not contain all known serovars; therefore, dogs considered to be at risk for infection can be vaccinated, but current products do not provide assurance of protection [Table 1].

*Leptospira spp.* products include two to four serovars; the efficacies of these products are estimated to be between 50% to 75% and the DOI ≤1 year for the majority of animals that do develop immunity [Table 2]. Immunity is an ill-defined term for *Leptospira spp.* products. If immunity is defined as protection from infection or prevention of bacterial shedding, then there is little or no enduring immunity. If protection is defined as prevention of clinical signs of disease, then duration of immunity could be >1 year. Thus, DOI for *Leptospira spp.* becomes a problem of definition as to whether the goal of vaccination is interruption of bacterial shedding and public health concerns, or the prevention of clinical disease in the dog. It is generally agreed that immunity, however defined, is serovar specific; thus, if only one serovar is present in the vaccine, any protection, if provided at all, is for that serovar (e.g., *Leptospira canicola*) and not the many others that can infect the dog.

**Bordetella bronchiseptica (B. bronchiseptica):** *Bordetella bronchiseptica* is another cause of the "kennel cough" syndrome. Infection in some susceptible dogs generally causes a self-limiting, upper respiratory disease and rarely causes life-threatening disease in otherwise healthy animals. Clinical disease resolves quickly when treated with appropriate antibiotics. Vaccination does not block infection but appears to lessen clinical disease, and vaccines provide a short DOI (≤1 year) [Table 2]. It is also unknown whether current vaccine strains protect against all field strains. Animals considered to be at risk may benefit from vaccination followed by boosters at intervals in line with their risk of exposure [Table 1].

**Borrelia burgdorferi (B. burgdorferi):** Infection with *B. burgdorferi* can cause clinical disease syndromes in some susceptible dogs; most dogs infected are subclinically infected. While the organism infects both humans and dogs, it is not a direct zoonosis but a shared-vector zoonosis. The distribution of the tick vector involved is geographically limited and therefore the incidence of exposure is similarly geographically limited. Dogs previously exposed to *B. burgdorferi* do not benefit from vaccination and prevention of exposure to the tick vector is an effective preventive approach. Animals considered to be at risk may benefit from vaccination followed by boosters at intervals in line with their risk of exposure [Table 1]. The minimum DOI for *B. burgdorferi* vaccines is 1 year [Table 2].

### Specific Vaccine Recommendations: Not Recommended Vaccines

**Canine Coronavirus (CCV):** Infection with CCV causes mild gastrointestinal disease unless concurrent infection with CPV occurs. The virus does not generally cause disease in dogs >6 weeks of age and is not indicated in adult dogs. In at least one study, it was shown that vaccination with CPV protected puppies against challenges with both viruses. The incidence of disease and DOI is not known. Vaccination is not indicated in puppies >6 weeks of age, and vaccination of adult dogs is not indicated [Table 1]. At present, there is no indication that this organism produces a disease of clinical significance; therefore, administration of a CCV vaccine is not recommended.

Similar to CPIV, CCV does not cause clinical disease in experimentally challenged susceptible puppies, even those as young as 4 to 6 weeks of age; thus, challenge studies cannot be done unless pups are given immunosuppressive doses of corticosteroids. Serum antibody titers do not correlate with protection from CCV infection. Thus, for a virus that has not been shown to cause significant disease, and where serum antibodies don't correlate with resistance to infection, DOI is impossible to determine [Table 2]. Duration of immunity for CCV is a moot point since a need for the vaccine has not been demonstrated. It has been reported that DOI for CCV is the lifetime of the animal whether vaccinated or not as a result of natural subclinical infection and age-related resistance. Revaccination with a CCV vaccine in the adult dog cannot be justified, nor has it been shown to have value in preventing disease.

**Giardia spp.:** Infection with *Giardia spp.* can be subclinical or can cause small bowel diarrhea. The incidence of disease is generally <10% and approximately 90% of dogs respond to therapy; the disease is usually not life-threatening. There are multiple strains of *Giardia*, and it is unknown whether the vaccine is of value in more than one heterogeneous isolate. The vaccine does not prevent infection but may reduce or eliminate shedding of the organism and reduce clinical signs, which are rarely seen except in very young puppies concurrently infected with certain viruses and/or bacteria. The DOI is considered to be 1 year [Table 2]. Vaccination against *Giardia spp.* is not generally recommended [Table 1].

**Canine Adenovirus-1 (CAV-1):** Infection with CAV-1 can cause acute and potentially fatal hepatic disease in unprotected animals, and some dogs can experience chronic debilitating disease. Although CAV-1 infection is rarely documented in dogs in North America, the organism is still maintained in nature, and if widespread vaccination were discontinued, it is likely that the incidence of the disease would become common. Nevertheless, since excellent cross immunity is provided against CAV-1 by administering the CAV-2 vaccine and the use of CAV-2 results in less frequent adverse events, vaccination using a CAV-1 vaccine is not recommended [Table 1].

## Discussion and Supporting Literature

The genesis of these canine vaccine guidelines and recommendations was to inform practitioners of the current vaccine controversy, clarify any misunderstandings, and encourage practitioners to recognize that immunization of patients is a medical procedure. In addition, the Task Force members felt it was important to provide practitioners with relevant supporting information. While it is beyond the scope of this report to thoroughly discuss the extensive body of knowledge with respect to vaccinology, certain key concepts and principles are fundamental to the understanding and critical evaluation of these guidelines and recommendations. What follows is a synopsis of some integral concepts pertaining to immunology, DOI, serological testing, vaccine production, adverse event reporting, legal implications of biological use, and potential practice impact and opportunities of adopting these guidelines. Some important vaccination "do's and don'ts" are summarized in Appendix 2.

## The Immune System as it Applies to Vaccination

Understanding the immune system provides a basis for comprehending the nature of vaccine immunity. The following summary of the salient principles is further supported by suggested texts with more comprehensive discussions and explanations.[6-13]

Two major types of immunity prevent or limit infectious diseases: nonspecific (innate) immunity and specific (adaptive) immunity. In nature, it is innate immunity (including skin, hair, tears, normal microbial flora, and mucus and acidity of the gut) that prevents a majority of pathogens from infecting and/or causing disease in animals. Innate immunity also includes type-1 interferons (IFNs), some cytokines (e.g., interleukin-1 [IL-1], tumor necrosis factor [TNF]), complement components, neutrophils, and natural killer (NK) cells. This first line of defense is already active or immediately activated in response to inherent or elaborated chemical substances of the infectious agent. Unfortunately, current vaccines only occasionally have a significant beneficial effect on innate immunity; however, immunomodulators (i.e., nonspecific immune stimulants), some new experimental vaccines, and certain drugs are being designed and targeted toward enhancing innate immunity as a nonspecific method for disease prevention.

Adaptive immunity is characterized by specificity and memory and is primarily or exclusively the type of immunity stimulated when an animal receives a vaccine. This specific immune system is comprised of:

1. **Humoral (antibody) immunity**, where differentiated B lymphocytes (plasma cells) produce the four immunoglobulin classes: IgG, IgM, IgA, and IgE; phagocytic cells and effector molecules (e.g., complement) also play an important role.
2. **Cell-mediated immunity (CMI)** is comprised of T lymphocytes and their effector molecules, including T helper cells, T regulatory cells, T cytotoxic cells, macrophages, and a number of products of the cells called cytokines (e.g., IFN-$\gamma$, IL-2, IL-4, IL-12, TNF).

### The Immune Response to Vaccination or Infection

When an animal is vaccinated or infected, the immune response includes differentiation and expansion of clones of antigen-specific T and B cells that serve as effector cells for immediate protection and memory cells that provide long-term immunity. The effector cells themselves are usually short lived, dying in days or weeks after stimulation. Memory cells, on the other hand, survive for years, often for the life of an animal for some vaccines and infections. Memory T and B cells and the antibodies produced by long-lived memory effector B cells cooperate to provide protection from challenge at a later time in life for the vaccinated animals that come in contact with the pathogen. Available information suggests that vaccinal protection from infection and/or disease in the dog is regulated primarily by humoral immunity and secondarily by cell-mediated immunity. This finding is particularly true when vaccination is known to prevent reinfection (sterilizing immunity). This is the ultimate form of immunity because disease cannot develop when infection is blocked or infection is significantly limited. Sterilizing immunity occurs after effective vaccination (protection) against certain pathogens such as CDV, infectious canine hepatitis, and CPV.

However, when vaccination fails to protect against infection and instead protects against the development of clinical disease (as is the case for parenteral CPIV vaccination), systemic and local CMI together with humoral immunity (including local IgA antibodies) all play a critical role in preventing or reducing the severity of disease—not by preventing infection but by limiting its effects or keeping the infection localized. A CMI response is generally most effective against intracellular pathogens, while antibodies are usually most effective against toxins or pathogens in the extracellular areas. Whether a CMI or humoral response or both are responsible for controlling or preventing the clinical disease depends on the route of infection and the pathogenesis (the colonization and replication) of the infectious agent. For instance, prevention of clinical disease by many of the respiratory or gastrointestinal tract pathogens requires generation of mucosal CMI and/or humoral immune responses, with IgA being the most effective antibody class.

It is essential to note that the mechanism of protective immunity in a vaccinated dog is very different from immunity in a naive dog that strives to recover from a natural infection. Antibody is usually present in a vaccinated dog and functions to limit or prevent infection. It is never present at the time of infection in a naive animal. Furthermore, CMI and humoral immunity due to memory cells is stimulated in minutes to hours (i.e., anamnestic response) when a vaccinated animal is infected; whereas it takes days or weeks (primary response) to be stimulated in a nonvaccinated, immunologically naive dog.[14,15]

### Types of Vaccines

Just as the natural immune response depends on the type of antigen and the pathogenesis of the organism, these factors must also be considered in order for a vaccine to induce an appropriate immune response. There are several different types of commercially available canine vaccines. The most common vaccines currently in use are infectious vaccines, including MLV and live vectored vaccines. There are also noninfectious vaccines, including killed whole cell vaccines, subunit killed vaccines, and recombinant subunit vaccines.[3,7,11-13]

Modified live virus vaccines, consisting of avirulent or attenuated viruses that infect the host, are the most common canine viral vaccines. Such vaccines are highly efficacious, inducing stronger local immune responses than comparable killed products through the induction of serum neutralizing antibodies, local antibodies, and systemic and local CMI responses. The MLV vaccines create an immunity that is similar to immunity after an animal recovers from natural infection. There are also modified live bacterial vaccines consisting of avirulent or attenuated bacteria (e.g., *B. bronchiseptica*) and, similar to MLV vaccines, the modified live bacterial vaccines are often more effective than their killed counterparts.

The canarypox viral vectored vaccine for canine distemper virus has the ability to induce CMI and humoral immunity, but the humoral response is not as rapid or robust as the antibody responses engendered by MLV-CDV vaccines. When the canarypox viral vectored vaccine is used in puppies, at least two doses are required for immunity; whereas one dose of the MLV-CDV vaccine induces a strong, long-lasting immunity when passively acquired CDV antibody is not present in the puppy (e.g., ≥12 weeks; see Duration of Immunity section). Recent serological data showed that a third dose of CDV recombinant canarypox viral vectored vaccine induces an anamnestic antibody response equivalent to the response achieved with a dose of MLV-CDV, suggesting immunity for the recombinant product will last for >1 year and likely up to 3 years.[b,16]

Killed canine viral vaccines include vaccines for CPV-2, CCV, and rabies virus. Killed vaccines generally require two doses (rabies is an exception), because the response is slower and the immunity is predominantly but not exclusively systemic antibody with CMI limited to T helper type-1 effector cells and little or no IgA antibody on mucosal surfaces. Similarly, the killed bacterial products produce predominantly a systemic antibody response. The killed and subunit products include two to four serovars of *Leptospira spp.*, killed *B. burgdorferi* (Lyme disease), *B. bronchiseptica*, and a killed parasite vaccine for *Giardia*. There is also an OspA *Borrelia burgdorferi* recombinant subunit vaccine.

### Immunological Factors Determining Vaccine Safety

Several characteristics of vaccines are integral to determining product safety and efficacy, including the nature and dose of the antigen, the use of adjuvants, and the number of vaccinal components in any given product. Although increasing the number of components in a vaccine may be more convenient for the practitioner or owner, the likelihood for adverse effects may increase. Also, interference can occur among the components. Care must be taken not to administer a product containing too many vaccines simultaneously if adverse events are to be avoided and optimal immune responses are sought.

It is often stated that MLV vaccines are the most efficacious but that killed vaccines are the safest products; however, in light of advances in vaccine technology, this statement should be carefully re-examined.[11,13,14] Presumably, killed vaccines are safest because they cannot cause the disease for which the vaccine was designed to prevent; however, killed vaccines are much more likely to cause hypersensitivity reactions (e.g., immune-mediated disease). If they fail to protect because of poor or no CMI or local humoral immunity, or because it takes much longer to provide protection (e.g., the requirement for two doses of killed CPV-2 for protection), then they clearly are not "safer." Modified live virus vaccines can and do cause disease because attenuation is a balance between maintaining infectivity while eliminating its pathogenicity. Individual response is dependent on the status of the recipient's immune system. Thus, an attenuated pathogen in a host which is severely immunosuppressed, or genetically more susceptible, may result in the vaccine causing the disease for which it was designed to prevent. For example, an MLV canine distemper vaccine given to black-footed ferrets will induce clinical disease and death.[17] Furthermore, in a small percentage (estimated 0.01%) of dogs, the MLV-CDV vaccine may cause postvaccinal encephalitis.[15,18]

### The Immune System and Frequency of Revaccination

When vaccinating an animal, the age of the animal, the animal's immune status, and interference by maternal antibodies in the development of immunity must be considered. Research has demonstrated that the presence of passively acquired maternal antibodies significantly interferes with the immune response to many canine vaccines including CPV, CDV, CAV-2, and rabies vaccines. Age of the animal is also an important consideration. Puppies <4 months of age may be more susceptible to disease, and they are the main target for core vaccines. Also, very young and possibly very old animals may have a diminished response to vaccination due to age-related suppression of the immune system. Several

other illnesses (e.g., neoplasia, immune-mediated disease, endocrine diseases) and their treatments (e.g., chemotherapeutic medications, immunosuppressive drugs) can influence the immune response to vaccines and should be taken into account when vaccinating individual animals.[11-13,18,19]

When a healthy puppy's immune system is initially activated by vaccines through antigenic stimulation, a robust humoral and CMI response is expected to develop with concomitant effector and memory cells. If a pup fails to respond, primarily due to interference by passively acquired maternal antibody, it is necessary to revaccinate at a later time to ensure adequate immunity. Multiple vaccinations with MLV vaccines are required at various ages only to ensure that one dose of the vaccine reaches the puppy's immune system without interference from passively acquired antibody. Two or more doses of killed vaccines (except rabies) and vectored vaccines are often required to induce an immune response, and both doses should be given at a time when the passively acquired antibody can no longer interfere. Thus, when puppies are first vaccinated at ≥16 weeks of age (an age when passively acquired antibodies generally don't cause interference), one dose of an MLV vaccine, or two doses of a killed vaccine, are adequate to stimulate an immune response. When MLV vaccines are used to immunize a dog, memory cells develop and likely persist for the life of the animal. Resident memory cells respond rapidly providing an anamnestic immune response at the time of challenge (infection) with the pathogen.

So why revaccinate animals with these products annually when the minimum DOI (memory cells and antibody) is many years, if not a lifetime, for some of the vaccines? Ironically, there is no scientific basis for the recommendation to revaccinate dogs annually with many of the current vaccines that provide years of immunity (e.g., CDV, CPV-2, rabies); however, there are other vaccines that often provide <1 year of immunity (e.g., *B. bronchiseptica*, *Leptospira spp.*).[3,14,15]

Vaccinating an animal multiple times at intervals <2 weeks is likely to cause a hypersensitivity reaction in genetically predisposed animals, and a less than robust protective immune response develops.[15]

*The Critical Interplay Among Vaccine Efficacy, Safety, and Frequency of Administration (CDV as an example)*

Obviously, a killed CDV vaccine (none are available commercially) will not cause disease, but the killed CDV vaccines produced prior to the 1960s failed to protect most dogs from disease, and when protection was inferred, it was short lived. That is the main reason why killed CDV vaccines are currently not produced. Another reason is the inability of biologics producers to make an efficacious product for dogs although effective killed CDV vaccines have been produced for use in zoo and wildlife species.[17,18] In contrast to both conventional MLV and killed CDV vaccines, the canarypox viral vectored CDV vaccine won't cause disease (e.g., postvaccinal encephalitis), but, unlike killed vaccines, it does provide immunity. The kinetics of the immune response are much slower with the vectored CDV vaccine than with the MLV-CDV vaccine, because for immunity to develop, a second dose of vectored vaccine is required. Thus, in humane shelters or puppy rearing facilities where exposure to CDV is common, MLV vaccines are essential if a vaccine is expected to protect prior to infection with wild type (i.e., street virus) CDV. In fact, the best product in an environment where CDV is prevalent is a combined vaccine that contains both measles virus (MV) and CDV. This type of vaccine is recommended because MV will provide protection from disease with CDV at a much earlier age than CDV-only vaccines, as the MV vaccine is not inhibited by passively acquired CDV antibody.[15,17]

## Duration of Immunity

*Estimating Duration of Immunity and Frequency of Revaccination*

It's believed that the annual revaccination recommendation originated in the late 1950s when MLV-CDV vaccines were first introduced. This recommendation was based in part on the observation that approximately one-third of the dogs vaccinated with a first generation CDV vaccine as part of a limited experimental trial did not have antibody titers considered protective 1 year after vaccination. Therefore, to ensure the canine population had a protective antibody titer, James A. Baker recommended that all dogs should be revaccinated annually as it was not practical nor cost effective to test each animal for antibody.[20] At that time, there were very few vaccines (notably CDV and CAV-1), few people were vaccinating their dogs, and the practice of vaccination for companion animals was not well established or accepted. In 1961, Piercy wrote the following regarding annual administration of the canine distemper vaccine:

"It is felt, therefore, that the usefulness of booster injections in dogs already immune is still open to question and cannot be truly evaluated until considerably more research has been done. The value of revaccinating dogs whose antibodies have declined to a low level, however, is not in doubt. Although a serum analysis (antibody titer) is the most scientific way of judging the need for revaccination, in practice the owner would presumably be obliged to pay a fee for the examination and a further fee should revaccination be advised. The alternative, and less expensive way to the owner, is simply to have the animal revaccinated if there is a reason to doubt its immune status and it is likely to be exposed to infection. The practitioner is favorably placed to advise what should be done in light of such local circumstances as the incidence of canine distemper in his district, the history of the animal concerned, the risk involved in going to shows and kennels and other similar hazards."[21]

Thus, the practice of annual revaccination was accepted as a "principal of vaccination." Forty years later, we are finally reviewing the recommendation of annual revaccination. This critical review is based on scientific information and the knowledge of vaccines and immunity which have accumulated over that period.

As we analyze Piercy's statements, it is obvious that a significant amount of information has been developed to answer the questions posed 40 years ago, but the practice of vaccinating dogs has not changed.

1. Piercy stated: "The usefulness of booster injections in dogs already immune is still open to question and cannot be truly evaluated until considerable more research has been done." This statement was made with specific reference to the CDV vaccine. We now know that booster injections are of no value in dogs already immune, and immunity from distemper infection and vaccination lasts for a minimum of 7 years based on challenge studies and up to 15 years (a lifetime) based on antibody titer [Table 2].

2. Piercy comments: "The value of revaccinating dogs whose antibodies have declined to a low level, however, is not in doubt." Indeed, it is in doubt! Dogs with a CDV antibody titer, no matter how low when challenged, may become infected if antibody levels are below titers which provide sterilizing immunity (i.e., resistance to infection), but they will have protection from clinical disease mediated by an anamnestic humoral and CMI response. However, if after vaccination "no antibody" is detected in the dog's serum, then there is "no doubt," as suggested by Piercy, that revaccination will be of value in boosting the animal's immune response.

3. Piercy was very perceptive when he stated, "a serum analysis is the most scientific way of judging the need for revaccination." This is absolutely correct, and antibody titer is of great scientific value in determining if the dog has sterilizing immunity. Piercy emphasized the importance of antibodies since he didn't know about CMI; however, antibody is very important for protecting the vaccinated dog from CDV, as well as several other canine viral infections.

4. The economics of the 1960s remains unchanged today. Piercy's statement that "it would be less expensive to vaccinate than to have the animal bled and an antibody titer performed" remains, for the most part, relevant to today's practice economics. However, the ethical issue that our profession struggles with today is whether economics justifies giving an animal a drug (vaccines are biologic drugs) that is not necessarily required. As a minimum, we should allow pet owners to make this choice rather than make it for them.

5. Piercy's advice on risk assessment analysis and making the decision to vaccinate is an important medical issue and excellent advice that should receive careful attention whenever vaccines are administered. Which vaccines should be given? When and how often do they need to be given? The answers will undoubtedly vary according to which geographic region the dog resides, the lifestyle of the dog, the age and medical history of the dog, as well as the needs and expectations of the owner. Such questions must be asked if the animal is to receive the best medical care.

There are very few published studies on the minimum DOI for canine and feline vaccines and this is compounded by the fact that the criteria for determining DOI cannot be easily agreed on. Some researchers suggest that the only true way to determine DOI is by way of a prospective study that would be comprised of two (one group vaccinated; one group nonvaccinated) relatively large groups of dogs (representing common breeds) housed within a pathogen-free environment; therefore, at the end of the study, the nonvaccinated group would remain antibody-negative. Both groups would then be challenged with virulent isolates of each of the pathogens for which the vaccines were designed to provide protective immunity. Few minimum DOI studies using this study design have been done, and few, or none, will be done due to the high cost and difficulty of maintaining control (i.e., negative) animals. More important, based on current knowledge of immunity resulting from vaccination, studies of this type need not be done.[17,18,22-26]

There is no indication that the immune system of canine patients functions in any way different from the human immune system. In humans, the epidemiological vigilance associated with vaccination is extremely well-developed and far exceeds similar efforts in animals whether companion or agricultural. This vigilance in humans indicates that immunity induced by vaccination in humans is extremely long lasting and, in most cases, life-long. Current information (as presented in the section on Task Force Recommendations Regarding the Selection and Use of Canine Vaccine Antigens and Table 2) supports the contention that immunity to canine vaccines persists for years.

The canine core viral vaccines have been demonstrated by challenge studies to provide a minimum DOI of at least 3 years, and up to 7 years for some vaccine antigens.[3,14,15,27-29] When antibody titers considered to provide sterilizing immunity are evaluated, this minimum DOI is even longer [Table 2].[3,14,15,18,30] Duration of immunity for bacterial vaccines is considerably different than for viral vaccines. In contrast to viral immunity, bacterial immunity from vaccination is generally limited to ≤1 year, and the efficacy of most of the bacterial products is considerably less than for the viral products and directed at minimizing clinical signs of the disease in question. Protection from reinfection (sterilizing immunity) generally does not occur with canine bacterial vaccines.

Antibody titers from bacterial vaccines generally do not correlate directly with sterilizing immunity, and they would be significant only if there was no antibody detected after vaccination.[30] This would be a clear indication that the vaccine failed to stimulate an immune response. Such vaccines should be given again or another product should be used. Bacterial vaccines, especially killed whole organism products like certain *Leptospira spp.* products or *B. bronchiseptica* given systemically, are much more likely to cause adverse reactions than subunit or live bacterial vaccines or MLV vaccines, especially if given topically. Several killed bacterial products are used as immunomodulators/adjuvants. Thus, their presence in a combination vaccine product may

enhance or suppress the immune response or may cause an undesired immune response (e.g., IgE hypersensitivity or a class of antibody that is not protective).[3,14]

## Serological Tests to Monitor Immunity

Antibody titer tests are controversial, generally because many individuals fail to understand their significance. Furthermore, there is substantial confusion regarding the roles of humoral immunity and CMI in vaccinated versus naive animals.[31] When the protective mechanism of immunity in a naive dog infected with CDV is considered, the mechanism of recovery involves CMI and antibody, with CMI playing a primary and critical role. When one considers protective immunity to CDV in a vaccinated animal, antibody plays the primary role, because it prevents infection (sterilizing immunity) or limits the infection, and CMI plays a minor role.[17,18,31] When naive animals are infected with CPV-2, virus-neutralizing antibody promotes recovery and viral elimination; CMI plays a limited role in this scenario.[32] Conversely, in a vaccinated animal, antibody prevents infection. If infection occurs, antibody increases rapidly and restricts infection (often to lymphoid cells) so there is little or no viral infection of gut epithelial cells and no fecal shed of the virus. These are only two examples, but there are many more examples where antibody plays the principle role in protective immunity in the vaccinated, but not necessarily the naive, animal.[14,15]

How then should antibody titers be used in clinical practice to monitor vaccine immunity? They can be helpful in the following ways:

- to determine if there has been an immune response following vaccination
- to determine the duration of immunity
- to ensure the vaccine is immunogenic
- to know precisely when to vaccinate the puppy
- to determine whether the animal is a "low or nonresponder" to certain vaccines

The important issue regarding antibody titers is not their value but the accuracy of the results reported from various laboratories. To have any clinical value, any test used to determine an individual's immunity must be standardized against an accepted reference and demonstrate a very high degree of specificity and sensitivity. It is reported in the literature that titers of 20 for CDV and 80 for CPV are protective.[30,32] However, what is often not reported, or little understood, is that the test for CDV must be the virus neutralization (VN) test, and the test for CPV-2 should be the hemagglutination inhibition (HI) test performed with pig or monkey erythrocytes or the VN test, if those titer values are to be used. Those are the tests (VN and HI) that correlate with immunity by challenge studies. None, or few, of the commercial laboratories perform these tests, and the results of enzyme-linked immunosorbent assay (ELISA) or fluorescent antibody (FA) tests may not correlate with the titers from the VN and HI tests. Thus, antibody titers are useful if

you have a laboratory that performs the correct test, or if a test like the VN and HI or another test that has been standardized to correlate with protective immunity were available. Veterinarians should be sure that the laboratories they use for serological testing adhere to these principles.

Recently an "in-office test" was approved for detection of antibody to CDV and CPV-2 in dogs.[c] The test is designed so that a positive sample indicates that the antibody level in the sample is above the titer that provides sterilizing immunity for these respective viruses. A negative test result shows the titer to be below the level providing sterilizing immunity but does not indicate the animal would be susceptible to developing clinical disease if challenged by exposure, because infection could lead to an anamnestic (secondary) response, thus no clinical disease. The test is useful if the clinician needs to have some assurance that a vaccinated animal has immunity to CDV and/or CPV-2. These are the two most important viruses in the list of core vaccines. It is not necessary to determine a titer for rabies since revaccination once every 3 years after the first year is required and the 3-year rabies vaccines have that period as a minimum DOI. The CAV-1/CAV-2 titers need not be done, because exposure as well as vaccination with CAV-2 ensures protection from CAV-1, the more important pathogen of the two CAVs.

Although the committee does not feel it is necessary to determine titers to these core viruses on an annual basis because of the long minimum DOI for these products, titers can be used for your and/or your client's assurance that the animal has immunity. Experience with postvaccination titers for CDV, CAV, and CPV shows that sterile immunity lasts for years; thus, if the test is positive 1 year after vaccination, it is likely to be positive ≥3 years after vaccination. The primary reason for the test is to ensure that you have a positive test after completing the puppy vaccination series. For example, if you have vaccinated at 6 to 8, 9 to 11, and 12 to 14 weeks of age and test the serum ≥2 weeks after the final vaccination at 14 to 16 weeks, the test should be positive. If the test is negative, then you should revaccinate again immediately. If the test is not positive shortly (≥2 weeks) after the final vaccination, it suggests that the animal was not immunized. If you waited until 1 year of age, as we do now, the animal would potentially be susceptible during the most critical time in its life, the time when the animal needs to have vaccinal immunity. Experience with the test demonstrates greater than 90% of the dogs tested after the puppy series and up to 3 years after vaccination are positive, an indication they have sterile immunity and don't need to be revaccinated with core vaccines.[33]

## Licensing of Vaccine Products

The licensing and production of veterinary biological products is regulated by the U.S. Department of Agriculture (USDA) under federal legislation, 21 U.S.C. § 151, *et. seq.,* commonly known as the Virus-Serum-Toxin Act (VSTA) of 1913 (amended in 1985 and again in 1988).[34] This legislation gives the Secretary of Agriculture the ability to prohibit

the sale of any "worthless, contaminated, dangerous, or harmful virus, serum, toxin, or analogous product intended for use in the treatment of domestic animals." The regulations created by the Secretary of Agriculture under the VSTA are found in Title 9 of the Code of Federal Regulations (9 CFR).[34] These regulations define "biological products" as all viruses, serums, toxins, or analogous products which are intended for use in the treatment of animals and which act primarily through the direct stimulation, supplementation, enhancement, or modulation of the immune system or immune response. The Center for Veterinary Biologics (CVB) is the regulatory agency within the USDA responsible for overseeing veterinary biological products. Its mission is to ensure that pure, safe, potent, and effective veterinary biologics are available for the diagnosis, prevention, and treatment of animal diseases. The CVB reviews license applications for production facilities and biological products, establishes licensing and testing requirements and procedures, reviews supporting data involved in the licensing process, works to ensure that veterinary biological products are produced and maintained in compliance with regulations, and conducts assays on veterinary biological products.

The following is intended to provide a general overview of the considerations used by the CVB for licensure of biological products. In order to provide pure, safe, potent, and efficacious products, the CVB requires each manufacturer to file an "Outline of Production" for each product, which details how and where the product will be manufactured. Products can only be manufactured in an approved facility that undergoes periodic inspection. However, in the licensure of biological products, the exception is the rule. This is due to the nature of biological products and evolving technologies. The requirements set forth in the regulations can be modified by agreement of the CVB and the manufacturer as specified in the Outline of Production.

## Overview

In order to market a veterinary biological product, a firm must obtain a product license and an establishment license from the CVB. In order to obtain an establishment license, firms must establish the appropriateness of the facility for the product in question as well as the appropriateness of the qualifications of the personnel involved in developing and producing the product, and the facility must be inspected by the CVB. In order to obtain a product license, firms must submit:

- An application that includes an Outline of Production, which is a detailed analysis of the proposed production. Once approved, firms cannot deviate from the Outline of Production without permission from the CVB.
- The labels and claims to be used with the product, which must be reviewed against data submitted and approved by the CVB.
- Supporting data, including data from studies to support efficacy, safety, and field studies. The CVB reviews and approves protocols prior to the initiation of the studies to ensure quality of design and acceptability of the data

generated. Applicants must demonstrate to the satisfaction of the CVB that the proposed product is pure, safe, potent, and efficacious.
- Three consecutive serials for testing by the CVB. A "serial" is an identifiable, homogeneous quantity of completed commercial product. Each serial must be produced according to the Outline of Production from separate batches of medium, cells, production serum, and other applicable production components. The purpose is to demonstrate commercial consistency of production.
- Samples and the firm's test results from each serial must be sent to the CVB once the product and establishment are licensed. The serial cannot be released for commercial sale until the firm is notified by the CVB.

## Purity

Purity is the quality of a biological product (in its final form) that ensures the product is free of extraneous microorganisms and material (organic or inorganic) which can adversely affect safety, potency, or efficacy (9 CFR 1.101.5 (c)). Purity of biological products is determined by test methods or procedures established by the Animal Plant Health Inspection Agency (APHIS) or established in the approved Outline of Production for the product. Purity is first determined (by the firm) and confirmed (at the CVB) by testing of Bacterial Master Seeds, Viral Master Seeds, and/or viral Master Cell Stocks created (in a licensed biological production facility) and used to produce the product.

Purity evaluations of biological products continue throughout the production process and conclude with final product testing. This testing ensures, to a reasonable level of confidence, that all components of biological products are correctly identified and free of contaminating agents (pathogenic or not). The exact specifications of the testing performed depend to a great extent on the nature of the antigen (or microorganism).

## Safety

Safety is defined as freedom from properties causing undue local or systemic reactions when used as recommended or suggested by the manufacturer (9 CFR 1.101.5 (d)). As with purity, safety testing begins with evaluation of the Master Seed and concludes with testing of each serial prior to release. For Master Seed evaluation, an amount of Master Seed equivalent to one dose is administered to each of 10 susceptible dogs, followed by daily observation for 14 days. The Master Seed is found unsatisfactory if unfavorable reactions occur in any of the dogs during the observation period. This test is designed to detect major safety problems. Relatively rare safety issues will be seen either during field safety tests that involve larger numbers of animals or by postmarketing surveillance. One of the requirements for product licensure is to test the final product (at the titer and dose for commercially released product) using vaccine from at least two prelicensing serials in a minimum of 600 animals, of which at least one-third needs to be of minimum age. Many companies use 1,000 or more animals. Safety

testing for serial release involves the administration of 10 dog doses to each of two healthy dogs for 14 days.

### Potency

Potency is the relative strength of a biological product as determined by test methods or procedures established by the CVB, or in the approved Outline of Production for a product (9 CFR 1.101.5 (f)). The purpose of potency testing is to ensure that each serial of vaccine produced is equal to, or more potent than, a reference serial (equal to or more antigen than a reference) or the minimum antigenic content as specified through licensure. The type of potency assay used can be both product (antigen) and firm specific. Standard potency assay requirements for some established canine antigens can be found in 9 CFR. As standard assays are developed for emerging antigens, the procedures should become available from the Center for Veterinary Biologics-Laboratory (CVB-L) as a "supplemental assay method" (SAM).

Due to the heterogeneity of antigens required to protect the health of canine patients, a multitude of potency assay formats exist. These include laboratory animal based *in vivo* tests, target animal based *in vivo* tests, and *in vitro* tests. Regardless of the format, all potency assays must be approved by the CVB and be correlated to efficacy. Making the reference vaccine a serial that was used to demonstrate efficacy generally allows a firm to make this correlation. While this system of potency testing ensures that each serial produced contains a minimum amount of antigen, no upper limits to antigen content currently exist. This should be given further consideration as excessive amounts of antigen could result in both safety and efficacy concerns.

### Efficacy

The efficacy of a biological product is the specific ability or capacity of the product to effect the result for which it is offered when used under the conditions recommended by the manufacturer (9 CFR 1.101.5 (g)). In other words, efficacy is generally thought of as the ability of a product to stimulate the immune response required to provide protection from challenge (i.e., protective immunity). In contrast, immunogenicity is the ability of a product to elicit an immune response whether or not the response is correlated to protection. As with potency, standard efficacy requirements for some established canine antigens can be found in 9 CFR, Part 113. Where they exist, these standard requirements for efficacy determinations must be followed.

In general, two types of standard procedures exist for efficacy testing. In the first case, a product can be approved based on a serological response in which at least 75% of vaccinated animals develop an antibody titer greater than a reference value. In the second case, efficacy of a product can be established using a challenge model where 80% of the vaccinated animals are protected while 80% of the nonvaccinated control animals develop clinical disease or lesions. In many cases, challenge typically occurs within a month of completing the vaccination schedule and typically only a small number of animals are evaluated due to animal welfare concerns.

While these standard procedures allow at least a limited comparison of efficacy between vaccines, they do not exist for all canine antigens. For antigens that fall outside standard procedures, the variety of efficacy tests becomes much more complex and any ability to compare vaccines is lost. For these antigens, each firm is given an opportunity to develop their own efficacy data in support of licensure, usually based upon standards developed from information published in the scientific literature. All procedures for generating efficacy data must be approved by the CVB. However, considerable variability could exist in how similar products are evaluated for efficacy. In addition, there is currently no method or requirement that would allow for the simultaneous evaluation of products with similar antigenic components using a single efficacy study.

## Vaccine Adverse Event Reporting

### Background

The National Childhood Vaccine Injury Act (NCVIA) of 1986 mandated the reporting of certain adverse events following the vaccination of children to help ensure the safety of vaccines distributed in the United States. The Act led to the establishment of the Vaccine Adverse Event Reporting System (VAERS) in November 1990 by the Department of Health and Human Services. Today, VAERS provides a database management system for the collection and analysis of data from reports of adverse events following vaccination of humans. However, there is currently no federal or state mandate for veterinarians to report adverse events associated with animal vaccination. Practitioner reports of known or suspected vaccine adverse events in animals may be voluntarily submitted to either the vaccine manufacturer, the U.S. Department of Agriculture Center for Veterinary Biologics, or the United States Pharmacopeia (USP) through the Veterinary Practitioners' Reporting Program (VPRP).

At the time of this writing, an amendment[35] to the Virus-Serum-Toxin Act has been proposed by the U.S. Animal and Plant Health Inspection Service to:

1. require veterinary biologics manufacturers (licensees and permittees) to record and submit reports to the APHIS concerning adverse events associated with the use of biological products they produce or distribute,
2. require veterinary biologics manufacturers to report to the APHIS the number of doses of each licensed product they distribute, and
3. provide definitions for **adverse event** and **adverse event report**.

**NOTE**: The definitions and information provided below on vaccine adverse events and adverse event reporting are subject to change if this amendment is approved.

### Definition

For purposes of this discussion, a *vaccine adverse event* is defined as any undesirable side effect or unintended effect (including lack of desired result) associated with the administration of a licensed biological product (vaccine).

For vaccines administered to animals, adverse events are those involving the health of the treated animal and include the apparent failure to protect against a disease. It is important to note that an adverse event includes any injury, toxicity, or sensitivity reaction associated with the use of a vaccine, *whether or not the event can be directly attributed to the vaccine*. In other words, it is appropriate to report any known or suspected event associated with vaccination. A *vaccine adverse event report* may be defined as a source of communication concerning the occurrence of one or more suspected adverse events, which identifies the product(s), animal(s), and person making the report.

## Purpose of Reporting

Reporting field observations of unexpected vaccine performance is the most important means through which the manufacturer and the regulating agency (and the American Veterinary Medical Association) can be made aware of potential vaccine safety or efficacy problems that, if necessary, warrant further investigation. If a particular adverse event is well documented, reporting serves to provide a baseline against which future reports can be compared. In addition, reported adverse events could lead to the detection of previously unrecognized reactions, to the detection of increases in known reactions, to the recognition of risk factors associated with reactions, to the identification of vaccine lots with unusual events or unexpected numbers of adverse events, and to further clinical, epidemiological, or laboratory studies. Therefore, veterinarians are encouraged to report any clinically significant adverse event occurring during or after administration of any vaccine licensed in the United States. Reporting a vaccine adverse event is not an indictment against a particular vaccine. Reporting simply facilitates review of temporally associated conditions and adds to the safety database of the product.

## Reporting a Vaccine Adverse Event

The AVMA Council on Biologic and Therapeutic Agents has reported that the current adverse event reporting system needs significant improvement in the capture, analysis, and reporting of adverse events.[36] Veterinarians are encouraged to participate in the vaccine adverse event reporting process by reporting suspected and known adverse events to any of the following three locations:

1. The vaccine manufacturer, usually through telephone communication with technical services [Table 3];
2. the USDA-CVB by toll-free call (800-752-6255); or
3. the United States Pharmacopeia (USP) Veterinary Practitioners' Reporting Program (VPRP) by toll-free call (800-487-7776; press #3), by fax (301-816-8373), or online (*www.usp.org/vprp*).

Reports made to the USDA are forwarded directly to the vaccine manufacturer without specific action. Although adverse event reports made to the USP VPRP are collected and maintained in a database, individual vaccine adverse event reports are not necessarily forwarded by USP to the vaccine manufacturer. While still available, the future of the USP VPRP is currently under review.

## Event Criteria

Reporting a known or suspected vaccine adverse event should include the:

1. Manufacturer's name
2. Product brand name, lot/serial number, and expiration date
3. U.S. veterinary license number and product code
4. Signalment (age, species, breed, gender) of patient affected
5. A description of the clinical signs or diagnosis associated with administration of the vaccine. Although specific reporting criteria are not defined for clinical events, the type of reaction and length of time between administration of the vaccine and onset of the adverse event should be documented using the following guidelines:
   a. Local (injection-site) reactions occur exclusively at or around the site of inoculation. They may occur at the time of injection, or several minutes, hours, or days later and may persist from minutes (e.g., pruritus) to months (e.g., granuloma). Reports should include the route of administration (i.e., subcutaneous, intramuscular, or topical [oral, conjunctival, or nasal]). Examples of injection-site (local) reactions following vaccination include pain, pruritus, swelling, injection-site alopecia, abscess formation, granuloma formation, and neoplasia. Infection and skin necrosis are rare but have been reported. Vaccines licensed for administration by the topical (conjunctival/intranasal) route have been associated with sneezing (persisting ≥3 days), nasal and oral ulceration, ocular discharge, and cough (persisting ≥24 hours).
   b. Systemic reactions are events that involve the entire body or a defined location/region other than the injection site. Like injection-site reactions, systemic reactions typically don't occur at the time of injection but can develop within minutes or hours and may persist for hours or days. Examples of systemic reactions following vaccination include angioedema, especially involving the face, muzzle, and ears (most often reported in dogs); anaphylaxis and collapse; polyarthritis (lameness); vomiting with or without diarrhea (most often reported in cats); respiratory distress; fever; and lethargy. Severe events that may be vaccine associated requiring long-term medical intervention and patient follow-up include immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, icterus, renal failure, and glomerulonephritis.
   c. Vaccine-associated death, although rare, does occur. In dogs, anaphylactic shock is the most commonly reported adverse event leading to death. There has been no trend to suggest an association between anaphylaxis and a particular manufacturer's vaccine. Veterinarians are strongly encouraged to report any death suspected or known to be associated with vaccination to the vaccine manufacturer [Table 3].

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**Table 3**

Technical Services Toll-Free Phone Numbers (U.S.) for Major Vaccine Manufacturers

| Manufacturer | Toll-Free Number |
| --- | --- |
| Bayer Corporation | 800-422-9874 |
| Elanco Animal Health | 800-428-4441 |
| Evsco Pharmaceuticals | 800-387-2607 |
| Fort Dodge Animal Health | 800-477-1365 |
| Heska Corporation | 888-437-5287 |
| Intervet | 800-992-8051 |
| Merial Ltd. | 888-637-4251 |
| Novartis Animal Health | 800-637-0281 |
| Pfizer Animal Health | 800-366-5288 |
| Pharmacia & Upjohn | 866-493-1954 |
| Schering-Plough Animal Health | 800-224-5318 |
| Synbiotics | 800-228-4305 |

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## Legal Implications of the Discretional Use of Biologics

As a general rule, the use of biological products by small animal veterinary practitioners is left to their professional judgment. The latitude afforded practitioners is broad, but there are boundaries.

The analysis of the law governing use is complicated. The USDA-CVB regulates the licensure and preparation of most veterinary biologics. The Virus-Serum-Toxin Act empowers the CVB to stop the sale, barter, or exchange of "any worthless, contaminated, dangerous, or harmful virus, serum, toxin, or analogous product." If veterinary use of a CVB-regulated product was viewed as unsafe, the CVB could initiate an enforcement action; however, unless a safety issue is implicated, the USDA has historically not considered such enforcement to be a priority. In addition, some vaccines are licensed with specific restrictions regarding their use, which will be noted in their labeling.

The FDA's Center for Veterinary Medicine (CVM) also regulates some products that most practitioners would consider biologics. The jurisdictional gray zone between the two agencies is confusing, constantly blurred, and evolving. Products regulated by the CVM are covered by the Animal Medicinal Drug Use Clarification Act, which established specific rules for "extra-label" drug use.

### Potential Liability

Potential liability for medical decision making is a fact of life for any health-care provider, including veterinarians. This potential professional liability encompasses all aspects of veterinary practice, including the selection and use of vaccines and other biological products. Generalizations about potential legal liability are as difficult to make as generalizations about medical practice. The range of possible legal liability theories used in litigation is broad and limited only by the creativity of the plaintiff's attorney. To further complicate matters, there are variations, some subtle and some not, between states. However, most lawsuits against practitioners are grounded in negligence theory, although other possibilities include product liability, breach of express or implied contract, breach of express or implied warranty, guaranty, battery, and breach of fiduciary relationship. These principles apply to all aspects of professional veterinary practice, not simply vaccine or biological issues. Discussed below are some types of negligence suits that could arise out of use of biological products.

**Malpractice:** Negligence actions involving veterinarians are usually cast as traditional medical malpractice cases. The law of professional medical negligence has evolved in the context of human medicine. Most jurisdictions will apply the legal concepts developed in the litigation of physician malpractice cases to veterinary malpractice cases. The traditional elements of a medical malpractice lawsuit are the duty to conform to a certain standard of care, a failure to conform to the required standard, actual injury or damage, and a legally sufficient causal connection between the conduct and the injury. The duty arises out of the veterinary-client-patient relationship (VCPR) and is typically stated as the duty to exercise reasonable care. That is, the duty to exercise the same level of care and competence as a reasonably prudent practitioner, with the same or similar training, under the same or similar circumstances. This duty is often referred to as the "standard of care." In this context, standard of care is a legal term of art and does not necessarily equate with professional practices or standards. Establishment of the relevant standard of care and whether a practitioner deviated from it, with few exceptions, must be established by competent expert testimony.

In practice, many medical negligence cases become a "battle of experts." The plaintiff, using an expert witness, presents a standard of care and the opinion that the practitioner failed to meet the standard, and that such failure caused the plaintiff's injury or damages. In turn, the defendant practitioner offers differing expert testimony, establishing a different standard of care, that the defendant veterinarian met the standard, and that the defendant's conduct did not legally cause the plaintiff's injury or damage. Faced with conflicting evidence, the jury resolves the issue based on innumerable variables, including the qualifications and presentation of the various experts and the defendant.

The scenarios that could give rise to a lawsuit are as varied as the imagination allows. For example, a practitioner who chooses not to vaccinate an animal could be potentially sued for negligence if the animal contracts the disease the vaccination could have prevented. In such a case, the plaintiff would be required to have expert testimony that the defendant's failure to vaccinate the animal was a departure from the standard of care and the cause of the injury to the animal. On the other hand, a practitioner who vaccinates an animal could potentially be sued for negligence if the animal has a complication from the use of the vaccine. In such a case, the plaintiff would be required to have expert testimony that the defendant's vaccination of the animal was a departure from the standard of care and the cause of the injury to the animal. Whether a plaintiff would prevail on such theories will depend on the facts of the individual case, the qualifications of the defendant and the experts, and the intangible items that always come into play in trials.

**Informed Consent:** The legal doctrine of informed consent arises out of the obligation to obtain consent prior to providing care to a patient. The essence of informed consent is that a practitioner informs the client of the material risks of a proposed treatment or procedure and potential alternatives, including the risk of no treatment, and the client/patient, having been informed, either gives or withholds consent. It is important to remember that the informed consent of the patient/client is the goal, not simply the act of obtaining a signature on a form. One of the best deterrents to an informed consent lawsuit (or any other for that matter) is to communicate with, not talk at, clients and document the discussions.

The laws governing this area developed as human medicine evolved from a paternalistic profession to one that recognizes the importance of a patient's self determination. Informed consent cases are common in human medicine and could also be brought against veterinarians. These cases are often based on negligence principles, due to the manner in which they developed in physician malpractice cases. In some jurisdictions, they may be brought under other legal principals, such as battery. Most informed consent cases arise out of a patient's/client's misunderstanding, misperception, and from the practitioner's perspective, sometimes unreasonable expectations.

The complicating factor is a split of authority on the standard by which a practitioner's actions are judged in informed consent cases. There are two primary standards utilized, with a fairly even split between those states that use a practitioner-focused inquiry and those that use a patient/client-focused inquiry. Thus, the standard by which a veterinarian's conduct will be evaluated depends upon the state in which one practices.

Under the practitioner-focused standard, the inquiry is whether the defendant provided the information that a reasonable practitioner would disclose under the circumstances. The level of the required disclosure is established by expert testimony. Under the patient/client-focused standard, the inquiry is whether the practitioner provided sufficient information (in understandable terms) to allow a "reasonable person" to make decisions about the course of treatment. The real issue becomes, under the circumstances, what information would a reasonable person need to make informed, rational decisions. Regardless of which standard is employed, the other elements of a negligence case, including the causal connection, would have to be established in order for a plaintiff to prevail.

Whether the use of written consent forms deter informed consent cases is often discussed. Documentation of informed consent discussions is always helpful in the defense of an informed consent case. The documentation often ranges from a note in the chart (with or without cosignature by the client), to a generic consent form signed by the client, to a very detailed document specific to the treatment or procedure contemplated. The more general the language used, the less helpful, and, conversely, the more specific the language the more helpful in the defense of a case. It is important to note that in human medicine, most informed consent lawsuits have signed consent forms in the chart. While they are helpful tools, they do not preempt all lawsuits over consent issues. In fact, there are times that consent documents could be harmful to the defense of a case. Some consent forms for vaccination estimate the odds of disease exposure or the chance of an adverse event occurring following vaccination. The practitioner should have a medically or scientifically defensible basis for making any such precise representations in a consent document. If precise numbers cannot be justified, more general statements are preferable. For example, a statement indicating that the true incidence of a particular adverse reaction is not known, but is believed to be low, or has been reported in the literature to be in the range of "X%–Y%" would be appropriate. In addition, a statement that the exact chances of exposure to a particular disease cannot be quantified but should be less where the animal is not exposed to other animals would be more defensible. Such statements may be harder to craft, but a practitioner would not want to be in the unenviable position of explaining to a jury that the representations made to a client prior to a treatment or procedure were simply a "guesstimate," leaving the practitioner to explain the basis for the statements. There is obviously room for professional judgment, but very specific numbers

based solely on experience or judgment will be harder to defend. One of the best methods for crafting consent forms for use in a practice is to talk with an attorney who has defended informed consent cases in your state. They can provide invaluable assistance in understanding the laws in your jurisdiction and crafting consent documents that best meet your particular needs.

## Vaccinations as a Component of Comprehensive, Individualized Care

For many years, the practice of veterinary medicine has benefited from the annual administration of vaccines. By encouraging dog owners to bring their pets in yearly for vaccinations, veterinarians have been able to recognize and treat disease earlier than might otherwise have been the case. The annual visit has also provided an opportunity to inform clients of important aspects of canine health care; therefore, vaccinations are a component but not the principle aspect of a comprehensive, individualized wellness program for patients. This annual general examination and client interaction is good veterinary medicine and good veterinary business practice.

Unfortunately, many clients have come to believe that vaccination is the most important reason for annual veterinary visits. Veterinarians are justifiably concerned that a reduction in vaccination frequency will cause clients to forego routine annual visits for their dogs and that the quality of care they deliver will be diminished. To avoid this consequence, it is vital that veterinarians stress the importance of all aspects of a comprehensive, individualized health-care program. Clients should be informed that dogs with serious disease often appear healthy and that regularly scheduled health evaluations facilitate early detection. Emphasis should be placed on a comprehensive physical examination performed by the veterinarian as well as individualized patient care. The importance of dental care, proper nutrition, appropriate diagnostic testing, and the control of parasites and other zoonotic diseases should also be addressed during each patient evaluation. Behavior concerns should be discussed, as should the necessity for more frequent examination of puppies and geriatric dogs.

Each patient's vaccination needs should be assessed at least yearly and, if appropriate, vaccination schedules should be modified on the basis of changes in the dog's age, health status, home and travel environment, and lifestyle. An explanation of the types of vaccines currently available, their potential benefits and risks, and their applicability to the particular dog given its lifestyle and risk of exposure should be undertaken. The regional incidence and risk factors for various infectious diseases should also be discussed. With a focus on the welfare of the patient, these discussions should take place even with clients who choose to vaccinate their pets themselves or have them vaccinated by individuals other than the primary care veterinarian. Ways to reduce the impact of acquired disease (e.g., avoiding overcrowding, improving nutrition, and restricting access to infected animals) should also be reviewed.

Vaccinations should be considered just one component of an individualized, comprehensive preventive health-care plan based on the age, breed, health status, environment (potential exposure to harmful agents), lifestyle (contact with other animals), and travel habits of the dog.

### Age

Obviously age has a significant effect on the preventive health-care needs of any individual. Puppy programs have traditionally focused on vaccinations, parasite control, and sterilization. Today, opportunity exists to incorporate behavior counseling and zoonotic disease management as well. With aging pets, tiered senior care programs are increasingly popular. Nutritional, dental disease, and parasite control assessment and counseling should take place throughout the life of the pet.

### Breed

It's common knowledge that certain breeds are predisposed to various diseases. Early detection and management of breed-associated disease can significantly improve the quality of a dog's life.

### Health Status

Dogs with chronic medical conditions, such as diabetes mellitus, hypothyroidism, heart disease, renal failure, hyperadrenocorticism, hypoadrenocorticism, glaucoma, and keratoconjunctivitis sicca, warrant periodically scheduled medical examinations and testing designed to monitor the progression of diseases and provide for therapeutic adjustments. Dogs receiving certain medications also warrant therapeutic monitoring of blood levels and/or organ systems. The development of recheck protocols for chronic diseases and medications, which can be included in reminder systems, can greatly improve client compliance and accordingly patient care.

### Environment

The environment in which a pet resides can profoundly affect the health status of that pet. Exposure to trauma (e.g., automobiles, animal fights, high rise syndrome), weather (e.g., heat stroke, frostbite), water (e.g., drowning), toxins (e.g., antifreeze, human medications, poisonous plants, household and industrial toxins), sunlight (e.g., solar dermatitis), as well as internal and external parasites should be assessed during annual health-care visits in order to define risk factors and appropriate preventive measures.

### Lifestyle

By determining the extent to which dogs come in contact with other animals either in controlled or unobserved circumstances, veterinarians can assess the need for noncore vaccinations. Dogs that visit kennels, grooming salons, common areas, and wooded, tick-infested areas are at greater risk from certain infectious diseases than dogs that do not frequent these areas.

*Travel Habits*

Just as the human population has become much more mobile, so has the canine population, resulting in potential exposure to infectious agents, parasites, and environmental hazards not found in the home environment. The determination of past and anticipated future travel of dogs during each preventive care visit allows for greater individualization of preventive care and diagnostic testing plans.

*Medical Record Documentation*

At the time of vaccine administration, the following information should be recorded in the patient's permanent medical record: date of vaccine administration, identity (employee name, initials, or code) of the person administering the vaccine, vaccine name, lot or serial number, manufacturer and expiration date, and site and route of vaccine administration. The use of peel-off vaccine labels and stamps that imprint the medical record with the outline of a dog facilitate this type of record keeping. Adverse events should be recorded in a manner that will alert all staff members during future visits. Informed consent should be documented in the medical record in order to demonstrate that relevant information was provided to the client and that the client authorized the procedure. At the very least, this notation should indicate that a discussion of risks and benefits took place prior to vaccination.

## Conclusion

The burgeoning knowledge in the fields of vaccinology and immunology, together with the continued enhancements of vaccine efficacy and safety, have placed the traditional approaches to vaccine use in doubt and engaged our profession in a long overdue debate. What is clear is that the complexity of the issues involved make it impossible for our profession to make blanket statements with respect to vaccine selection and use—one size simply does not fit all. This underscores the fact that vaccination is a medical procedure and, as such, needs to be tailored to the individual and administered under a valid VCPR on the basis of informed consent. Not all vaccines are indicated in all animals and no vaccine should be given without a thorough knowledge of the risks of acquiring the disease, the potential for adverse reactions to vaccination, and the health of the animal in question. Current knowledge clearly indicates the need to refine vaccine selection and to re-establish vaccine protocols when revaccinating animals >1 year of age that have undergone an initial vaccine series. In the case of core vaccines (i.e., CDV, CPV, CAV-2, and rabies virus), every 3 years is considered adequate to maintain appropriate protection. Regardless of your eventual decision, we challenge you to keep an open mind and critically evaluate and incorporate new information as it becomes available.

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## Acknowledgments

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## Appendix 1

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## Appendix 2

### Important Vaccination "Do's and Don'ts"

1. **Do Not Vaccinate Needlessly**
   Don't revaccinate more often than is needed and only with the vaccines that prevent diseases for which that animal is at risk.

2. **Do Not Mix Vaccines in a Single Syringe**
   If the vaccines are not combined by the company as a multicomponent licensed product, do not combine them prior to administration. Follow the manufacturer's administration recommendations.

3. **Do Not Split Doses**
   For miniature/toy or any other breeds.  If you are concerned about the volume, reconstitute vaccine with ¼ or ½ the recommended diluent (e.g., sterile water).

4. **Do Not Vaccinate Anesthetized Patients**
   Should an anesthetized animal develop a hypersensitivity reaction, they may vomit and are at increased risk of aspirating.

5. **Do Not Vaccinate Pregnant Dogs**
   The dog may abort or fetuses may get infected.

6. **Do Not Vaccinate Animals on Immunosuppressive Therapy**
   These animals may not develop an adequate immune response, but even worse, they could develop disease (e.g., postvaccinal distemper, clinical canine parvovirus).

7. **Do Not Administer Multiple Dose Vaccines Any More Frequently Than Every 2 Weeks**

8. **Do Not Vaccinate Puppies <2 Weeks of Age**

9. **Do Make Sure the Last Dose of a Puppy Immunization Series is Administered ≥12 Weeks of Age**
   At ≥12 weeks of age, interference by maternal antibody is less of a concern and the puppy's immune system is more mature; thus, there is a greater opportunity for a robust immune response to the vaccine.

10. **Do Not Give an Inactivated Product Prior to a Modified Live Product**
    This will interfere with the ability of the modified live product to immunize (e.g., canine parvovirus-2).

11. **Do Not Administer a Canine Distemper-Measles Vaccine Subcutaneously (SC)**
    It has been shown that poor immunity results when this product is administered SC.

12. **Do Not Assume that Vaccines Cannot Harm a Patient**
    Vaccines are potent medically active agents and have the very real potential of producing adverse events.

13. **Do Not Use Nosodes (Holistic Vaccines) to Vaccinate a Puppy**
    Nosodes do not provide immunity; thus, the puppy will remain susceptible to the disease the nosode was designed to prevent. Use a USDA-licensed vaccine to immunize puppies.

14. **Do Not Revaccinate a Dog With Vaccines Previously Known to Induce Anaphylaxis in that Dog**
    Test the animal's serum for antibody to determine if the animal is immune.  The risk from vaccine-induced anaphylaxis may be much greater than the risk of infection.