2011 AAHA Canine Vaccination Guidelines*†

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Introduction

The previous versions of the American Animal Hospital Association (AAHA) Canine Vaccine Guidelines, published in 2003 and 2006, and updated in 2007, represented a collaborative effort by academicians, private practitioners, and industry to facilitate efforts of veterinarians in the United States (US) and Canada in making decisions regarding the selection and use of canine vaccines. Vaccination guidelines for shelter-housed dogs were also included in 2006. Since that time, new canine vaccines have been licensed, others have been withdrawn, and new information on existing vaccines has led to the revision of current recommendations. The 2011 AAHA Canine Vaccination Guidelines offer a comprehensive review of canine vaccines currently available in North America, updated recommendations on administration of core versus noncore vaccines, and revised recommendations for vaccination of shelter-housed dogs. Also included are updated recommendations on serologic testing as a means of documenting and monitoring immune responses to vaccines, an expanded discussion on vaccine adverse events (AEs), and an updated review of the legal implications associated with administering vaccines in clinical practice.

The reader is reminded that scientific studies and refereed journal publications are not available to support all of the vaccination recommendations included within this document. Some recommendations are based on unpublished studies, current knowledge of immunology, and the experience of experts in the field. To that point, the reader is referred to a new section of the AAHA Canine Vaccination Guidelines, entitled Frequently Asked Questions (FAQs). Within this section, the Task Force addresses several topical and controversial canine vaccination issues posed by practicing veterinarians. The section is subdivided into four categories to address questions on Administration of Vaccines, Vaccine Products, Adverse Reactions to Vaccines, and Legal Issues related to administration of vaccines, and is intended to provide additional advice on key points of concern where scientific documentation may not be available.

The AAHA Canine Vaccination Task Force developed the 2011 Guidelines in a manner consistent with best vaccination practices. The Guidelines include expert opinion supported by scientific study and encompass all canine vaccines currently licensed in the US and Canada. The Guidelines include recommendations that may differ from statements on product labels and product literature, especially with respect to initial vaccination and revaccination (booster) intervals. It is the view of the Task Force that veterinarians have considerable latitude in the selection and use of veterinary biologic products licensed for dogs, with rabies vaccine being a noted exception, and that these Guidelines, although not intended to dictate an exclusive protocol or standard, do meet accepted standards of professional practice.

This document was developed by AAHA through a collaborative effort among Task Force members to aid practitioners in making decisions about appropriate care of their canine patients with respect to currently available vaccines. The Task Force included experts in immunology, infectious diseases, internal medicine, law, and clinical practice.

The Guidelines are supported by professional, scientific, and clinical evidence, as well as published and unpublished documentation.

These Guidelines and recommendations should not be construed as dictating an exclusive protocol, course of treatment, or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and

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limitations unique to each individual practice setting. The Guidelines are not intended to be an AAHA standard of care.

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Acronyms and Terms

Regulatory Agency Acronyms

AMDUCA *Animal Medicinal Drug Use Clarification Act—applies only to animal drugs regulated by FDA, not veterinary biologics regulated by USDA;* **APHIS** *Animal and Plant Health Inspection Service—an agency of the USDA*; **CFIA** *Canadian Food Inspection Agency—the agency responsible for licensing veterinary vaccines made and/or used in Canada*; **CVB** *Center for Veterinary Biologics*; **FDA** *Food and Drug Administration—licenses all human vaccines and veterinary pharmaceuticals;* **USDA** *United States Department of Agriculture—licenses all veterinary vaccines*

Vaccine Terms and Acronyms

Avirulent live *attenuated bacterial vaccine*; **bacterin** *whole killed cell bacterial vaccine;* **killed antigen** *inactivated vaccine antigen (viral or bacterial);* **infectious vaccines** *vaccines that infect the host's cells to induce a protective immune response (e.g., modified-live [attenuated] viral vaccines [see text for specific examples]);* **noninfectious vaccine** *vaccines that are incapable of infecting host cells to produce additional antigen (e.g., killed [inactivated] vaccines [see text for specific examples]);* **r** *recombinant vaccine antigen—this notation generally precedes the name of the vaccine (e.g., recombinant canine distemper virus [rCDV]);* **subunit vaccine** *a vaccine produced using conventional or recombinant technology that contains specific subunits rather than a complete virus or bacteria;* **viral vector** *a live nonpathogenic (or attenuated) virus in which selected DNA or RNA of a pathogenic virus is recombined for purposes of vaccine development; virus vectored vaccines represent one form of recombinant vaccine technology.*

AAHA *American Animal Hospital Association;* **AE** *adverse event;* **Bb** *Bordetella bronchiseptica;* **CAV-1** *canine adenovirus, type 1 (cause of canine viral hepatitis); protection from CAV-1 infection is provided by parenterally administered CAV-2 vaccine;* **CAV-2** *canine adenovirus, type 2;* **CCoV** *canine coronavirus cause of enteric coronavirus infection (antigenically distinct from the canine respiratory coronavirus [CRCoV]);* **CDV** *canine distemper virus;* **CIV** *canine influenza virus—H3N8;* **CPiV** *canine parainfluenza virus;* **CPV-2** *canine parvovirus, type 2;* **DOI** *duration of immunity;* **HI** *hemagglutination inhibition—a laboratory technology used to measure antibody levels (e.g., parvovirus antibody);* **HOD** *hypertrophic osteodystrophy;* **IgG** *immunoglobulin G—a class of humoral antibody; most common type associated with immune response to parenteral vaccine; also the most common class of antibody measured as serum titers;* **IgM** *immunoglobulin M—a class of antibody, generally short lived and associated with early infection and initial*

vaccination; **IM** *intramuscular (route of administration);* **IN** *intranasal or mucosal (route of administration);* **MDA** *maternally derived antibody;* **MLV** *modified live virus, attenuated virus vaccine;* **MV** *measles virus;* **NSAIDs** *nonsteroidal anti-inflammatory drugs;* **OMC** *outer membrane component—used in reference to bacterial surface proteins (subunit antigens) in selected bacterins; also referred to as "conventional" subunit vaccines;* **OspA** *outer surface protein A (antigen) of* Borrelia burgdorferi*;* **OspC** *outer surface protein C (antigen) of* Borrelia burgdorferi*;* **PCR** *polymerase chain reaction—a very sensitive test that measures the presence or amount of RNA or DNA of a specific organism;* **RV** *rabies virus;* **SAE** *serious adverse event;* **sIgA** *secretory immunoglobulin A—a class of antibody, most commonly associated with a local (mucosal) immune response after IN vaccination;* **SQ** *subcutaneous (route of administration);* **US** *United States;* **VN** *virus neutralization—a laboratory technology used to measure antibody levels (e.g., canine distemper antibody)*

Part I: Canine Vaccination in General Veterinary Practice

Vaccines provide proven life-saving benefits, are associated with minimal risk, and should be part of routine preventative health care. Life stage and lifestyle, risk of exposure, and underlying medical conditions should all be considered when developing a vaccination protocol.

Vaccine Types

Over the last 5 decades, significant advances in vaccine technology have resulted in many types of biologicals (vaccines) being licensed by the U.S. Department of Agriculture (USDA) and Canadian Food Inspection Agency (CFIA) for use in dogs. The two general types of vaccines now available include the noninfectious (inactivated, killed, dead, conventional and recombinant subunit, plasmid DNA, and avenomous) vaccines and the infectious (attenuated, avirulent, modified live, recombinant viral vectored) vaccines.[1–4] The availability of a wide variety of products provides veterinarians with multiple options when selecting and administering core and noncore vaccines. The following section provides a summary of the theory and technology behind the different types of canine vaccines currently on the market.

Noninfectious (Inactivated, Killed) Vaccines

The noninfectious (inactivated, killed) vaccines include killed viral (e.g., rabies virus [RV], canine influenza virus [CIV], and canine coronavirus [CCoV]), whole killed cell bacterins (certain Lyme, *Leptospira*), bacterial subunit (recombinant outer surface protein A [OspA] Lyme, and conventional subunit *Leptospira* outer membrane component [OMC] vaccines), a cellular antigen extract of the *Bordetella bronchiseptica* (Bb) vaccine, and Western diamondback rattlesnake avenomous vaccine (**Table 1**). As the name "noninfectious" implies, these vaccines do not infect the host to produce new antigen. Thus, they must contain adequate amounts of antigen to immunize. Because the antigen alone may not be adequate to immunize a dog, many of the noninfectious vaccines must also contain adjuvant. Adjuvants include a wide variety of substances that maintain or depot the antigen as well as stimulate an inflammatory response to provide a more robust immune response to the vaccine antigens.[5,6] This increased nonspecific stimulation of the immune system caused by adjuvants is required to induce a protective response to antigens. Some of the killed whole cell bacterial vaccines do not require the addition of adjuvant because the bacterial cell walls or portions of cell wall (e.g., lipopolysaccharide, peptidoglycans) of *Bordetella*, *Leptospira*, or *Borrelia* have adjuvant properties, in addition to serving as antigens.[5,6] Together, the antigen and adjuvant are designed to stimulate a protective immune response.

Critical to production of a noninfectious vaccine is the process used to inactivate the virus or bacteria, to ensure that it is dead. At the same time, this process must not significantly alter the antigenic properties of the organism. Chemicals, ionizing irradiation, and other methods are used to kill the organisms. Chemicals used for inactivation include formalin, β-propiolactone, ethylenediamine, and other agents. Some of these agents cannot be completely eliminated from the final product. Injection site pain or hypersensitivity have sometimes been attributed to the residual chemicals.[7] When compared with infectious (attenuated, avirulent, modified live, recombinant viral vectored) vaccines, noninfectious vaccines are more likely to produce local and systemic adverse reactions in some dogs.[7–9] These AEs can be caused by the antigen (e.g., virus or bacteria), the adjuvant, serum or cellular proteins, or a combination of vaccine components. Noninfectious vaccines are more stable than infectious vaccines, as the microbial agents do not need to remain viable (i.e., do not need to infect cells) to immunize.

Noninfectious vaccines are often considered to be the safest vaccine type because the immunizing agent (virus or bacteria) is dead; thus, it cannot revert to virulence and cannot cause the disease that the vaccine was intended to prevent.[1–10] However, it should be understood that hypersensitivity reactions are more common with the noninfectious vaccines than infectious vaccines; thus, they may not be perceived to be as safe as the infectious

TABLE 1

2011 AAHA Canine Vaccination Guidelines* for the General Veterinary Practice

Vaccine†	Initial Vaccination (<16 wk of age)	Initial Vaccination (>16 wk of age)	Revaccination (Booster) Recommendation	Comments and Recommendations
CDV (MLV) or rCDV	Puppies should be vaccinated every 3–4 wk between the ages of 6 and 16 wk (e.g., at 6, 10, and 14 wk, or 8, 12, and 16 wk). To minimize the risk of maternal antibody interference with vaccination, the final dose of the initial series should be administered between 14 and 16 wk of age, regardless of the product used.	One dose is considered protective and acceptable. Revaccination is recommended every ≥3 yr after completion of the initial vaccination, regardless of the product used.	Dogs (puppies) completing the initial vaccination series by 16 wk of age or younger should receive a single booster vaccination no later than 1 yr after completion of the initial series and be revaccinated every ≥3 yr thereafter, regardless of the product used.	Core • Among healthy dogs, all commercially available distemper vaccines are expected to induce a sustained protective immune response lasting at least ≥5 yr. • Among healthy dogs, the rCDV vaccine has been shown to induce a protective immune response lasting at least 5 yr. • Although rare, some dogs are genetically predisposed "nonresponders" and are incapable of developing protective immunity subsequent to CDV vaccination. • The rCDV vaccine can be used interchangeably with MLV-CDV vaccine. • It is recommended that all CDV vaccines be administered within 1 hr after reconstitution; vaccine held >1 hr should be discarded. MLV-CDV vaccine is particularly vulnerable to inactivation after reconstitution (rehydration).
MV (MLV–an aid in the prevention of CDV infection in puppies only) (Note: measles antigen is currently available in a 4-way combined MLV vaccine: CDV + measles + CAV-2 + CPiV) and a 2-way combined MLV vaccine: CDV + Measles IM route only	A single dose is recommended for administration to healthy dogs between the ages of 6 and 12 wk.	Not recommended	Not recommended	Noncore • Measles vaccine is only intended to provide temporary immunization of young puppies against CDV. MV has been shown to cross-protect puppies against CDV in presence of MDA to CDV. • These vaccines should not be administered to dog <6 wk or female dogs >12 wk of age that will be used for breeding, as these puppies may have maternally derived measles antibody and will block MV induced immunity. • After administration of a single dose of measles virus-containing vaccine, subsequent vaccination with a CDV vaccine that does not contain MV is recommended at 2–4 wk intervals until the patient is 14–16 wk of age. • Vaccine that contains MV must be administered by the IM route. • It is recommended that MV-containing vaccine be administered within 1 hr after reconstitution; vaccine held >1 hr should be discarded.

(Table continues)

TABLE 1 (continued)

Vaccine†	Initial Vaccination (<16 wk of age)	Initial Vaccination (>16 wk of age)	Revaccination (Booster) Recommendation	Comments and Recommendations
CPV-2 (MLV)	Puppies should be vaccinated every 3–4 wk between the ages of 6 and 16 wk (e.g., at 6, 10, and 14 wk, or 8, 12, and 16 wk). To minimize the risk of maternal antibody interference with vaccination, the final dose of the initial series should be administered between 14 and 16 wk of age, regardless of the product used.	One dose is considered protective and acceptable. Revaccination is recommended every ≥3 yr after completion of the initial vaccination, regardless of the product used.	Dogs (puppies) completing the initial vaccination series by ≤16 wk of age should receive a single booster vaccination not later than 1 yr after completion of the initial series and be revaccinated every ≥3 yr thereafter, regardless of the product used.	Core • All MLV-CPV-2 vaccines available today are expected to provide immunity from disease caused by any field variant recognized today (CPV-2a, -2b, and -2c). • As new variants of CPV-2 occur, those variants will need to be evaluated, as the previous ones have, to ensure vaccines in use at the time are protective. • Among healthy dogs, all commercially available MLV-CPV-2 vaccines are expected to induce a sustained protective immune response lasting at least 5 yr. • Although rare, some dogs are genetic nonresponders and are incapable of developing protective immunity subsequent to CPV-2 vaccination no matter how often vaccine is administered. • Today, specific breed-susceptibility to CPV-2 nonresponsiveness is not recognized. There is no value in extending initial CPV-2 vaccination series beyond 16 wk of age. • It is recommended that CPV-2 vaccine, especially when administered in combination with CDV vaccine, be administered within 1 hr after reconstitution; vaccine held >1 hr should be discarded.
CAV-2 (MLV parenteral)	Puppies should be vaccinated every 3–4 wk between the ages of 6 and 16 wk (e.g., at 6, 10, and 14 wk, or 8, 12, and 16 wk). To minimize the risk of maternal antibody interference with vaccination, the final dose of the initial series should be administered between 14 and 16 wk of age, regardless of the product used.	One dose is considered protective and acceptable. Revaccination is recommended every ≥3 yr after completion of the initial vaccination, regardless of the product used.	Dogs (puppies) completing the initial vaccination series by ≤16 wk of age should receive a single booster vaccination not later than 1 yr after completion of the initial series and be revaccinated every ≥3 yr thereafter, regardless of the product used.	Core • CAV-2 induces protection against CAV-1 (canine hepatitis virus) as well as CAV-2 (one of the agents known to be associated with canine infectious respiratory disease). • Among healthy dogs, all commercially available MLV-CAV-2 vaccines are expected to induce a sustained protective immune response lasting at least 7 yr. • It is recommended that CAV-2 vaccine, especially when administered in combination with CDV vaccine, be administered within 1 hr after reconstitution; vaccine held >1 hr should be discarded.

(Table continues)

TABLE 1 (continued)

Vaccine†	Initial Vaccination (<16 wk of age)	Initial Vaccination (>16 wk of age)	Revaccination (Booster) Recommendation	Comments and Recommendations
Rabies 1 yr (killed)	Administer a single dose not earlier than 12 wk of age or as required by state, provincial, and/or local requirements.	Administer a single dose of a "1-yr" rabies vaccine.	Administer a single dose of a"1-yr" rabies vaccine annually. State, provincial, and/or local laws apply.	Core • State, provincial, and local statutes govern the frequency of administration for products labeled as "1-yr" rabies vaccine. • Route of administration may not be optional; see product literature for details.
Rabies 3 yr (killed)	Administer a single dose of a "3-yr" rabies vaccine not earlier than 12 wk of age or as required by state, provincial, and/or local requirements.	Administer a single dose of a "3-yr" rabies vaccine or as required by state, provincial, and/or local requirements.	Administer a single dose of a "3-yr" rabies vaccine within 1 yr after administration of the initial dose, regardless of the animal's age at the time the initial dose was administered. Subsequently, revaccination with a "3-yr rabies" vaccine should be administered every 3 yr thereafter, unless state, provincial, and/or local requirements stipulate otherwise.	Core • State, provincial, and local statutes govern the frequency of administration for products labeled as "3-yr rabies" vaccines. • Use of rabies vaccine multidose ("tank") vials in companion animals is not recommended. • Route of administration may not be optional; see product literature for details.
CPiV (MLV) For parenteral administration only. (Available only as a combined product for parenteral administration)	Parenteral CPiV vaccine is only available in combination with core vaccines (CDV-CPV-2 and CAV-2). Therefore, veterinarians who elect to administer parenteral CPiV vaccine should follow the same administration recommendations as outlined above for the core vaccines.	Veterinarians who elect to administer parenteral CPiV vaccine should follow the same administration recommendations as outlined above for the core vaccines.	Veterinarians who elect to administer parenteral CPiV vaccine should follow the same administration recommendations as outlined above for the core vaccines.	Noncore • Parenterally administered CPiV vaccine does prevent clinical signs but has not been shown to prevent infection and shedding. • Use of the parenteral vaccine is recommended for use in those patients that aggressively resist IN vaccination.
Bb (inactivated-cellular antigen extract) For parenteral administration only.	Administer first dose at 8 wk of age and second dose at 12 wk of age (see comments).	Two doses, 2–4 wk apart are required.	Annually	Noncore • There is no known advantage to administering parenteral and IN Bb vaccines simultaneously. • On initial vaccination, administration should be scheduled such that the second dose can be administered at least 1 wk before exposure (kennel, dog show, daycare, etc). • The parenteral vaccine is not immunogenic if administered by the IN route.
Bb (live avirulent bacteria) For IN administration only.	A single dose should be administered in conjunction with 1 of the core vaccine doses. Note: The initial IN dose may be administered to dogs as young as 3–4 wk of age (depending on manufacturer) when exposure risk is considered to be high (see comments).	A single dose is recommended.	Annually or more often in high-risk animals.	Noncore Transient (3–10 days) coughing, sneezing, or nasal discharge may occur in a small percentage of vaccinates. IN Bb vaccine must not be administered parenterally.

(Table continues)

TABLE 1 (continued)

Vaccine[†]	Initial Vaccination (<16 wk of age)	Initial Vaccination (>16 wk of age)	Revaccination (Booster) Recommendation	Comments and Recommendations
CPiV (MLV) For IN administration only. (IN CPiV vaccine is only available in combination with IN Bb vaccine or Bb + CAV-2)	A single dose should be administered in conjunction with 1 of the core vaccine doses. Note: The initial IN dose may be administered to dogs as young as 3–4 wk of age (depending on manufacturer) when exposure risk is considered to be high (see comments).	A single dose is recommended.	Annually or more often in high-risk animals.	Noncore • When feasible, IN vaccination is recommended over parenteral vaccination. Parenterally administered CPiV vaccine does prevent clinical signs, but has not been shown to prevent infection and shedding. IN CPiV vaccine prevents not only clinical disease but also infection and viral replication (shedding).
CAV-2 (MLV) (for IN administration only) (Available only in combination with IN Bb and CPiV vaccine)	A single dose should be administered in conjunction with 1 of the core vaccine doses. Note: The initial IN dose may be administered to dogs as young as 3–4 wk of age (depending on manufacturer) when exposure risk is considered to be high (see comments).	A single dose is recommended.	Annually or more often in high-risk animals.	Noncore • Administration of IN CAV-2 vaccine is recommended for use in dogs considered at risk for respiratory infection caused by the CAV-2 virus. • IN CAV-2 vaccine may not provide protective immunity against CAV-1 (canine hepatitis virus) infection and should not be considered a replacement for parenteral MLV-CAV-2 vaccination.
Canine influenza vaccine (killed virus)	Administer 1 dose not earlier than 6 wk of age and a second dose 2–4 wk later.	Two doses, 2–4 wk apart are required. A single initial dose will not immunize a seronegative dog.	Annually	Noncore
Borrelia burgdorferi (Lyme disease) (killed whole cell bacterin) or *Borrelia burgdorferi* (rLyme: rOspA)	Administer 1 dose not earlier than 12 wk of age and a second dose 2–4 wk later. For optimal response, do not administer to dogs <12 wk of age.	Two doses, 2–4 wk apart. A single initial dose will not immunize a seronegative dog.	Annually. Alternatively, it has been recommended that initial vaccination or revaccination (booster) be administered before the beginning of tick season, as determined regionally.	Noncore • Generally recommended only for use in dogs with a known risk of exposure, living in or visiting regions where the risk of vector tick exposure is considered to be high, or where disease is known to be endemic. • In addition to vaccination, prevention of canine Lyme borreliosis includes regular utilization of tick control products.
Leptospira interrogans (4-way killed whole cell or subunit bacterin) Contains serovars *canicola* + *icterohemorrhagiae* + *grippotyphosa* + *pomona*	Administer 1 dose not earlier than 12 wk of age and a second dose 2–4 wk later. For optimal response, do not administer to dogs <12 wk of age.	Two doses, 2–4 wk apart. A single initial dose will not immunize a seronegative dog.	Annually. Administration of booster vaccines should be restricted to dogs with a reasonable risk of exposure.	Noncore • Specific vaccination recommendations vary on the basis: (1) known geographic occurrence/prevalence, and (2) exposure risk in the individual patient. • It is recommended that the first dose of leptospira vaccine be delayed until 12 wk of age. • DOI based on challenge studies has been shown to be approximately 1 yr.

(Table continues)

TABLE 1 (continued)

Vaccine†	Initial Vaccination (<16 wk of age)	Initial Vaccination (>16 wk of age)	Revaccination (Booster) Recommendation	Comments and Recommendations
Leptospira interrogans (2-way killed bacterin) Contains serovars *canicola* + *icterohemorrhagiae* only	*Intentionally left blank*	*Intentionally left blank*	*Intentionally left blank*	Not recommended
Canine oral melanoma (plasmid DNA vaccine-expresses human tyrosinase). Availability is currently limited to practicing oncologists and selected specialists.	Not applicable. See Manufacturer's indications for use.	See Manufacturer's indications for use.	See Manufacturer's indications for use.	Use of this vaccine is limited to the treatment of dogs with malignant melanoma. • This vaccine aids in extending survival times of dogs with Stage II or III oral melanoma and for which local disease control has been achieved (negative local lymph nodes or positive lymph nodes that were surgically removed or irradiated). The human tyrosinase protein will stimulate an immune response that is effective against canine melanoma cells that over express tyrosinase. • Vaccination is not indicated for the prevention of canine melanoma.
Crotalus atrox (Western Diamondback rattlesnake vaccine) (toxoid)	Initial vaccination recommendation may depend on size of the individual dog. Refer to manufacturer's label. Current recommendations are to administer 2 doses, 1 mo apart, to dogs as young as 4 mo.	Initial vaccination recommendation may depend on size of the individual dog. Refer to manufacturer's label. Current recommendations are to administer 2 doses 1 mo apart.	Refer to manufacturer's label. Annual revaccination requirements vary depending on prior exposure, size of dog, and risk of exposure. Refer to manufacturer's label.	Field efficacy and experimental challenge data in dogs are not available at this time. • Intended to protect dogs against the venom associated with the bite of the Western Diamondback rattlesnake. Some cross-protection may exist against the venom of the Eastern Diamondback rattlesnake. There is currently no evidence of cross-protection against the venom (neurotoxin) of the Mojave rattlesnake. • Vaccine efficacy and dose recommendations are based on toxin neutralization studies conducted in mice. Conventional challenge studies in dogs have not been conducted. Neither experimental nor field data are currently available on this product. Note: Veterinarians should advise clientele of vaccinated dogs that vaccination does not eliminate the need to treat individual dogs subsequent to envenomation.
Canine coronavirus (CCoV) (killed and MLV)	*Intentionally left blank*	*Intentionally left blank*	*Intentionally left blank*	Not recommended • Neither the MLV vaccine nor the killed CCoV vaccines have been shown to significantly reduce disease caused by a combination of CCoV and CPV-2. Only CPV-2 vaccines have been shown to protect dogs against a dual-virus challenge.

(Table continues)

TABLE 1 (continued)

Vaccine†	Initial Vaccination (<16 wk of age)	Initial Vaccination (>16 wk of age)	Revaccination (Booster) Recommendation	Comments and Recommendations
				• DOI has never been established. In controlled challenge studies, neither vaccinates nor control dogs developed clinical evidence of disease after experimental virus challenge.

*The AAHA 2011 Canine Vaccine Guidelines 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 nor are they intended to represent a universal vaccination protocol applicable for all dogs.
†Route of administration is SQ (subcutaneous) or IM (intramuscular) unless otherwise noted by the manufacturer.
Bb, *Bordetella bronchiseptica*; CAV-1, canine adenovirus, type 1 (cause of canine viral hepatitis); protection from CAV-1 infection is provided by parenterally administered CAV-2 vaccine; CAV-2, canine adenovirus, type 2; CCoV, canine coronavirus cause of enteric coronavirus infection (antigenically distinct from the canine respiratory coronavirus [CRCoV]); CDV, canine distemper virus; CIV, canine influenza virus—H3N8; CPIV, canine parainfluenza virus; CPV-2, canine parvovirus, type 2; DOI, duration of immunity; IN, intranasal; MLV, modified live virus, attenuated virus vaccine; MV, measles virus; OspA outer surface protein A (antigen) of Borrelia burgdorferi; RV, rabies virus.

vaccines.[11] In general, all canine vaccines are quite safe and only a small percentage of vaccinated dogs, regardless of type of vaccine, develop severe adverse reactions.[12–24]

Vaccine Stability

Because the antigenic bacteria or virus used in noninfectious (killed) vaccine is incapable of replicating, killed vaccines are prepared and sold as an aqueous (liquid) product that can be directly administered to the patient. During storage, noninfectious vaccines are highly stable. Although refrigeration is recommended, noninfectious vaccines are significantly less susceptible to heat inactivation than infectious vaccines. Noninfectious vaccines can, however, be denatured. If exposed to chemicals (e.g., rewashed, reused syringes), a noninfectious vaccine could become ineffective. Therefore, sterile, unused syringes should be used when administering vaccines. Noninfectious vaccines should be administered before the expiration date printed on the vial.

Both infectious and noninfectious vaccines are important and required in every canine vaccination program. However, it is important not to mix noninfectious vaccines with infectious vaccines in the same syringe, unless specified by the manufacturer.[14,19–24]

Multiple Dose Vials

Multiple dose, also called "tank" vials, of killed rabies vaccine are available. Typically prepared in 10 mL (10 dose) vials, these products should only be used for high volume vaccination clinics or by shelter immunization programs where large numbers of dogs are vaccinated over a short period of time (same day). Multiple dose vials require multiple needle penetrations over time, thereby increasing the risk for contamination. Tank vials should be shaken frequently to ensure the concentration of antigen/adjuvant is consistent among doses withdrawn from a single vial. Single-dose vials are available and are strongly recommended for use in general veterinary practice.

Routes of Administration

Because noninfectious canine vaccines cannot infect or replicate, they must be administered parenterally (subcutaneously [SQ] or intramuscularly [IM]); noninfectious vaccine should not be administered directly onto mucosal surfaces (e.g., intranasal [IN] administration). Noninfectious canine vaccines stimulate primarily systemic humoral immunity (immunoglobulin-M [IgM] and -G [IgG]) with limited or no cell mediated immunity, depending on the antigen and the adjuvant.[11,24]

The canine oral melanoma vaccine is a noninfectious recombinant (DNA) vaccine licensed for needle-free transdermal administration only. It is currently the only vaccine licensed for transdermal administration in dogs.

Initial Vaccination

Most noninfectious vaccines require at least two initial doses to immunize, regardless of the dog's age.[1,14,25,26] The first dose of a noninfectious vaccine generally primes the immune response and the second dose, which should be administered 2–6 wk later, provides the protective immune response. Immunity typically develops approximately 7 days after the second dose. Therefore, the minimum time for onset of immunity is approximately 3 wk after administration of the first dose of a noninfectious vaccine.

When the interval between the initial two doses of a noninfectious vaccine exceeds 6 wk, it is recommended the dog be revaccinated, administering two doses, 2–6 wk apart, to ensure protective immunity has developed.

Rabies vaccine is the obvious exception. Rabies vaccine antigen is highly immunogenic. Throughout the US and Canada, a single dose, administered at ≥12 wk of age, is considered to induce protective immunity. It should be noted that the onset of immunity after administration of the initial rabies vaccine may be defined by applicable legal requirements.

Minimum Age at the Time of Initial Vaccination

Administration of a noninfectious vaccine to a dog <12 wk of age may be blocked by maternally derived antibody (MDA). A second dose, even if given after 12 wk of age, would not be expected to immunize the patient (rabies being the exception). To ensure that puppies are effectively immunized, it is recommended that the first vaccine dose in the initial series of most noninfectious (inactivated, killed) vaccines be administered not earlier than 12 wk of age. Among orphans or those puppies that are known not to have received colostrum, the first dose of a noninfectious vaccine may be administered as early as 6 wk of age.

Immunization in the Presence of Maternally Derived Antibody

The mechanism whereby MDA interferes with noninfectious vaccine is different than that for infectious vaccine. Through a mechanism known as "antigen masking," MDA covers, or "masks," antigenic epitopes on the vaccine virus or bacteria that are necessary to elicit a protective immune response. In an effort to overcome MDA-induced interference with noninfectious vaccines, vaccine manufacturers can use a variety of methods, including the addition of adjuvant as well as increasing the antigen concentration in each dose of vaccine.

Because high titers of MDA specific for protective epitopes are generally required to cause "antigen masking," MDA interference to most bacterins is uncommon after 6–9 wk of age. However, as noted previously, two doses of a noninfectious vaccine are required to induce a protective immune response. If sufficient MDA is present to interfere with the first dose, the second dose will not immunize. Therefore, it is recommended that the earliest age for administering the first dose of a noninfectious vaccine be 12 wk. Also, it is recommended that the noninfectious bacterins (e.g., *Leptospira* or Lyme) be given at ≥12 wk because the immune system is more mature. Thus, it is more likely that a protective immune response, rather than hypersensitive response, will develop.[1]

Onset of Immunity

After initial vaccination, the onset of protective immunity requires more time to develop with noninfectious vaccines than with infectious vaccines. With most noninfectious vaccines, the minimum time from administration of the first dose in the initial vaccination series to development of protective immunity in a naïve dog is 3 wk (2 wk minimum interval between doses plus 1 wk for antibody production, for a minimum of 3 wk).[14]

The immune (antibody) response after administration of a single dose of a noninfectious vaccine in adult dogs that have been vaccinated within the previous year is considered to be rapid (hours to days) and protective.

The legally defined onset of immunity after administration of the first dose of a rabies vaccine is usually stipulated by state, local, or provincial requirements. Because the defined interval between the rabies vaccination and rabies immunization may vary among states and within states, veterinarians are encouraged to contact appropriate authorities regarding a specified onset of immunity interval for rabies.

Missed Dose—Initial Series

When administering a noninfectious vaccine for the first time in the life of a dog, at least two doses, administered 2–6 wk apart, is recommended. If the interval between the first two doses exceeds 6 wk, it is recommended that two additional doses be administered at an interval of 2–6 wk, thereby insuring that both immune priming and immunization occur.

Missed Dose—Adult Booster

Because noninfectious vaccines generally have a duration of immunity (DOI) that is shorter than infectious vaccines, annual

revaccination ("booster") is commonly recommended. A dog that failed to receive a noninfectious vaccine at the recommended interval of 12 mo is unlikely to maintain protective immunity for the same length of time (years) that occurs after administration of infectious viral (core) vaccines. At some point beyond 12 mo, administration of a single dose of a noninfectious vaccine may fail to induce a protective immune response (due to loss of immunologic "memory"); in such cases, administration of two doses, 2–6 wk apart, may be required to immunize.

However, intervals defining when two doses versus one dose would be required to immunize have not been established. Specific intervals will vary, depending on: (1) the vaccine, (2) the patient's (intrinsic) immune response, (3) time elapsed since administration of the last dose, and (4) total lifetime doses the dog received. The decision to revaccinate a dog with two doses versus one dose is left to the discretion of the veterinarian.

The following general guidance is offered for dogs that are overdue for a noninfectious vaccine and are considered to be at risk for exposure.

- Leptospirosis: limited studies have been conducted to assess immune response to a single dose of vaccine in dogs that have not received a booster vaccination in >12 mo. Among dogs with a high risk of exposure, it is reasonable to consider administering two doses of vaccine, 2–6 wk apart, if the interval between doses exceeds 24 mo.[14]
- Lyme disease: only limited (unpublished) studies have been performed to evaluate the immune response to a single dose of vaccine in dogs that have not received a booster vaccination in >12 mo. Although a single dose of Lyme vaccine given years after the initial doses can raise antibody levels, the protective quality of these antibodies has not been confirmed by challenge. Among dogs with a high risk of exposure, it is reasonable to consider administering two doses of vaccine, 2–6 wk apart, if the interval between doses exceeds 24 mo.[27]
- CIV: studies have not been performed to evaluate the immune response to a single dose of vaccine in dogs that have not received a booster vaccination in >12 mo. Among dogs having a high risk of exposure, it is reasonable to consider administering two doses of vaccine, 2–6 wk apart, if the interval between doses exceeds 36 mo.
- Rabies: revaccination with killed rabies vaccine in dogs that exceeded the stipulated interval, 1 yr (initial two doses) or 3 yr (revaccination), is defined by applicable legal requirements. In most states, a dog that exceeded the defined interval for rabies vaccination may receive a single dose of a 3 yr vaccine regardless of the time elapsed since administration of the last dose; that dose will be considered protective for up to 3 yr.

Duration of Immunity and Booster Recommendations

Several noninfectious vaccines are routinely administered to dogs in the US and Canada. Although DOI studies are limited, it is reasonable to recommend annual boosters with most noninfectious vaccine in dogs considered to be at reasonable risk of exposure to the infectious agent.[14,24,28,29]

RV antigen (glycoprotein G) is highly immunogenic, especially in the presence of adjuvant. Therefore, the DOI in dogs vaccinated with two initial doses, 12 mo apart, is expected to be 3 yr (when using a 3 yr rabies vaccine) in dogs that are ≥1 yr of age.

Infectious (Attenuated, Avirulent, Modified Live, Recombinant Viral Vectored) Vaccines

Infectious vaccines must infect the host's cells to immunize. These vaccines are the most effective because they can provide the same types of immunity (cellular, humoral, systemic, and local) that are produced by natural exposure (i.e., immunity after recovery from infection or disease). However, the vaccine organisms are attenuated and will not cause disease.[14,19,22,26,30–33]

When the first modified live canine distemper virus (CDV) vaccines were made in the 1950s and 1960s, some vaccines were highly virulent, causing distemper-like disease, including encephalitis, in a high percentage of vaccinated dogs.[20,31,34] Since the late 1980s, recombinant DNA technology, or genetic engineering, has been used in the production of veterinary vaccines. The first canine vaccine developed and licensed in 1997 using recombinant DNA technology was the canarypox-vectored recombinant CDV (rCDV) vaccine. The advantage of this technology is that the recombinant viral vectored CDV vaccine, unlike the modified live CDV virus vaccines, cannot revert to a virulent form, because there is no CDV virus present in the canarypox vaccine. Furthermore, rCDV vaccine cannot replicate in lymphocytes or in the brain of vaccinated dogs or in wildlife and exotic species that are susceptible to CDV.[35–38]

Current canine parvovirus, type 2 (CPV-2) vaccines contain either CPV-2 or the CPV-2b variant. Vaccines from all the major manufacturers have been shown to provide sustained (several years) protection from all the current CPV-2 variants (CPV-2a, b, and c).[20,39–44]

The original canine adenovirus, type 1 (CAV-1) vaccines, which are no longer available in the US or Canada, caused allergic uveitis and other allergic reactions in a high percentage of dogs; therefore, CAV-1 vaccines were replaced in the US and Canada by the safer, but equally or more effective, CAV-2 vaccines. CAV-2 vaccines are used to provide immunity to CAV-1 virus, the cause of canine infectious hepatitis. Also, they provide protection

against CAV-2, a virus that causes and contributes to canine infectious respiratory disease complex.[1,20,22,45]

Vaccine Stability

Because antigenic virus/bacteria in infectious vaccines is live, these products often inherently lack thermostability.[33] To extend the stability of infectious vaccines during shipment and storage and to sustain vaccine efficacy, manufacturers typically prepare and sell infectious vaccines in a lyophilized (freeze-dried) state. Dehydrating the product into a "cake" significantly extends the shelf-life of perishable infectious vaccine antigens. Once diluent is added to the lyophilized product, the vaccine antigens quickly regain instability and may lose efficacy over time. Stability after reconstitution can vary among the various vaccine antigens in combination (multivalent) products (e.g., modified live virus [MLV] CDV + CPV-2 + CAV-2). It is recommended that infectious vaccines, after reconstitution, be administered within 1 hr. Reconstituted vaccine that is not administered within 1 hr should be discarded.

Once rehydrated, infectious vaccines are highly susceptible to chemical inactivation. For this reason, it is generally not recommended to cleanse the skin with alcohol before inoculation. Furthermore, syringes should never be washed and reused. Chemical residues in the syringe can easily inactivate the infectious vaccines. Infectious vaccines should be administered before the expiration date printed on the vial, as infectivity is lost over time.

It is important not to mix noninfectious vaccines with infectious vaccines in the same syringe, unless specified by the manufacturer, and even then, there may be advantages to administering a noninfectious vaccine in a different site on the animal from the infectious vaccine's administration site.[1,14,25]

Multiple Dose Vials

Infectious vaccines licensed for use in dogs are not commonly sold in multiple dose (also called "tank") vials. For the same reasons outlined previously for noninfectious vaccines, use of multiple dose vials of infectious (parvovirus) vaccine is not generally recommended.

Routes of Administration

Infectious vaccines contain avirulent live virus or bacteria that are capable of infecting cells in much the same manner as the virulent virus or bacteria does during natural infection. Therefore, infectious vaccines may be administered by the IN route (e.g., Bb + canine parainfluenza virus [CPiV]) as well as by the parenteral route (SQ or IM). Vaccines intended for IN administration must never be administered parenterally. Furthermore, IN vaccines administered orally are quickly inactivated and will not immunize.

Initial Vaccination

One dose of infectious vaccine will prime, immunize, and boost the immune response, provided the MDA does not interfere with the vaccine antigen (virus or bacteria). Because it is not practical to establish the level of maternal antibody in every puppy presented for initial vaccination, it is recommended that puppies receive doses of infectious vaccine (e.g., CDV + CPV-2 + CAV-2) every 3–4 wk between 8 and 16 wk of age. The final dose administered at 14–16 wk of age should insure the puppy will receive at least one dose of vaccine at an age when the level of MDA is insufficient to prevent active (vaccine-induced) immunity. Administration of infectious vaccine to dogs $<$6 wk of age, even in the absence of MDA, is not recommended.[1,14,24]

Because dogs older than 14–16 wk of age are not likely to have interfering levels of MDA, administration of a single initial dose of an infectious vaccine to an adult dog can be expected to induce a protective immune response. The administration of a single, initial dose of infectious vaccine to dogs $>$16 wk of age is considered protective and acceptable (Table 1). It is common practice, however, in the US and Canada, to administer two initial doses, 2 to 4 weeks apart, to adult dogs without a history of prior vaccination.

Minimum Age at the Time of Initial Vaccination

In practice, predicting the exact age at which a puppy will first respond to administration of an infectious vaccine is difficult. MDA is the most common reason early vaccination fails to immunize. Puppies that received colostrum from an immunized dam might not respond to vaccination until 12 wk of age. In contrast, orphan puppies and puppies that were denied colostrum might respond to initial vaccination much earlier. The minimum age recommended for initial vaccination with an infectious (core) vaccine is 6 wk. Even in the absence of MDA, administration of an infectious vaccine to any dog $<$6 wk of age may result in a suboptimal immune response due to age-related immunologic incompetency.

In contrast, administration of an infectious vaccine labeled for IN administration (e.g., IN Bb + parainfluenza virus) may induce a protective, local (mucosal) immune response as early as 3–4 wk of age. MDA does not interfere with local immunity.

Immunization in the Presence of Maternally Derived Antibody

In general, MDA is more effective at interfering with infectious vaccines than noninfectious vaccines. Various mechanisms have been suggested, including rapid neutralization of infectious vaccine

virus by maternal antibodies, prevention of replication, and insufficient antigen to prime B cells.[1,14,25]

Different vaccine manufacturing methods have been successful in developing infectious vaccines that are able to overcome MDA in puppies at an earlier age. Such methods include increasing the virus titers within the product (e.g., "high titer" CPV-2 vaccine), using a more infectious virus (which often means more virulent), or administering the infectious vaccine via the IN route where the MDA is either limited or not present.

Like the heterotypic measles virus (MV) vaccine, the rCDV canarypox vectored vaccine has been shown to immunize puppies 2–4 wk earlier than MLV CDV vaccines.[46,47] However, neither of these vaccines can immunize puppies that have very high levels of MDA because of antigen masking. Thus, with all the methods used to avoid blocking by MDA, it may be possible to immunize earlier (days or weeks), but not to immunize all puppies at any age.[19,22,30,37,45–49]

Onset of Immunity

The onset of immunity after administration of a single dose of infectious core vaccine is approximately 4±3 days in the absence of MDA. Variability among individual dogs and among different vaccines may alter these times slightly, with CDV providing the earliest protection within 1–2 days, CPV-2 providing protection in about 3 days, and CAV-2 providing protection in 5–7 days.[38,50,51] However, a small percentage of dogs are genetically incapable of developing an immune response to CPV-2 vaccines (estimated 1/1,000 dogs) or to CDV vaccines (estimated 1/5,000 dogs). These dogs are described as "nonresponders." Immunologic unresponsiveness to vaccination is determined by genetic factors.

Because the number of nonresponders and low responders within the canine population is considered low, and nonresponder status is difficult to confirm, unique breed-specific vaccination recommendations for dogs are not stipulated in the Guidelines, but they may be recommended by some breed organizations.

Missed Dose—Initial Series

When administering an infectious vaccine for the first time in the life of a dog that is ≥6 wk of age, a single dose, in the absence of MDA, will immunize. If a puppy exceeds the recommended interval between doses of the initial vaccination series, it is left to discretion of the veterinarian whether to administer one or two additional doses.

If a puppy receives the first dose in the initial series of core vaccines between 6 and 8 wk of age but fails to return until 12 or 14 wk of age, administration of two doses, at least 2 wk apart, is recommended. In contrast, if the same puppy is >14 wk of age when returning to the veterinarian, administration of a single dose of an infectious vaccine is expected to immunize.

Missed Dose—Adult Booster

The DOI conferred by infectious core vaccines is known to last for many years. Even if serum antibody levels are determined to be below "protective" levels, immunologic memory (T- and B-lymphocytes) is likely to be sustained. Therefore, a single dose of infectious vaccine administered to an adult dog is considered protective regardless of the time since a previous vaccine was administered.[20,31,43,52–54]

Duration of Immunity and Booster Recommendations

In general, DOI to infectious viral and bacterial vaccines is longer than to noninfectious viral and bacterial vaccines, and immunity conferred is generally much longer to viral vaccines than to bacterial vaccines. DOI is often related to the immunologic mechanisms of killing or control of the pathogens, and also to the complexity of the disease and the disease agent.

Infectious core vaccines are not only highly effective, they also provide the longest DOI, extending from 5 yr up to the life of the dog. A ≥3 yr interval is currently recommended for revaccinating adult dogs with infectious viral core vaccines. In contrast, revaccination of dogs with infectious bacterial vaccines (specifically IN Bb vaccine) is recommended annually. The ≥3 yr recommendation for core vaccines is made on the basis of minimum DOI studies over the past 30 yr for canine vaccines. These studies were done by all of the major vaccine companies, as well as by independent researchers. The results of the studies conducted by the major manufacturers for canine core vaccine demonstrated that a minimum DOI for their core vaccines (CDV, CPV-2, CAV) was ≥3 yr, based on challenge and/or serologic studies. Similar minimum DOI studies were conducted for the 3 yr rabies vaccines using challenge studies only.[14,20,30,52–68]

Box 1 summarizes key immunologic features of noninfectious and infectious vaccines.

Vaccine Licensure in the United States

Requirements

In the US, the Animal and Plant Health Inspection Service (APHIS), a multifaceted agency of the USDA, is responsible for regulating veterinary biologics (vaccines, bacterins, antisera, diagnostic kits, and other products of biologic origin) intended for the diagnosis, prevention, or treatment of animal diseases. For domestic manufacture, a facility license is required, along with a license for each product to be distributed. Imported products are

Box 1

Key Immunologic Features of Noninfectious and Infectious Vaccines

	Noninfectious Vaccines (inactivated/killed/conventional and recombinant [r] subunit /avenomous/plasmid DNA)	Infectious Vaccines (MLV/attenuated/recombinant viral vectored)
Vaccine examples	RV CCoV CIV Bb–injectable *Leptospira*–2 way/4 way/whole cell and conventional subunit Lyme–whole cell/recombinant OspA subunit *Crotalus atrox* (Western Diamondback rattlesnake avenomous vaccine) Canine oral melanoma (plasmid DNA vaccine)	CDV, rCDV CAV-2 CPV-2 CCoV MV Bb–IN CPiV
Initial doses to immunize (in absence of MDA)	• Generally 2 doses Interval of time between doses: minimum: 2 wk; maximum: 6 wk. Exceptions: • Rabies–1 dose initially at ≥12 wk of age, followed with a second dose within a year after the first dose • Melanoma vaccine–4 doses	1 dose adequate. Optional–2 doses (not <2 wk interval between doses)
Parenteral (IM or SQ) route of administration	Required to be given parenterally	Yes Exception: Never give infectious (IN) *Bordetella* parenterally, as it can cause severe disease and death.
Mucosal (IN) route of administration	No–should never be given locally on mucosal surface	Yes, when recommended
Transdermal route of administration	The oral melanoma vaccine is required to be administered transdermally with a bioinjector.	No
Maternal antibody interference	Yes, but less likely, especially in dogs ≥12 wk of age because of higher antigenic mass in vaccine and because the agent does not need to infect and replicate.	Yes. However, MV and rCDV can immunize at an earlier age in presence of MDA than MLV CDV. Infectious (attenuated, avirulent, modified live, recombinant viral vectored) vaccines are more readily inactivated (blocked) by MDA than noninfectious (inactivated, killed) vaccines, thus it is necessary to give final dose of puppy series at 14–16 wk of age.
Replicates in host	No (inactivated virus and bacteria are incapable of replication)	Yes (must) Recombinant viral vectored canarypox CDV infects host cells, but new infectious canarypox virus is not produced
Onset of immunity in absence of MDA	Minimum 3–4 wk from the first dose, can be longer	1–2 days for CDV, 3–5 days for CPV-2, CAV-2, (parenteral), as well as IN Bb, CPiV, and/or CAV-2
Duration of immunity	Leptospirosis, Lyme, parenteral *Bordetella* are probably the shortest (≤1 yr) Rabies vaccine longest (≥3 yr)	Many years to a life time (e.g., parenteralCDV/CPV-2/CAV-2) 1 yr for IN Bb, CPiV, and CAV-2
Revaccination booster	Yes. Annually or more often. Exception: Rabies–3 yr booster after 1st dose and dose at 1 yr	≥3 yr longer for viral vaccines (CDV, CPV-2, CAV-2) IN–annual
Humoral (antibody) response	Systemic: excellent Local (mucosal) immunity: little or none	Systemic (IgM, IgG) and local (sIgA): excellent
Cell mediated immunity (CMI)	Limited, but some systemic CMI may be stimulated depending on type of adjuvants used	Excellent–both systemic and local CMI with parenteral and local (IN) vaccination.

(Box continues)

Box 1 (continued)

	Noninfectious Vaccines (inactivated/killed/conventional and recombinant [r] subunit /avenomous/plasmid DNA)	Infectious Vaccines (MLV/attenuated/recombinant viral vectored)
Stability	Excellent, but limited to expiration date and must be stored properly	Lyophilized—excellent, but limited to expiration date and must be stored properly Reconstituted—hours depending on the vaccine components Administration should occur within 1 hr after reconstitution of all infectious (attenuated, avirulent, modified live, recombinant viral vectored) vaccines.
Adjuvant	Generally required, but not always	Rarely, if ever, required
Use in pregnant dogs	Not recommended	Not recommended
Prophylactic	Yes	Yes
Therapeutic	Only the transdermally administered oral melanoma vaccine is labeled for therapeutic use.	No
Safety Issues		
Reversion to virulence	No reversion to virulence	Reversion to virulence is of minimal concern with current infectious (attenuated, avirulent, modified live, recombinant viral vectored) vaccines when used in dogs ≥6 wk of age and not used in pregnant dogs. However, reversion to virulence is a major concern when the MLV vaccines are used in certain exotic or wild animal species or used in puppies <4 wk of age. These practices are not recommended. Reversion to virulence is not a concern with the recombinant vectored CDV vaccine.
Acute adverse reactions (e.g., hypersensitivities)	Anaphylaxis, injection site pain, angioedema (facial edema), injection site granulomas, local inflammation abscesses, lameness, reactivation of immune-mediated diseases in predisposed dogs	Fever, lethargy, injection site pain, anaphylaxis, reactivation of immune-mediated diseases in predisposed dogs
Delayed adverse reactions (e.g., hypersensitivities)	Ischemic vasculitis (skin), increase in severity of type I atopic disease, reactivation of immune-mediated diseases (e.g., IMHA, IMTP, RA, etc.), and other hypersensitivity disorders possible in predisposed dogs (rarely occurs).	Reactivation of immune-mediated diseases (e.g., IMHA, IMTP, RA, etc.), and other hypersensitivity disorders possible in predisposed dogs (rarely occurs).

Bb, *Bordetella bronchiseptica*; CAV-1, canine adenovirus, type 1 (cause of canine viral hepatitis)—protection from CAV-1 infection is provided by parenterally administered CAV-2 vaccine; CAV-2, canine adenovirus, type 2; CCoV, canine coronavirus cause of enteric coronavirus infection (antigenically distinct from the canine respiratory coronavirus [CRCoV]); CDV, canine distemper virus; CIV, canine influenza virus—H3N8; CPiV, canine parainfluenza virus; CPV-2, canine parvovirus, type 2; DOI, duration of immunity; IgG, immunoglobulin G—a class of humoral antibody; most common type associated with immune response to parenteral vaccine; also the most common class of antibody measured as serum titers; IgM immunoglobulin M—a class of antibody, generally short lived and associated with early infection and initial vaccination; IM, intramuscular (route of administration); IMHA, immune-mediated hemolytic anemia; IMTP, immune-mediated thrombocytopenia; IN, intranasl; MLV, modified live virus—attenuated virus vaccine; MV, measles virus; OspA, outer surface protein A (antigen) of Borrelia burgdorferi; RA, rheumatoid arthritis, RV, rabies virus; sIgA, secretory immunoglobulin A—a class of antibody, most commonly associated with a local (mucosal) immune response after IN vaccination; SQ, subcutaneous.

issued a permit for sale and distribution. This work is done by APHIS's Center for Veterinary Biologics (CVBs).

Before the issuance of a license or permit, the manufacturer of a vaccine intended for sale and distribution within the US must demonstrate, to the satisfaction of the USDA CVB, that the proposed product is pure, safe, potent, and efficacious. The facility in which the product is prepared must meet USDA standards and pass inspection by the CVB. After licensure, each batch of vaccine is subject to random premarketing testing by the CVB to verify the manufacturer's quality assurance and quality control.

Purity assures the final product is free of extraneous microorganisms and extraneous material (organic or inorganic).

Safety is defined as freedom from properties causing undue local or systemic reactions when the vaccine is used as labeled. As part of the prelicense process, attenuated (live, whole agent) vaccines are evaluated in dogs to assess the potential of the vaccine organism to revert to virulence and the potential for dogs to shed the vaccine virus and/or bacteria. In addition, field safety studies are performed in a large group of dogs (typically at least 600), a substantial proportion of which must be at the minimum age indicated for administration. Postmarketing surveillance, including investigation of consumer complaints, is intended to identify relatively rare or uncommon safety issues that might not be detected in a prelicense field safety study. It should be noted safety studies are not a guarantee that a vaccine, once released for sale, will be entirely free of risk.

Efficacy is the ability or capacity of the product to effect the result for which it is offered when the product is used according to its label. Vaccine efficacy is conventionally determined through defined vaccination-challenge studies conducted by the manufacturer. Although challenge methods and criteria for evaluating protection will vary with the immunizing agent, tests are generally conducted under controlled conditions using seronegative dogs of the youngest age recommended on the label.

Potency is the relative strength of a biologic product as determined by test methods approved by the CVB. Potency testing is intended to assure that each serial (batch) of vaccine marketed is equal to, or more potent than, a defined reference serial of known efficacy.

DOI is noted here due to its interest to practitioners. However, the definition of the term is often interpreted differently in different contexts. The CVB views DOI as confirming, typically by a vaccination-challenge study, that the immunity conferred by the product lasts at least as long as indicated on the label. Practitioners may view these studies as confirming efficacy at a specified point, rather than a demonstration of the maximum reasonable duration of immunologic protection conferred to patients. Traditionally, vaccine challenge models were intended to demonstrate the onset of immunity in younger dogs using products titrated to the minimum protective dose. These products typically carried the historically based label recommendation for annual revaccination. Therefore, for most of the canine vaccines licensed in veterinary medicine, the CVB has not required manufacturers to conduct DOI studies, unless making a specific claim differing from 1 yr. Current CVB policy requires manufacturers to conduct DOI studies for all rabies vaccines and all new (novel) antigens, regardless of the revaccination interval.

Conditional Licensure

The time to market for a new vaccine can require several years. The USDA utilizes a pathway called conditional licensure to speed the availability to veterinarians of vaccines that address unmet needs, emergencies, or other special circumstances. In this process, a manufacturer is required to demonstrate that the product is safe, pure, has a reasonable expectation of efficacy, and that it is manufactured in compliance with standard USDA regulations. The USDA typically places time limits on such a license, during which the manufacturer must provide data to fully demonstrate efficacy or appropriate progress toward so doing. The USDA requires distinctive labeling to differentiate those products marketed under a conditional license, and the label must state that the product is conditionally licensed. The DOI of a conditionally licensed vaccine has not been confirmed by a vaccination-challenge study at the time the product is released for sale in the US.

(Conditional canine vaccines at this writing are: Crotalus atrox toxoid [Western Diamondback rattlesnake vaccine].)

Vaccine Licensure in Canada

The CFIA, under the legislative authority of the Health of Animals Act and Regulations, is responsible for regulating veterinary biologics in Canada. This regulatory program forms an integral part of Canada's National Animal Health Program, which strives to protect the health of food producing animals, domestic pets, wildlife, and the Canadian public, as well as to safeguard the environment by preventing the introduction and spread of infectious animal diseases.

Responsibilities of the CFIA in licensing vaccines for use in veterinary medicine include:

- Licensing of veterinary biologics, including verification of master seeds and prelicensure product evaluation
- Licensing of veterinary biologics manufacturing facilities
- Issuance of import and/or export permits to Canadian importers and/or exporters of veterinary biologics
- Postlicensure monitoring, including:

  - –serial release monitoring of veterinary biologics for purity, potency, and safety
  - –investigations of consumer complaints
  - –inspections of manufacturers and Canadian importers of veterinary biologics
- Scientific research in support of regulations
- Technology development, including collaborative research with industry partners.

The standards for licensure of any veterinary vaccine in Canada are similar to those required in the US. Regulated products include vaccines, immunoglobulin products, and diagnostic kits that are used for the prevention, treatment, or diagnosis of diseases in animals, including domestic livestock, poultry, pets, wildlife, and fish. To meet the requirements for licensure, veterinary biologics must be shown to be pure, potent, safe, and effective when used in the target species according to the manufacturer's label recommendations. In addition, the licensing submission must also contain supporting data demonstrating that the product can be manufactured and used without adversely affecting animal health, human health, food safety, or the environment.

Serologic Testing to Determine and Monitor Immunity

Interpreting Results of Serologic Tests

Despite the confusion and controversy surrounding antibody testing, these serologic tests are useful for monitoring immunity to CDV, CPV-2, CAV-1, and RV. Because of this, many practitioners perform large numbers of tests for antibodies on a routine basis at state diagnostic and commercial laboratories or the tests are done with in-house diagnostics. The tests are also medically useful to ensure that a dog responds to a specific core virus vaccine and/or to determine if immunity is present in a previously vaccinated dog. Those tests are also used to demonstrate protective immunity as well as DOI.[56–69]

Antibody assays for CDV and CPV-2—the two tests performed most often—are the tests of greatest benefit in monitoring immunity, especially after the puppy vaccination series. The serologic test considered the "gold standard" for CDV is virus neutralization (VN). VN and hemagglutination inhibition (HI) are the gold standard tests for antibodies to CPV-2.[1,14,67] Although most state diagnostic laboratories use the gold standard tests, most commercial laboratories use other methods, such as immunofluorescence assays or enzyme immunoassays. During the past 5 yr, most, if not all, laboratories have qualified and standardized their methodologies with samples that were tested by the gold standard methods. Also, standardization of these tests was done with samples collected from dogs protected from challenge with virulent virus.[54]

Notwithstanding this development, titer results may vary among tests and between laboratories. Most state diagnostic laboratories report classic titers, in which two-fold dilutions of serum are made and the highest dilution that neutralizes the virus (CDV, CPV-2, CAV-1, RV), inhibits hemagglutination by the virus (CPV-2), or binds to viral antigen and is detected with a fluorescent or enzyme probe (CDV, CPV-2, RV) is reported. Using the standard two-fold dilution technique, the amount of error is approximately a four-fold dilution. The titer of a single serum sample would be in the range of one doubling dilution below the reported value and one doubling dilution above the reported value. For example, a CDV virus neutralization titer reported at 128 in reality is between 64 and 256; similarly, a CPV-2 HI titer of 1,280 is between 640 and 2,560. Some laboratories simply report results of >5 as positive and <5 as negative, and other tests are simply positive (antibody is present) or negative (no antibody was detected).

There are currently two in-hospital tests that provide a positive or negative result that have been approved by the USDA. A positive CDV result on these tests indicates that a serum sample has an antibody titer that is >8 on the VN test. A positive result for CPV-2 indicates the serum sample has an antibody titer that is >20 with the HI test. A negative test indicates that the dog has a titer less than these values or that it has no antibody. Obviously, some dogs with a negative result on this test are immune, but most of these dogs would benefit from revaccination by developing a higher titer. After performing and comparing many serologic tests for thousands of dogs, researchers found that approximately $15\pm5\%$ of dogs will have low ($\leq$32 VN) or no antibody to CDV. A similar percentage but different dogs will have low or no antibody to CPV-2 ($\leq$80 HI) on the test. With CDV and/or CPV-2 tests, dogs with a negative result, regardless of the test used, should be considered as having no antibody and may be susceptible to infection with CDV and/or CPV-2; thus, these dogs should be revaccinated to ensure there is immunity. In contrast, any dog with a positive result, regardless of the test performed, should be considered immune and does not need to be revaccinated.[42,54]

Applications of Serologic Testing

On completion of the puppy core vaccination series with the last dose given at 14–16 wk of age, a dog can be expected to have an antibody titer or positive test result, regardless of the serologic test performed, provided the serum sample is collected $\geq$2 wk after the last dose of vaccine. If the dog does not have antibody, it should be revaccinated, perhaps using a different product, and then retested $\geq$2 wk later. If the antibody test is again negative,

the individual dog should be considered a low responder or a nonresponder (see Part I, Types of Vaccines) and possibly incapable of developing a protective antibody response.

Challenge with virulent virus or serologic testing is the only practical way to ensure a puppy develops an immune response after vaccination. The serologic test is the only acceptable way to ensure a client-owned dog develops an immune response. Young dogs are at greatest risk of infection from CDV and CPV-2, and these infections lead to severe disease and death in ≥50% of susceptible puppies. Antibody tests are useful as a medical procedure to ensure the dog develops an immune response to CDV and CPV-2 vaccines after the primary series of vaccinations. Vaccines can fail for various reasons.[25] However, the following are the three main reasons for vaccination failure: (1) the puppy has a sufficient amount of MDA to block the vaccine; (2) the vaccine is not immunogenic (e.g., if the vaccine was improperly stored); or (3) the dog is a poor or nonresponder (i.e., the immune system fails to recognize the antigenic determinants of the specific vaccine).

The most common reason for vaccination failure in young dogs is that MDA blocked the vaccine response. During the initial puppy vaccination series, the last dose of CDV and CPV should be administered at 14–16 wk of age. At this age, MDA should be at a level that will not block active immunization in most puppies (>98%) when a combination MLV vaccine is administered.[1,24,25] When the puppy fails to produce antibody ≥2 wks after a dose of vaccine administered at 14–16 wk, the practitioner must consider the other two explanations for vaccine failure. If, after one or more attempts at revaccination with a product different than the one originally used, the dog fails to develop an antibody response to CDV or CPV-2 by VN or HI test, the dog should be considered a transient or permanent nonresponder.

Because immunologic nonresponsiveness is genetically controlled, certain breeds or families of dogs may be suspected to have a higher prevalence of low or nonresponders than the general canine population. It is believed by some (but not proven) that the increased susceptibility to CPV-2 recognized in certain rottweilers and Doberman pinschers during the early and mid-1980s (regardless of their vaccination history) was due to an increased prevalence of nonresponders; it was also demonstrated that some early vaccination failures were attributable to the poor quality vaccines available at that time. Today, these two breeds appear to have no greater numbers of low or nonresponders than other breeds.[52,68]

A high titer of antibody to CDV and/or CPV-2 as a result of active immunization from vaccination or from natural exposure protects from infection; therefore, no detectable virus replication occurs. Although a virus may be capable of replicating in a dog whose antibody titers have decreased, memory B and T cells should provide an anamnestic (secondary) humoral- and cell-mediated immune response that limits virus replication and prevents disease. Immune responses to modified live vaccines like CDV, CPV-2, and CAV-2, because of their complexity, always stimulate both humoral- and cell-mediated immunity. Although antibody is a product of humoral immunity, cellular immunity is always required for antibody production, as T-helper cells must be activated by the virus to produce a B-cell response. Therefore, although rarely considered, the presence of antibody in the dog to specific viruses demonstrates not only humoral immunity but also that cell-mediated immunity was stimulated as well. It is also incorrectly assumed that antibody to MLV vaccines containing CDV, CPV-2, and CAV-2 often disappears after relatively short periods of time (e.g., months or a few years). It was shown in many studies that antibody to those viruses persisted for many years, even in the absence of the viruses or revaccination.

The persistence of antibody to these viruses is from a population of long lived plasma cells that has been referred to as "memory effector B cells." This is a population of cells that continues to produce the antibody they were programmed to produce (e.g., CDV) long after vaccination. Too much emphasis has been placed on the antibody titer (dilution of antibody that is positive). It was found repeatedly in controlled challenge studies with CDV, CPV-2, and CAV-1 that actively immune dogs (vaccinated at 14–16 wk of age or younger dogs without MDA) with actively produced antibody, regardless of titer or test used to detect the antibody, were resistant to challenge. Therefore, it is not necessary, as some have suggested, to have an antibody titer of ≥32 with the serum neutralization test for CDV or a titer of ≥80 on the HI test for CPV-2 for the vaccinated dog to be completely protected when challenged. Thus, most of the concerns expressed about the variability in titers among serologic tests have little or no validity when applied to protection from CDV, CPV-2, CAV-1, and RV. Furthermore, with the development of some of the in-hospital tests, serum dilutions are not performed and titers are not the end point; instead, the test is considered positive or negative.[43,54]

Application of Serology to Evaluate Duration of Immunity

Antibody tests can also be used to demonstrate the DOI to vaccines or from natural immunization. As discussed previously, dogs were shown to maintain antibody titers to the core viruses CDV, CPV-2, and CAV-1 in viral-free environments for many years. In a study reported in 1997, dogs vaccinated with a product containing CDV and then placed in an environment without CDV maintained

antibody titers for at least 10 yr.[61] In a more recent controlled study of puppies without MDA vaccinated at 7 and 10 wk of age (and housed with nonvaccinated dogs to ensure CDV, CPV-2, and CAV-1 were not present), it was shown that vaccinated dogs maintained antibody titers for >4 yr.[61,54,69] These and other studies clearly demonstrated that antibody correlated with protection from infection and/or protection from disease because the vaccinated antibody-positive dogs remained healthy after experimental challenge with virulent strains of the viruses. These and other studies also clearly demonstrated that antibodies to the core vaccine viruses might persist in the absence of revaccination for many years. All of the major vaccine manufacturers have products that were shown to provide a minimum DOI of 3 yr. In addition, it was demonstrated that antibody correlated with protection from infection and/or protection from disease because the vaccinated antibody-positive dogs remained healthy after experimental challenge with virulent strains of the viruses.[55–57,69] In contrast, vaccinated dogs that did not develop antibody to CDV, as well as unvaccinated control dogs that were antibody negative, became infected. Many dogs develop disease and die when challenged. When antibody is absent (irrespective of the serologic test used to determine this fact), it should be assumed the dog is susceptible to infection and may develop disease. Therefore, antibody negative dogs should be revaccinated. Similarly, dogs that have been actively immunized by vaccination or naturally by infection that have antibodies to CDV, CPV-2, or CAV-1 do not need to be revaccinated. Some clients are now having titers performed for CDV and CPV-2 in lieu of revaccinating.

Antibody titers to additional vaccine antigens are sometimes determined to diagnose susceptibility to disease, but the best correlations between antibody and protective immunity are as stated previously for CDV, CPV-2, CAV-1, and RV. Very sensitive and well-documented titers to RV are done by a small number of approved laboratories. Although most widely used when shipping dogs to rabies-free countries, rabies titers are sometimes performed in dogs that developed an adverse reaction to the vaccine.[70–72] However, RV titers cannot currently be used in place of revaccination, which is required on an annual or triennial basis depending upon governing law. Medical exemption laws exist in certain areas where a dog with a known medical condition can be exempted from rabies vaccine. However, a titer cannot be used in place of vaccination. When RV vaccination is not current, the dog must be considered unvaccinated, and if it bites someone, it must be quarantined.

Antibody titers to vaccines other than CDV, CPV-2, CAV-1, and RV have limited or no value because the antibody may persist for a short time (e.g., *Leptospira* products), or there is no known correlation between serum antibody test routinely performed and protection (e.g., CPiV, Lyme, *Leptospira*). However, researchers are attempting to find serologic correlates of protective immunity for diseases other than the four core viruses (CDV, CPV-2, CAV, and RV).

Vaccine Adverse Events

Since the original canine vaccines were developed and licensed >50 yr ago, there has been a continuing effort to make canine vaccines safer and more efficacious. Today, it is generally agreed that canine vaccines have an excellent safety record. Although AE documentation in veterinary medicine is limited, severe adverse reactions are considered uncommon. Vaccines are, however, biologic products and can cause unpredictable adverse effects in some dogs after administration. The following section is intended to characterize types of vaccine AEs possible in dogs, provide information on how to report known and/or suspected AEs, and offer suggestions for mitigating the risk of vaccination in patients with a history of AEs.

Vaccines are biologic products and, as such, provoke a series of complex immune reactions that may culminate in rapid-onset side effects lasting from a few hours to a few days. Rarely do these self-limiting side effects escalate into serious AEs (SAEs). For this reason, veterinarians are encouraged to inform clientele that their pet, regardless of breed or size, may manifest transient side effects for up to 2, and possibly 3, days after administration of any vaccine or any combination of vaccines. Side effects commonly observed include: reduced or loss of appetite (lasting for one or two feedings), pain at the injection site, lethargy (lack of activity), reluctance to walk and/or run, and mild fever. Treatment is usually not indicated; however, some veterinarians have reported administering short-term symptomatic treatment (e.g., a nonsteroidal anti-inflammatory drug [NSAIDs]). It is recommended that clientele be advised to contact the practice in the event any physical and/or behavioral manifestations progressively worsen or continue beyond 2–3 days. Clientele should be advised to contact the practice at any time if signs of systemic illness, such as vomiting, diarrhea, seizures, facial swelling, collapse, or difficulty breathing, develop.

Vaccine AEs are underreported in veterinary medicine. However, mechanisms are in place for reporting such reactions; veterinarians are strongly encouraged to participate by reporting all known or suspected AEs associated with vaccine administration.

In the US and Canada, vaccine AEs should be reported to the Technical Services section of the manufacturer of the vaccine(s) believed to be associated with the AE. If multiple vaccines from different manufacturers were administered to an individual patient

at the same appointment, reports should be submitted to each manufacturer. Furthermore, it is recommended that reports include reference to any concurrently administered drug and/or therapy. Reports can be made directly to the manufacture via (toll-free) telephone call.

In the US, vaccine AEs may also be reported on-line to the CVB (reporting information is outlined in the following).

In Canada, vaccine AEs may also be reported to the CFIA (reporting information is outlined in the following).

What Constitutes a Vaccine Adverse Event?

A vaccine AE is generally defined as any undesirable side effect or unintended effect (including lack of desired result) associated with the administration of a licensed biologic product (vaccine). For vaccines administered to dogs, AEs are those involving the health of the treated dog and include the apparent failure to protect against a disease. An AE event includes any injury, toxicity, or sensitivity reaction associated with the use of a vaccine, whether the event can be directly attributed to the vaccine. In other words, it is appropriate to report any known or suspected negative event associated with vaccination.

Although the incidence of vaccine AEs is unknown and causality cannot always be confirmed, the list that follows includes categories of adverse reactions that have been attributed to vaccine administration. The list of categories is not considered comprehensive; other, undocumented adverse reactions associated with vaccine administration could occur. Furthermore, causality has not been definitively established for each of the categories listed:

- **Injection-site reactions**: lumps (abscess, granuloma, seroma), pain, swelling, hair loss associated with ischemic vasculitis
- **Transient postvaccinal nonspecific illness**: lethargy, anorexia, fever, regional lymphadenomegaly, soreness, abortion, encephalitis, polyneuritis, arthritis, seizures, behavioral changes, hair loss or color change at the injection site, respiratory disease
- **Allergic (hypersensitivity) and immune-mediated reactions**:
  - –Type 1 (acute anaphylaxis): angioedema (especially the head), anaphylaxis (shock), and death
  - –Type 2 (cytolytic): immune-mediated hemolytic anemia, immune-mediated thrombocytopenia (suspected only; causality has not been confirmed)
  - –Type 3 (immune-complex): cutaneous ischemic vasculopathy associated with rabies vaccine, corneal edema ('blue-eye') associated with CAV-1 vaccine, immune-mediated disease
- **Failure to immunize**: maternal antibody interference with vaccination is considered the most common cause; administration of vaccine at a volume and/or dose less than that prescribed by the manufacturer; "nonresponder" (genetic predisposition?); inactivation of vaccine antigen (e.g., allowing reconstituted infectious [attenuated, avirulent, modified live, recombinant viral vectored] vaccine to stand at room temperature for >2 hr), mixing of incompatible vaccines in the same syringe
- **Tumorigenesis**: vaccine-associated sarcoma or other tumors
- **Multisystemic infectious/inflammatory disorder of young Weimaraner dogs**: may be genetically linked to both a poorly characterized immunodeficiency and to autoimmune disorders (e.g., hypothyroidism and hypertrophic osteodystrophy [HOD] that are detected shortly after vaccination
- **Vaccine-induced immunosuppression**: associated with first or second dose of combination MLV vaccines containing CDV and CAV-1 or CAV-2 with or without other vaccines (e.g., CPV-2, CPI). Immunosuppression begins 3 days after vaccination and persists for 7–10 days. The suppression may be associated with increased susceptibility to other diseases.[17]
- **Reactions caused by the incorrect or inappropriate administration of vaccine**: fatalities have been reported after subcutaneous administration of an avirulent-live Bb bacterin (intended for IN administration); inadvertent or intentional administration of vaccine by the intravenous route
- **Reactions associated with residual virulence attenuated vaccine**: postvaccinal sneezing associated with IN administration of attenuated vaccine (e.g., Bb + parainfluenza virus)
- **Vaccine-induced interference with diagnostic tests**: false-positive polymerase chaine reaction (PCR) test results for parvovirus antigen in feces in dogs recently receiving a MLV parvovirus vaccine. Not an adverse reaction.
- **Reversion of vaccine virus to a virulent pathogen**: generally considered rare to nonexistent among currently licensed canine vaccines when vaccines are used in the species for which they were licensed. This can become a significant problem when vaccine is used in the wild and/or exotic animals.[8,9,12,13,16–18]

How to Report a Known or Suspected Vaccine Adverse Event

Veterinarians are encouraged to participate in the vaccine AE reporting process by reporting suspected and known AEs to one of the following:

- **Vaccine Manufacturer:** Companies that manufacture vaccines maintain a technical services section that will accept and address AE reports from veterinarians who use their product(s). Veterinarians are encouraged to report AEs to the manufacturer(s) before contacting the appropriate regulatory agency. Manufacturers are required to maintain files of any reported vaccine AE. However, manufacturers are under no obligation to compensate the owner or the veterinarian for diagnostic or treatment services related to a known or suspected AE.

- **CVB:** Subsequent to reporting a known or suspected vaccine AE to the manufacturer, veterinarians practicing within the US may contact the USDA, APHIS CVB in one of the following ways:

Once an adverse event has been reported to the manufacturer, the CVB may be contacted:

- Online: https://web01.aphis.usda.gov/CVB/adverseeventreport.nsf/Adverse%20Event%20Report%20Form?OpenForm
- By fax or mail: download the PDF form at http://www.aphis.usda.gov/animal_health/vet_biologics/publications/adverseeventreportform.pdf and FAX to (515) 337–6120 or by mail to the CVB.
- By telephone: AEs may also be reported by calling the CVB at (800) 752–6255.

Canadian Food Inspection Agency

In Canada, CFIA is responsible for licensing veterinary biologics, including veterinary vaccines, manufactured and/or used in Canada. The licensing program operates under the Health of Animals Act and Regulations, and is administered by the Canadian Centre for Veterinary Biologics.

The Canadian Health of Animals Regulations require all holders of product licenses and import permits to report all "serious expected" or "serious unexpected" suspected AEs, including lack of efficacy, to the Canadian Centre for Veterinary Biologics of the CFIA within 15 days of receiving notice of the event from a veterinarian or animal owner. This can be done by notifying Canadian Centre for Veterinary Biologics directly or through the licensed vaccine manufacturer or importer.

In Canada, Form CFIA/ACIA 2205 "Notification of Suspected Adverse Events to Veterinary Biologics" can be used to report suspected AEs: http://inspection.gc.ca/english/for/pdf/c2205e.pdf

The Canadian "Veterinary Biologics Guideline 3.15E: Guideline for Reporting Suspected Adverse Events Related to Veterinary Biologics" (available: http://www.inspection.gc.ca/english/anima/vetbio/info/vb315e.shtml) provides guidelines for defining a suspected AE related to veterinary biologics as one of the following: AE, SAE, unexpected AE, and lack of efficacy. The definitions for AE, SAE, and unexpected AE are found in Section V of this guideline and are consistent with the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH)*'s Guideline 24: Pharmacovigilance of veterinary medicinal products: management of adverse event reports (AERs)*. A causality assessment should also be assigned to each SAE. Each case should be classified as probable, possible, unlikely, or unknown.

Managing Adverse Event Risk in Individual Patients

Specific recommendations for mitigating the risk of a vaccine AE in dogs have not been validated. Efforts to manage risk are highly varied and largely unsubstantiated. It is not possible to completely avoid a vaccine AE in any patient. Vaccine risk management should focus on dogs having a known or suspected history of a vaccine reaction and in small breeds. Recommendations are outlined in the following.

The reduction of vaccine volume to mitigate risk of an AE is not recommended. Doing so may result in suboptimal immunization or no immune response without reducing risk of an AE. Vaccine dose is not based on size (body mass); therefore, small dogs require the same dose of vaccines as large dogs.

Patients with a Known or Suspected Vaccine Adverse Event History

Acute hypersensitivity (nonsystemic) and injection-site reactions are among the most common vaccine AEs reported because they occur within hours or a few days after vaccination. The decision to administer vaccine to any patient with a history of having experienced an acute-onset (minutes to 1–2 days postvaccination) reaction is left to the discretion of the veterinarian. History of an acute-onset AE is not predictive of future risk.

Administration of an antihistamine or NSAID before vaccination to prevent transient postvaccinal nonspecific illness has not been studied adequately in dogs to make specific recommendations on their use or benefit. However, it is common practice to administer an antihistamine (diphenhydramine, 2–4 mg/kg orally or 1 mg/kg parenterally) to patients with a history of an acute adverse reaction. A single dose is generally administered 15–30 min before administering vaccine. In such cases, it is recommended that the patient remain at the practice and be monitored for at least 30 min postvaccination.

In an attempt to mitigate the risk associated with administering vaccine to any patient with acute-onset vaccine AE, veterinarians may also elect to administer the same vaccine type but one produced by a different manufacturer.

The decision to administer pretreatment and/or a vaccine produced by a different manufacturer to any patient with a history of having a known or suspected vaccine AE does not guarantee that an AE will be prevented.

It is reasonable to avoid administration of any vaccine to patients with a history of systemic disease suspected to be associated with previous vaccination (e.g., immune-mediated hemolytic anemia, immune-mediated thrombocytopenia) or known to be caused by vaccine (vaccination-site cutaneous ischemic vasculitis after administration of rabies vaccine). In lieu of annual or

triennial revaccination, assessment of antibody titers can be determined (CDV and CPV) (see "Serologic Testing"). Dogs with a "positive" titer are considered protected. These patients can be considered to have sufficient immune memory to mount a protective humoral immune response for several years and may not require vaccination. Dogs with a "negative" antibody titer may be susceptible to infection. Whether to administer vaccine to dogs with a negative antibody titer is left to the discretion of the veterinarian. However, a negative antibody test for CDV and/or CPV-2 may indicate the dog is susceptible to either of these significant diseases.

The decision not to administer rabies vaccine for health reasons is problematic in locations that require rabies vaccinations yet do not grant rabies exemption authority to veterinarians. Some states and/or provinces do grant rabies vaccination exemption authority to veterinarians who have examined a patient and determined, for health reasons, vaccine should not be administered. Such waivers generally remain in effect until the patient is deemed sufficiently healthy to receive the vaccine. Veterinarians are urged to contact state, provincial, and/or local authorities to determine whether such exemption authority exists.

Small Breed Dogs

One study addressed vaccine AEs in >1.2 million dogs that received >3.4 million doses of vaccine.[73] This study provided important insight on risk associated with administration of multiple vaccine doses to small breed dogs at the same appointment. History of a vaccine AE in a small breed dog is not predictive of future risk. Any dog, regardless of size, breed, gender, or age, can experience a vaccine AE.

Mitigating risk in small dogs (puppies and small breeds) by reducing the volume of vaccine is not recommended. Doing so may result in a suboptimal response to the vaccine and may not eliminate risk associated with hypersensitivity to one or more vaccine constituents. As with all dogs, small breed dogs should be assessed for risk of exposure to infectious pathogens and only those vaccines considered essential should be administered. Furthermore, prioritizing administration of core vaccines (CDV, CPV-2, CAV-2, and rabies) to all dogs at the appropriate age (see Table 1) is recommended.

The decision to administer one or more noncore vaccines to a dog should be based on reasonable knowledge of exposure risk in the individual patient. It should also be noted that most of the noncore vaccines listed within the Guidelines are inactivated (killed) vaccines and that these vaccines may be associated with a higher incidence of AEs when administered at the same time as other vaccines, particularly in small breed dogs. Therefore, veterinarians may wish to delay administration of inactivated noncore vaccines to small breed dogs until after completion of the initial core vaccine series.

Legal Considerations

- Veterinarians have considerable ability to use biologics in a discretionary manner.
- Continuous medical decision making is an inherent aspect of veterinary medicine. There is no reason to believe that decisions regarding vaccine selection and use will carry any greater legal risk than the myriad of other medical decisions made in daily practice. Relative risk for utilizing these guidelines in developing patient vaccination protocols is considered low.
- The best method for insulating a practitioner from legal liability relative to vaccination or anything else is effective client communication. Client communication of risk and/or benefit information should be in direct and simple terms.
- With respect to documentation, practitioners must determine the method that best suits their practice and level of risk tolerance.

Do Veterinarians Have Professional Discretion in the Use of Vaccines in Their Practice?

Yes, with a few limitations. The recommendations contained in the Guidelines may differ in places from statements on product labels. However, veterinarians in small animal practice in the US have considerable discretion in exercising their judgment relative to the use of veterinary biologic products licensed by the USDA within their professional practice.[a] The same is true for veterinarians in Canada using biologic products approved under the Canadian Food and Drug Act.[b] As such, practitioners have the ability to incorporate use of the Guidelines into their practices.

The USDA CVB regulates the licensure and preparation of most veterinary biologics, including all material on their labeling. CVB does not regulate the practice of veterinary medicine. Although CVB does have the statutory authority to stop the sale, barter, or exchange of "any worthless, contaminated, dangerous, or harmful virus, serum, toxin, or analogous product," they would only take action against a small animal practitioner under extraordinary circumstances. Before initiating such action, CVB would most likely contact the veterinarian and/or undertake a profession-wide educational initiative.[c]

Vaccines licensed by the USDA and prepared in establishments licensed by the USDA are not directly subject to the Animal Medicinal Drug Use Clarification Act (AMDUCA) or Food and Drug Administration's (FDA) implementing regulations. However, it is possible for the FDA's Center for Veterinary Medicine to regulate some products that most practitioners would consider

biologicals. Products that are approved by the FDA are subject to AMDUCA's and FDA's established specific rules for "extra-label" drug use. Products regulated by the USDA may be identified by the "USDA Establishment Number" that appears on labeling.

States may also regulate the discretionary use of biologic products by veterinarians. This can be confusing, as the state and federal terminology may be similar but applied differently. The state's definition of "drug" may include biologic products, and the state may use the term "extra-label" differently than the federal application.[d] Veterinarians should be aware of any state-specific restrictions in their state's veterinary practice act or implementing regulations. However, it is the authors' belief that such restrictions are sufficiently general that they should not interfere with the ability to use these Guidelines. In Canada, the provinces have the legal authority to regulate the veterinary profession but no authority whatever relating to trade in drugs, medications, and biologics. In this context, the provincial veterinary legislation may, for instance, require that a veterinarian obtain the informed consent of the client before using a substance in a manner that differs from its labeled indications.

Rabies vaccine represents a unique class of products due to the public health concern. The USDA places restrictions on the licenses for rabies products, such that their distribution in each state is limited to authorized recipients as designated by proper state officials (e.g., the state veterinarian) and under such additional conditions as these authorities may require. Each state, in turn, has its own rabies control program. The substance of this law varies among jurisdictions and can encompass state, provincial, and/or local requirements. A common theme to this regulation is compulsory vaccination, irrespective of the label statements that the products are for use in healthy animals. Sometimes veterinarians and/or clients desire to forego rabies vaccination, believing it to be contraindicated due to the health or age of the dog. Veterinarians must be very careful in such circumstances. Although some states have procedures for addressing this situation, it is not addressed in most states.[e] Veterinarians must not assume they have the discretion to recommend against vaccination in the face of mandatory state vaccination laws. Therefore, it is imperative that veterinarians investigate, understand, and follow the legal requirements for rabies vaccination in the areas in which they practice. The same approach is prudent in Canada.

Potential for Liability Associated with Vaccine Administration

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 biologic products. Most lawsuits against practitioners are grounded in negligence, although the range of possible legal liability theories is broad and limited only by the creativity of the plaintiff's attorney. There is no reason to believe a veterinarian's use of vaccines would be treated differently or carry any greater risk than other areas of small animal practice.

Medical Negligence

Legal actions against a veterinarian alleging professional negligence are commonly called "malpractice" or "medical malpractice" cases. The body of law for professional medical negligence has evolved in the context of human medicine. Most jurisdictions apply many of the legal concepts developed in the litigation of physician malpractice cases to veterinary malpractice cases, particularly the requirement for expert testimony. The traditional elements of a medical malpractice lawsuit are the duty to conform to a certain standard, a failure to conform to the required standard, actual injury or damage, and a legally sufficient causal connection between the conduct and the injury.[f]

Medical Negligence as It Applies to Vaccination Decisions

The basic scenarios that could potentially give rise to a claim or lawsuit are where (1) a patient that is not vaccinated contracts the disease for which vaccination was forgone; or (2) a patient experiences an AE attributed to a vaccination later considered unnecessary by the client. In either case, the plaintiff would be required to have expert testimony that the defendant's professional judgment under the specific circumstances was a departure from the standard of care and the cause of the injury to the dog. Although such claims do occur, the risk of a lawsuit is considered low and can be mitigated through effective, documented communication with the client.

Consent Versus Informed Consent

Consent is the giving of permission, approval or agreement. Consent can be expressed or implied, written or verbal, documented or not. A veterinarian should understand regulations relative to obtaining or documenting consent in states where they practice, as a state's practice act or regulations may address necessary documentation of client consent.[g]

Informed consent is consent based upon the disclosure of the material risks of a proposed treatment or procedure and potential alternatives, including the risk of no treatment.[h] The legal doctrine of informed consent developed as human medicine evolved from a paternalistic profession to one that recognizes the importance of a patient's self-determination. It is based upon the theory that a competent human being has the right to determine what is done with their body. To date, most states and provinces have not formally addressed the question of applying informed consent law

to veterinarians. There are, however, a few states and provinces with reported court decisions addressing the application of the doctrine of informed consent to veterinary practice in some fashion.[i] Additionally, there are a few states and provinces where the veterinary practice act and/or implementing regulations incorporate either the doctrine of informed consent or elements of it, and the American Association of Veterinary State Boards has developed a model practice act that recommends to states the incorporation of the requirement to obtain informed consent by board regulation.[j] However, within the US there remains ongoing debate about whether informed consent law should be applied to veterinary practice. This is not the case with Canada, where the incorporation into veterinary practice is readily accepted, either by regulation or convention. Some within the veterinary community advocate forgoing use of the term "informed consent" for other terms while incorporating risk communication elements in an analogous manner. The intent here is not to advocate for or against the doctrine of informed consent or its particulars. Rather, it is to acknowledge that allegations of a failure to obtain consent or informed consent, historically common in physician medical malpractice litigation, are not uncommon in complaints against veterinarians as well. Therefore, it is prudent to understand the issue and to understand that one of the best deterrents to an informed consent lawsuit (or other legal action for that matter) is effective communication with clients.

Documentation of Consent

Documentation of consent discussions is always helpful if there is ever need to defend a veterinarian's actions. Such documentation could include a note in the chart that such a discussion took place (with or without co-signature by the client); a note in the chart that in addition to discussion, a specific client handout was given[k]; or use of a consent form signed by the client. Although defense lawyers like more documentation, the task for practitioners is to determine the method that best suits their practice and level of risk tolerance.

Where consent forms are used, the more general the language used, the less helpful the documentation may prove in court; conversely, the more specific the language, the more helpful to the defense of a case. However, the practitioner should have a medically or scientifically defensible basis for making any representations in a consent document. If precise numbers cannot be justified, then more general statements are preferable.

Medical Record Documentation (AAHA Accreditation Standards)

At the time of vaccine administration, the following information should be recorded in the patient's permanent medical record:

- Vaccines recommended for this patient
- Date of vaccine administration
- Identity (name, initials, or code) of the person administering the vaccine
- Vaccine name, lot or serial number, expiration date, and manufacturer of vaccines actually administered
- Site and route of vaccine administration
- Any concurrent medications/therapy
- Future recommended vaccinations

AEs should be recorded in a manner that will alert all staff members during future visits. Consent should be documented in the medical record to demonstrate that relevant information was provided to the client and that the client authorized the procedure.

Part II: Vaccination of Shelter-Housed Dogs

The AAHA Canine Vaccination Task Force developed vaccination guidelines to facilitate the efforts of individuals responsible for purchasing vaccines, administering vaccines, and/or developing vaccination policy for shelter-housed dogs. The objective of writing vaccination guidelines for shelter-housed dogs is to provide essential recommendations to reduce, or eliminate when possible, the risk of infectious disease outbreak or illness in shelter animals. The Task Force recognizes that unique staffing and cost constraints may preclude the ability of all animal shelters to implement these Guidelines fully. However, the guidance provided in this section is intended to provide a basis for developing and implementing a rational vaccination program for animal shelters because these dogs are at particularly high risk of exposure to infectious disease.

The time and effort dedicated to controlling infectious diseases among shelter-housed dogs is only one of many variables in the complex shelter medicine and husbandry equation. The recommendations provided here attempt to address shelter-unique issues as they pertain to rational selection and use of vaccines. Other important factors, such as population density, ventilation, sanitation, staff training, etc., must be taken into consideration when implementing an infectious disease control plan.

Definition of a Shelter Environment

As used in the context of the Canine Vaccination Guidelines, an animal shelter is a holding facility for homeless animals, usually awaiting adoption, rescue, or reclaim by owners. In general, animal shelters are predominantly characterized as a random source population of dogs, as well as other animal species with a largely unknown health and vaccine history, high population turnover,

and significant potential for relatively high levels of infectious disease risk.

Within this broad definition, however, there is wide variation. The term "shelter" encompasses situations ranging from sanctuaries that possess a stable population to facilities that admit dozens or even hundreds of animals per day to rescue and foster homes that care for multiple litters or individuals at any given time. Just as the appropriate vaccine strategy varies with each individual pet, there is no one-size-fits-all strategy for vaccinating shelter animals. Shelters should interpret these Guidelines in light of the infectious disease risk and turnover rate within their own populations.

Special Considerations of a Shelter Vaccination Program

The relatively high likelihood of disease exposure in most shelters and the potentially devastating consequences of infection necessitate a clearly defined shelter vaccination program with exacting requirements. It is necessary to define not only what vaccines are appropriate, but also when vaccines should be administered with respect to shelter entry, which animals are candidates for vaccination, and how and by whom vaccines should be administered, including record keeping and documentation of AEs. For vaccines that offer significant protection against common and severe infectious diseases, the appropriate vaccination program may be one that is more aggressive than is generally indicated in private practice. Such a program may include, for example, vaccinating dogs at the short end of the suggested intervals or at a relatively early age.

With the use of vaccines at shorter intervals or in an expanded population, it is also important to minimize the vaccines given to those that are clearly indicated by the immediate and significant disease risks. Vaccines are often administered to stray dogs not legally belonging to the shelter and may be given by lay staff under indirect veterinary supervision. These considerations make it even more crucial to develop a vaccine program that minimizes the risk of vaccine-induced adverse reactions. Furthermore, cost differences that are trivial for one individual become significant when multiplied by thousands of doses. Therefore, only those vaccines that demonstrate a clear benefit against common and significant shelter diseases should be used. Adopters should be encouraged to discuss an individually tailored vaccination program with their own veterinarian after adoption.

Vaccination Guidelines for Shelters

Core Vaccines for Shelter-Housed Dogs

Vaccines for shelter use are categorized for pet dogs, as core and noncore (optional) (**Table 2**). A number of other vaccines discussed in the following are not recommended. Although the Task Force acknowledges that variable shelter circumstances make it impractical to provide universally applicable recommendations, those vaccines categorized as core are essential vaccines that should be administered to all dogs at the time of entry (CDV, CPV-2, CAV-2, IN Bb + CPiV) or at the time of release (RV).[51,74–77]

It is recommended that all dogs be vaccinated for rabies before release from a shelter. If a long-term stay is anticipated or for shelters where virtually all dogs will be adopted, rabies vaccine should be administered on intake with the other core vaccines. The earliest age at which rabies vaccine should be given is 12 wk, and it is recommended that it be given at a site on the body different than where the CDV, CPV-2, CAV-2 vaccines are administered. At open-intake shelters, rabies vaccine should be administered at the time of release. Although ideally vaccines should be given at least 2 wk apart to avoid vaccine interference, the public health benefit of ensuring rabies vaccination before release is considered to outweigh the small risk of interference in this case. If state or local requirements prevent issuance of a rabies certificate for vaccines administered at the shelter (e.g., due to lack of veterinary supervision), vaccination for the purpose of legal recognition and licensing should be repeated at the owner's veterinarian 2–4 wk later. Unless a certificate documenting previous rabies vaccination is available, it should be assumed that previous vaccination has not been received, and revaccination 1 yr later will be required.[69]

Noncore Vaccines for Shelter-Housed Dogs

The CIV vaccine may be recommended (noncore) in selected shelters located within endemic communities or in shelters that transport dogs to or from communities considered to be endemic for canine influenza. This is a killed vaccine that requires two doses be given at least 2 wk apart. Immunity is expected 1 wk after the second dose. Therefore, even in shelters located within endemic communities, the benefit of this vaccine will be limited if exposure cannot be prevented before onset of protection or in dogs unlikely to stay long enough to receive the full series of vaccines.[78,79]

Vaccines Not Recommended for Use in the Shelter Environment

The vaccines listed in the not recommended category are for diseases that do not represent a significant threat to the population of dogs residing in shelters, would not provide protection because there is inadequate time for immunity to develop, or that have limited efficacy against clinical disease. Among the various canine vaccines licensed for use within the US, the following vaccines are not recommended for routine use in shelter-housed dogs:

TABLE 2

2011 Canine Vaccination Guidelines for Shelter-Housed Dogs

Vaccine	Initial Vaccination	Revaccination (if indicated)	Comments
CDV + CAV2 + CPV2 Note: Use of a combination CDV vaccine + CAV-2 + CPV-2 vaccine with or without MLV CPiV is recommended. Killed (inactivated) virus vaccines are not recommended. Administer SQ or IM	Administer a single dose immediately before or at the time of admission to all dogs unless there are veterinary records showing the dog has been vaccinated at 18–20 wk of age or older with these core vaccines. Alternatively, if the dog is 18–20 wk of age or older and tested positive for antibody to CDV and CPV-2, it would not be necessary to vaccinate. Minimum age: It is recommended that vaccine not be administered to shelter dogs <4 wk of age.	Puppies (≤18 wk of age): Revaccination every 2 wk is recommended until 18–20 wk of age. Dogs (≤18–20 wk of age): Revaccinate at 1 year of age then revaccinate at 3 or more year intervals as for pet animals as long as the dog remains in the facility.	Core • When feasible, puppies should be housed separately from adult dogs, regardless of their vaccination status. All MLV-CPV-2 vaccines available today are expected to provide immunity from disease caused by any field variant recognized today (CPV-2a, -2b, and -2c). All current CDV vaccines are expected to provide immunity from disease caused by any of the current variants of CDV viruses. • MDA, if present, can interfere with immunization up to 16–18 wk of age. When distemper risk is high, inoculation with the rCDV and measles/distemper vaccines have been shown to protect puppies with MDA 2 wk earlier than the MLV CDV vaccines. The MLV or rCDV vaccine should be used when dogs are 16–18 wk or older, as both are highly effective in the absence of MDA. Because it is often difficult to know the exact age of puppies and because MDA are often higher in shelter puppies, they may still be sufficient to block immunization at 14–16 wk in a small percentage of puppies. Therefore, when feasible, shelter puppies should receive a final vaccine when estimated to be 18–20 wk of age. • Once the vaccine has been reconstituted and kept at room temperature, the dose should be administered within 1 hr to avoid inactivation of the vaccine virus, especially MLV CDV vaccine.
Intranasal Bb + CPiV. Use of a combination (bivalent) INI MLV (avirulent) Bb + MLV CPiV, vaccine is recommended, with or without CAV-2. Administer IN only. Do not administer SQ or IM.	Administer a single dose immediately before or at the time of admission. Vaccine can be administered as early as 3–4 wk of age (see manufacturer's administration recommendations). Do not administer SQ or IM.	Dogs ≤6 wk of age: For best results, an additional dose is recommended after 6 wk of age at a minimum vaccination interval of 2 wk. Dogs >6 wk of age: Administer a single intranasal dose every 6–12 mo as indicated. Do not administer SQ or IM	Core • Administration of MLV (avirulent) IN Bb by the SQ or IM route can lead to severe reactions, including death. • Onset of protective immunity after initial IN vaccination occurs within 72 hr; vaccines can reduce the severity of disease but will not entirely prevent canine respiratory disease complex. • Use of a trivalent IN vaccine that also contains MLV CAV-2 should be considered in shelter-housed dogs when the 2-way IN fails to provide acceptable protection.
Parenteral Bb Administer SQ. This vaccine is not effective if administered by the IN route.	Administer the first dose at the time of admission. Administer a 2nd dose 2 wk later if still in the facility. (see comments).	Regardless of the dog's age, 2 doses, 2 wk apart, are required to induce immunity unless previously vaccinated within the past 12 mo. Dogs that have previously received a 2-dose initial vaccination series or a booster vaccination within the past year require only a single dose at the time of admission.	Parenteral Bb vaccine is recommended only as an alternative when it is not possible or not feasible to administer an INI vaccine (above). Note: In previously unvaccinated dogs, a single dose of parenterally administered vaccine will not immunize. Immunity is expected 7–10 days after administration of the 2nd dose. • The parenteral Bb vaccine does not include protection against parainfluenza virus.

(Table continues)

TABLE 2 (continued)

Vaccine	Initial Vaccination	Revaccination (if indicated)	Comments
RV 1 yr. Use of a killed (inactivated) monovalent, single dose vaccine is recommended. Administer SQ or IM.	Administer 1 dose at the time of release from the facility. Dogs may be vaccinated as early as 12–16 wk of age depending on local regulations. If a long-term stay is anticipated, administer 1 dose on entry to the facility.	Revaccinate 1 yr after initial vaccination and then at 3 yr intervals with a 3 yr rabies vaccine as for pet animals as long as the dog remains in the facility.	Core: recommended for all dogs before release from shelter • Unless valid (signed) documentation of prior rabies vaccine administration is available, administration of a rabies vaccine is indicated for all dogs leaving the facility, regardless of age. Revaccination 1 yr later is required by most jurisdictions. • If local, state, or provential law does not permit issuance of rabies certificate for vaccines given at the shelter, vaccination can be repeated by the owner's veterinarian 2–4 wk after leaving the shelter. • Single dose vials are preferred to reduce the risk of contamination and ensure proper mixing and dosage of antigen and adjuvant.
CIV. A killed 2 dose vaccine. Administer SQ or IM.	Administer 2 doses 2 wk apart, with the first dose given before or immediately upon intake. Vaccine can be administered as early as 6 wk of age. Two doses must be given to provide immunity.	Revaccination with the 2nd dose should occur 2 wk after the first. For those dogs in long stay shelters, annual revaccination is recommended.	Noncore • Do not vaccinate a dog unless it is possible to give the initial 2 doses 2 wk apart, as 1 dose has not been shown to provide any benefit. • This vaccination should be considered for shelters in endemic communities or those that transport dogs to or from these locations.

leptospirosis; canine coronavirus; canine Lyme borreliosis (Lyme disease); *Crotalus atrox* (rattlesnake) vaccine; parenterally administered Bb (see Table 2 for exception); and parenterally administered CPiV. Because most of these vaccines are killed (inactivated) and, therefore, require two doses at least 2 wk apart, use of these vaccines is viewed as impractical and unnecessary in most shelter-housed dogs.

Vaccination Recommendations for Specific Cases in the Shelter Environment

Dogs with a Documented Vaccination History at Time of Admission

There is no compelling reason to administer vaccines to an individual dog at the time of admission to a shelter if clear documentation confirms current vaccination administered after the age of 16 wk is provided. The following is the minimum information acceptable as documenting proof that a valid vaccination has been administered:

- Proprietary name of product
- Manufacturer name
- Serial/lot number
- Date vaccine was administered (at least month and year)
- Expiration date of vaccine administered
- Signature of a licensed veterinarian

This information should be associated with a medical record that clearly describes the dog in question. If any of this information is not available at the time of admission or cannot be associated with a formal record for the dog, then immediate vaccination is indicated.

Long-Term Shelter-Housed Dogs

It is recommended that all dogs entering a long-term care facility (or any dog entering a shelter for which a long-term stay is anticipated) be inoculated with all core vaccines, including rabies vaccine, at the time of admission to the facility. If a dog is routinely exposed to the outdoors, then noncore (optional) vaccines should be considered (as for pet dogs), depending on the dog's risk profile.

Because it can be difficult or impossible to determine whether young dogs (<4 mo of age) have received any vaccines at all, implementation of an initial series (CDV, CPV-2, CAV-2 [IM, SQ], Bb, and CPiV [IN]), beginning as early as 4 wk of age (as early as 3–4 wk of age for IN administered vaccines), may be indicated. Parenterally administered core vaccines should not be administered before 6 wk of age. When it is the decision of the facility to initiate the series (i.e., "puppy shots") to an individual dog, then the recommended vaccines should be administered at 2 wk (rather than 3 or 4 wk) intervals until the dog reaches ≥16 wk of age.

Contact Information for Biologics Manufacturers

Company Name	Tech Services Phone (US)	Tech Services Phone (Canada)
Boehringer Ingelheim Vetmedica Inc.	866–638–2226	800–263–2425
Merck Animal Health	800–224–5318	800–361–2353
Merial	888–637–4251 (ext. 3)	888–637–4251 (ext. 57320)
Pfizer Animal Health Inc.	800–366–5288	800–461–0917
Red Rock Biologics	866–897–7625	No Canadian number provided

In the event that an individual dog resides in the facility long enough to justify booster vaccination, it is recommended that the revaccination schedule recommended for individual pets be followed (Table 1).[29,51,74,76,80–82]

Vaccination of Pregnant Dogs in the Shelter Environment

Shelter personnel may be faced with the dilemma of whether to vaccinate a pregnant dog upon admission to a facility. Historically, vaccination during pregnancy has not been recommended in small animal medicine. This is due in part to the paucity of data concerning vaccine safety and efficacy during gestation and the expectation that, in nonimmune pregnant bitches, MLV vaccine can cause fetal damage or death.[22,30,49] When the immunity of the dog is unknown, however, the risk of maternal, fetal, and neonatal infection with field strain virus must be weighed against the risk of vaccination. If nonimmune pregnant dogs are likely to be exposed to field strain infection with pathogens such as parvovirus or distemper, serious illness or death of both bitch and fetuses may result. Unless facilities are available to completely isolate them from other dogs, pregnant bitches should either be vaccinated or not remain in the shelter.

Vaccination of Sick Dogs in the Shelter Environment

As with pregnant dogs, veterinary medicine has advised against vaccination during illness, due to concerns about suboptimal protection, or worse, vaccine-induced illness. The decision to administer or delay vaccination because of a current illness depends on the severity of disease and its etiology.

The shelter environment does not usually permit the luxury of isolating dogs and delaying their vaccination until concurrent illness is resolved. Therefore, vaccination is advised upon admission for dogs with minor illness (e.g., otitis, dermatitis, upper respiratory tract infection with or without fever) or injuries. Vaccination of dogs with severe signs of disease ideally should be delayed whenever feasible. However, unvaccinated shelter dogs may develop more severe disease if left unvaccinated, and thus would be at greater risk of dying. In the high-risk shelter environment, vaccination of sick dogs with core vaccines should be the rule with very few exceptions.[51]

Appendix

PDF form for adverse event reporting (US).

PDF form for adverse event reporting (CANADA).[m]

2011 AAHA Canine Vaccination Guidelines Frequently Asked Questions

The frequently asked questions (FAQs) that follow are based on questions raised by practicing veterinarians regarding the use and selection of vaccines in dogs. The FAQs have been arranged in four categories: Adminisration of Vaccines, Vaccine Products, Vaccine Adverse Events, and Legal Issues Pertaining to Vaccination. Many of the FAQs included have been derived from, or are edited versions of, FAQs developed by the World Small Animal Veterinary Association's (WSAVA) Vaccine Guidelines Group (VGG). AAHA wishes to acknowledge the WSAVA and the VGG for their contributions and support.

Due to the nature of the questions listed in the following, scientific studies and publications supporting each response may not be available. However, the reader is reminded that the FAQ answers represent a consensus of opinion from Task Force members and are based on scientific literature in companion animal immunology and infectious diseases. Although some of the recommendations outlined may be viewed as controversial, these are not intended to be requirements. They are only intended to provide guidance on key points of concern to practicing veterinarians. Implementation of any of these recommendations is left to the discretion of the practicing veterinarian.

Questions Related to Administration of Vaccines

1. *Can different types of vaccines be mixed in the same syringe?* One should never mix different vaccine preparations in the same syringe unless specified on the label.
2. *Is it safe to inject different vaccines (not part of a single commercial product) into the same dog at the same appointment?* Different vaccine types can be injected into the same patient, but they should be injected into separate sites that are drained by different lymph nodes. For example, if a combination MLV (attenuated) vaccine (such as, CDV + CAV-2 + CPV-2) is administered SQ over the left shoulder, a killed (inactivated) leptospirosis or rabies vaccine could be administered SQ over the right shoulder.

3. *To reduce the risk of an adverse reaction, can the volume of an individual dose of parenteral vaccine be reduced for administration to small breed dog?*
   The volume (e.g., 1.0 mL) as recommended by the manufacturer generally represents the minimum immunizing dose; therefore, the total amount should be given to induce a protective immune response.
4. *Is it necessary to administer the entire volume of an IN "kennel cough" vaccine?*
   Although administration of the entire dose and/or volume of an intranasal vaccine is recommended, loss of some reconstituted vaccine is expected (induced sneezing or drainage) after administration. IN vaccines are attenuated (MLV and/or avirulent live bacteria) and, as such, will infect and replicate after administration (see FAQ 7). Loss of some vaccine volume after proper administration is not expected to compromise the local immune response.
5. *Should the large dog (e.g., Great Dane) be injected with the same volume of vaccine as the small dog (e.g., Chihuahua)?*
   Unlike pharmaceuticals (the dose of which is usually based on weight), a vaccine dose is not based on volume per body mass (size), but rather on the minimum immunizing dose (inactivated vaccine) or the minimum infectious dose (attenuated vaccine). Therefore, the entire dose should be administered as directed by the manufacturer. Administering less than the prescribed dose may not induce a protective immune response (see also FAQ 3).
6. *Should vaccine be administered to the anesthetized patient?*
   Doing so is not generally recommended. There is a small risk that a postvaccinal hypersensitivity reaction may lead to vomiting and an increased risk of aspiration. Also, some anesthetic agents may modulate the immune response to a vaccine.
   However, in the event there is limited opportunity to administer a vaccine (e.g., spay and neuter programs), administering vaccine during, or immediately on recovery from, anesthesia is acceptable.
7. *What's the difference between an "infectious" vaccine and a "noninfectious" vaccine?*
   An "infectious" vaccine is capable of replicating within the host after administration. All modified live (attenuated) viral and bacterial vaccines and virus-vectored recombinant vaccines are infectious (e.g., MLV-CDV, IN Bb, and rCDV).
   A "noninfectious" vaccine is not capable of replicating within the host after administration. All killed (inactivated) viral vaccines (e.g., rabies, CIV) and bacterial vaccines (e.g., *Leptospira* spp., Lyme, *Bordetella)* and certain subunit recombinant (rLyme OspA) vaccines are noninfectious.
8. *Should a pregnant dog be vaccinated?*
   Vaccination with MLV (attenuated) and/or killed (inactivated) vaccines during pregnancy should be avoided, if possible, to avoid potential injury to the fetus. There are exceptions, especially in shelters, where vaccination would be advised if the pregnant dog has never been vaccinated and there is risk of exposure to a highly pathogenic virus (e.g., CDV, CPV-2).
9. *Does glucocorticoid treatment in the dog interfere with core vaccine immunity during the primary or secondary (booster) vaccination programs?*
   Studies in dogs suggest that short-term glucocorticoid treatment, even at high doses (2.5 mg/kg) before or at the time of vaccination does not have a significant suppressive affect on antibody production. However, it is reasonable to revaccinate $\geq$2 or more weeks after long-term therapy has ended, especially when treatment occurred during administration of the initial series of core vaccines.
10. *Should vaccine be administered to pets that are receiving immunosuppressive drugs or cytotoxic therapy (other than glucocorticoids) (e.g., for cancer or autoimmune diseases)?*
    Manufacturers only recommend administration of vaccine to healthy dogs. Dogs receiving immunosuppressive chemotherapy should not be vaccinated. Doing so may result in a suboptimal immune response or may aggravate (reactivate) an immune-mediated illness.
11. *Can vaccine be administered weekly to puppies that may be at high risk of exposure to an infectious pathogen?*
    Ideally, vaccines should not be given more often than every 2 wk, even if different vaccines are administered. Transient downregulation of the immune system after administration may interfere with subsequent vaccine administration for up to 10 days. However, in certain situations (short-term stay in shelters), it may be necessary to vaccinate at intervals of $<$2 wk.
12. *When should the last vaccine dose of core vaccines be given during the initial (puppy) vaccine series?*
    The last dose of core vaccine, regardless of the number of doses previously administered, should be given at 14 to 16 wk of age or older (see Tables 1 and 2).
13. *Vaccines are indicated for administration to healthy dogs only. In locations that require dogs to be vaccinated against rabies, is the veterinarian still required to administer vaccine to a dog that has a chronic or systemic illness?*
    Rabies vaccination requirements for dogs are generally defined by state or provincial law; however, local municipalities

(counties or cities) may impose rabies vaccination requirements that are more restrictive, but never less restrictive, than those defined by the state or province.

Some, but not all, government agencies grant rabies vaccination waiver authority to veterinarians in the event an individual dog is determined by the veterinarian to be sufficiently ill that vaccination should be delayed. Physical examination and medical record documentation of the illness is generally required; it is the responsibility of the owner and the veterinarian to ensure the dog is revaccinated when or if the underlying medical condition is resolved.

Note: any dog that has exceeded the stipulated rabies revaccination ("booster") interval is not legally considered immunized against rabies, although a rabies vaccination waiver may be in effect. Due to the potential implications of a biting incident involving a dog that is not legally considered as immunized against rabies, the owner should be involved in the decision-making process of whether to vaccinate, and the veterinarian should document the discussion in the patient's medical record.

Veterinarians practicing in locations where rabies vaccination waiver authority is not specifically defined should contact the state or provincial Veterinary Medical Board or the Department of Health for guidance on this issue before vaccinating a dog with a medical condition that, in the veterinarian's judgment, precludes administration of rabies vaccine.

14. *What would happen if an avirulent live IN Bb vaccine is administered by the SQ or IM route?*

    IN Bb vaccine contains live, avirulent gram-negative bacteria that, if parenterally administered, can cause abscess formation at the injection site and may culminate in death associated with bacterial replication, bacteremia, and release of hepatotoxic proteins.

15. *Should a noninfectious (inactivated, killed) parenteral Bb vaccine be administered by the IN route?*

    No. Doing so will not stimulate a protective immune response to Bb.

16. *Have vaccination site recommendations been stipulated for the dog as they have for the cat?*

    Vaccination guidelines for the dog do not specify injection site recommendations. Veterinarians are strongly encouraged to document the inoculation site and vaccine type in the patient's medical record.

17. *Can different vaccine brands (different manufacturers) be administered to the same patient at the same time?*

    Doing so is safe and effective. However, vaccines should not be mixed within the same syringe or administered in the same location.

18. *Should a disinfectant (e.g., alcohol) be applied to the injection site before administering a vaccine?*

    Because disinfectant might inactivate an MLV (attenuated) product, and is not known to provide any benefit to the patient, doing so is not generally recommended.

19. *Will a single dose of infectious (attenuated, avirulent, modified live, recombinant viral vectored) core vaccines provide any benefit to the dog?*

    In the absence of MDA (especially dogs ≥16 wk of age), one dose of a MLV (attenuated) canine core vaccine (CDV, CPV-2, CAV-2) is likely to provide long-term immunity.

20. *When administering the initial doses of killed vaccines that require two doses to immunize (e.g., Leptospira, Lyme disease, CIV), and the dog does not return for the second dose within 6 wk after the first dose, is the dog considered to be immunized?*

    Noninfectious (inactivated, killed) vaccines require two doses on initial vaccination. The first dose primes the immune system, the second dose immunizes. If a second dose is not given within 6 wk of the first, two additional doses, administered from 2 to 6 wk apart, are recommended. Rabies vaccine is the exception.

21. *For how long can a reconstituted MLV vaccine remain at room temperature without losing activity?*

    At room temperature (e.g., 60–80°F), some of the more sensitive MLV vaccines (e.g., CDV) may lose their ability to immunize after 2–3 hr. It is recommended that MLV vaccines be discarded if kept at room temperature for ≥1 hr after reconstitution.

22. *What is the recommendation for revaccinating a dog with an infectious (modified-live, attenuated, or recombinant) core vaccine if that patient has not been properly revaccinated within the recommended time period stipulated for that vaccine?*

    A single dose of infectious (MLV, attenuated, or recombinant viral vectored) core vaccine is considered sufficient to ''boost' immunity in a dog that has previously been vaccinated (e.g., ≥3 yr). Because a single dose of MLV or recombinant core vaccine will both prime and immunize, it is not necessary to administer a series of two or three doses to "boost" the patient's immunity. *Note*: The reason for administration of an initial infectious core vaccine series to puppies is to administer at least one dose that will avoid interference by MDA.

23. *Does severe nutritional deficiency affect the immune response to vaccines?*
    It has been shown that certain severe deficiencies of vitamins and trace minerals (e.g., Vitamin E/Se) can interfere with the development of a protective immune response to certain vaccines, especially in puppies. Known or suspected nutritional deficiencies should be corrected by appropriate nutritional supplementation, and the dog should be revaccinated to ensure there is adequate protective immunity.
24. *If a puppy fails to receive colostrum (MDA) during the first 3 days of life, will it derive any passive antibody protection from the dam?*
    A puppy receives little or, most likely, no immune protection in the absence of colostrum. Approximately ≥95% of passive antibody for a newborn puppy is obtained from the colostrum, which is absorbed via the intestine into the systemic circulation for up to 72 hr after birth.
25. *If a puppy fails to receive colostrum (MDA), should it be vaccinated during the first few weeks of life?*
    To reduce the risk of the MLV core vaccine causing an adverse reaction, colostrum-deprived puppies should not be vaccinated until ≥4 wk of age. In the absence of MDA, certain modified live vaccines, when administered to colostrum-deprived pups <2 wk of age, can infect the central nervous system (e.g., CDV, CPiV) and/or the heart (CPV-2), and can cause disease.
26. *How can colostrum-deprived puppies be protected against the core diseases?*
    Artificial colostrum can be orally administered if the puppy is <3 days old and has never been fed a protein diet. Artificial colostrum can be formulated by administering a mixture of 50% milk replacer (e.g., Esbilac^{n} or other similar product) and 50% immune serum (preferably from the dam or other well vaccinated dog living in the same environment as the dam). *Note*: If a puppy received protein (e.g., milk replacer) orally or is ≥3 days of age, serum from a well-immunized adult dog can be given SQ or intraperitoneally (absorption via the intestinal tract does not occur in dogs that are >3 days of age). Alternatively, citrated plasma can be administered intravenously. Depending on size of the dog, approximately 3–10 mL of serum or plasma should be administered twice daily for up to 3 days.

Questions Related to Vaccine Products

27. *Will the administration of vaccine to a puppy "bind" or otherwise deplete MDA, leaving the dog susceptible to infection?*
    Vaccination in the presence of MDA can interfere with the vaccine but will not deplete, or measurably alter, the level of protection a puppy derives from passive (maternal) immunity.
28. *Is it possible to immunize puppies in the presence of MDA?*
    Although MDA may interfere with any vaccine, multiple factors influence the ability of any vaccine to immunize a dog in the presence of MDA; for example, antibody titer of dam, nursing history, concentration of MDA in the puppy, age of the puppy, health status of the puppy, the type of vaccine, and virulence and concentration of the vaccine antigen, etc. Limited studies demonstrated that the viral vectored rCDV vaccine and MV can immunize puppies in the presence of CDV MDA about 2 wk earlier than a MLV CDV vaccine. *Note:* High levels of MDA can still interfere with MV and recombinant (viral vectored) CDV vaccines.
29. *Can MDA interfere with active immunization by both modified-live (attenuated) and killed (inactivated) vaccines?*
    To some extent, all vaccines, both noninfectious (inactivated, killed) and infectious (attenuated, avirulent, modified live, recombinant viral vectored) vaccines, are susceptible to MDA interference.
    Noninfectious vaccines require a minimum of two initial doses (2–6 wk apart) to immunize: the first dose "primes" the immune response; the second dose immunizes. In dogs vaccinated at <12 wk of age, there is risk that MDA will interfere with (block) the first dose of inactivated vaccine. In such cases, the priming immune response does not occur. The second dose, therefore, would not immunize.
30. *It has been suggested that certain canine infectious (attenuated, avirulent, modified live, recombinant viral vectored) core vaccines need only be administered twice, with the last dose at an age as young as 10–12 wk. Is that accurate?*
    Some canine vaccines are recommended (label) for administration of two initial doses: the first dose at approximately 6 wk and a second dose at 10 wk of age. Serious reservations exist about discontinuing the initial core vaccine series in any dog before 14–16 wk of age. No combination core vaccine product currently available will immunize an acceptable percentage of puppies when the last dose is given at 10–12 wk of age.
    It is strongly recommended that the last dose in the initial series be administered at 14–16 wk of age, regardless of the product used or the number of doses administered earlier. If the initial vaccination series is discontinued by 10–12 wk, it is recommended that an antibody titer to CDV and CPV be obtained to ensure the animal develops an

immune response. During the interim, the individual dog's exposure to other dogs should be strictly limited.

31. *When two vaccine types (MLV and killed) are available for the same antigen, is there any benefit to administering both vaccines, parenterally and topically (e.g., Bb or parainfluenza virus), to an individual dog at the same appointment?*
    Doing so is not considered harmful. Beneficial effects associated with simultaneous administration of an IN and parenteral vaccine for the same antigen (e.g., Bb and parainfluenza virus) have not been clearly documented.
32. *Are there advantages to administering either IN Bb or parenteral Bb vaccine?*
    Studies have shown that both vaccine types, parenteral and IN, mitigate the severity of clinical signs among dogs challenged and/or exposed to Bb.
    Initial vaccination using an IN Bb vaccine provides rapid onset (within 3 days) protective immunity after a single dose. Initial vaccination with parenteral (cellular antigen extract) Bb vaccine requires administration of two doses, at least 2 wk apart, then an additional 7–10 days before immunity develops.
    Dogs vaccinated with IN Bb had significantly lower cough scores and shed significantly fewer challenge organisms (challenged 63 days postvaccination) compared with dogs vaccinated with parenteral Bb. Therefore, in high-risk environments (e.g., shelters), IN Bb vaccine, in combination with parainfluenza virus vaccine, is recommended over parenteral vaccine.
    Use of parenteral vaccine is recommended for use in those patients that aggressively resist IN vaccination.
33. *How long after administration of the core vaccines does it take for a healthy dog that does not have MDA to develop immunity that will prevent severe disease?*
    This is dependent on the dog, the vaccine, and the vaccine virus. After a single dose of core vaccine:
    - MLV and rCDV: immunity to CDV begins within hours after administration. This very early immunity does not prevent infection but does prevent severe disease (especially neurologic), and death, if administered 2–3 days before exposure.
    - MLV CPV-2: immunity to CPV-2 develops in as few as 3 days and is usually protective (based on challenge studies) by 5 days postvaccination.
    - MLV CAV-2: parenterally administered CAV-2 vaccine provides protection against canine hepatitis virus infection (CAV-1) and is expected to induce protective immunity by 5–7 days postvaccination. In contrast, IN administered CAV-2 vaccine (combined with Bb and CPiV vaccine) provides protection against CAV-2, one of the pathogens associated with canine infectious respiratory disease and is likely to induce protective immunity within 3 days postvaccination.
34. *How efficacious are the core vaccines in the properly vaccinated puppy/dog?*
    Ninety-eight percent or more of dogs vaccinated at 14–16 wk of age with a MLV CPV-2, a MLV CAV-2, and a MLV or rCDV vaccine should develop a protective immune response after parenteral administration of a single dose.
35. *Are there new variants of CDV in the field for which current CDV vaccines do not provide protective immunity?*
    All of the current infectious CDV (MLV and recombinant) vaccines provide protection against all the known isolates (variants) of CDV.
36. *Do the current infectious CPV-2 vaccines provide protection from disease caused by the new variant CPV-2C?*
    All current infectious CPV-2 vaccines induce a protective immune response (e.g., antibody response) that provides long term (≥4 yr) protection from all known CPV-2 variants (2a, 2b, and 2c). Protection was documented after both natural and experimental challenge.
37. *Can parvovirus vaccines (e.g., CPV-2) be administered orally?*
    CPV-2 vaccines, when administered orally, will not immunize. The most effective route of administration is parenteral (SQ or IM) vaccination.
38. *Are serum antibody titers useful in determining vaccine immunity?*
    Serum antibody titers correlate with protective immunity against CDV, CPV-2, and CAV-1 immunity (induced by CAV-2 vaccine). RV antibody titers can be determined for individual patients (certificated laboratories only) and do reflect an immune response to vaccination; however, at the present time, such titers generally are not used to establish protective immunity in an individual dog. Likewise, postvaccination rabies titers generally cannot be used to replace the requirement for revaccination.
    Serum antibody titers currently available are of limited or no value as a measure of protective immunity for the noncore vaccines. See also page 17 of the Guidelines for additional information on serum antibody titers.
39. *When a noninfectious (inactivated, killed) Leptospira vaccine (bacterin) is administered, should it be a product containing 2 serovars or 4 serovars.*
    There is little or no cross protection induced by the various *Leptospira* serovars. Therefore, it is recommended that for dogs deemed to be at risk for exposure, a four-way

leptospirosis vaccine should be administered annually after the initial puppy series of two doses (see also Table 1).

40. *Do Leptospira vaccines provide the same degree of long-term immunity as core vaccines?*
    Leptospira vaccines provide short-term immunity (e.g., up to 12 mo) and the efficacy may be <70% for certain serovars. The immunity among the serovars varies and immunity varies among vaccinated dogs. Persistence of detectable antibody after vaccination will often be only a few months and immunologic memory for protective immunity may only last approximately 1 yr. Therefore, when a dog is at risk for leptospirosis and has not been revaccinated during a period of ≥2 yr, two doses 2–6 wk apart should be given instead of a single dose.
41. *How many doses of vaccine should be given to a dog presented for their initial vaccine series if the patient is older than 14–16 wk of age?*
    Most manufacturers recommend administering two doses, 3–4 wk apart. When using noninfectious (inactivated, killed) vaccine, two doses are essential to immunize (rabies is the only exception). However, when administering an infectious modified-live attenuated or a recombinant distemper virus vaccine to healthy dogs older than 14–16 wk of age, 1 dose is considered sufficient to immunize.
42. *Can infectious (attenuated, avirulent, modified live, recombinant viral vectored) vaccines be administered to dogs already infected as a means of "treating" the clinical disease or shortening the course of infection?*
    Administering vaccine to clinically ill patients as a means of treating the disease is neither effective nor is it recommended. By the time clinical signs develop, the infection is well established. However, in a kennel or shelter situation, because dogs are in various stages of exposure, vaccination of the entire group will often prevent or end a significant outbreak.
43. *What is "nonsterile immunity"?*
    Many vaccines serve only as an "aid in the prevention of clinical signs" associated with exposure to pathogenic viruses/bacteria. Such vaccines do not prevent infection, may not completely prevent development of clinical signs and, may not completely prevent shedding (CIV, CAV-2, parenteral Bb, and leptospirosis are vaccine examples), but should prevent or reduce disease.
44. *What is "sterile immunity"?*
    Some vaccines induce protective immunity, and prevent infection, thus clinical signs will not occur following exposure. These vaccines induce "sterile" immunity (e.g., CPV and CDV).
45. *Will the current 'kennel cough' vaccines provide protection from disease caused by the CIV?*
    None of the current vaccines used to prevent Bb, parainfluenza virus, or CAV-2 (causes of canine infectious respiratory disease; also called "kennel cough"), provide any protection against CIV.
46. *Is there a vaccine available to aid in the prevention of disease caused by CIV?*
    There are licensed vaccines available that are designed to aid in the prevention of influenza in dogs caused by the H3N8 influenza virus. The products are adjuvanted killed vaccines that, like all noninfectious (inactivated, killed) vaccines, requires two initial doses, administered parenterally, given 2–4 wk apart. Immunity develops approximately 1 wk after the second dose. This vaccine is monovalent and is not currently available in combination with any other vaccines.
47. *Can nosodes (holistic preparations) be used to immunize pets?*
    Nosodes cannot be used for the prevention of any infectious disease. They do not immunize because they do not contain antigen, which is required for the development of cell mediated and/or humoral immunity.

Questions Related to Adverse Reactions to Vaccines

Note: Vaccine adverse events are significantly underreported in veterinary medicine. The USDA, the CFIA, and the vaccine manufacturers strongly encourage reporting of any known, or suspected, adverse event following administration of a veterinary vaccine. Reporting instructions can be found on page 20 of the guidelines.

48. *Is there a risk of over-vaccinating a pet (e.g., injecting it too often, or using vaccines that are not required for the specific pet)?*
    Vaccines are biologic products; administration should be tailored to the needs of the individual dog and should never be given needlessly. All vaccines have the potential to cause adverse reactions following administration. See page 19 of the guidelines for additional discussion on vaccine AEs.
49. *Are certain vaccines or combinations of vaccines more likely to cause adverse reactions than others?*
    Although the development of an adverse reaction may be dependent on the genetics of the dog (e.g., small breeds), certain vaccines have a higher likelihood of producing adverse reactions, especially reactions caused by Type I (anaphylaxis due to IgE) and/or Type III (Ag-Ab complex)

hypersensitivities. See page 19 of the guidelines for additional discussion on vaccine AEs.

50. *Should dogs with a history of acute postvaccinal adverse reaction (hives, facial edema, anaphylaxis, etc.) or immune-mediated diseases (such as IMHA) receive booster vaccines?*
    There may be risk in doing so. If the vaccine known or suspected to have caused the adverse reaction is an attenuated (MLV) core vaccine (e.g., CDV or CPV-2), a serological (serum antibody) test can be performed. If the dog is found to be positive, the dog is considered immunized and revaccination is not necessary.
    If the vaccine is a noncore vaccine (e.g., *Leptospira*, *Bordetella*, Lyme bacterin), revaccination is discouraged (serum antibody titers are not reflective of the patient's immune status).
    If rabies vaccine is implicated as the cause of an adverse event, appropriate authorities should be consulted to determine whether rabies vaccination can be exempted (waivered).
    In the event vaccination is deemed necessary, administration of an alternative product (by a different manufacturer or different type of vaccine) may be helpful. However, there is no guarantee that a dog will not develop an adverse event if a different product is administered.
    Hypersensitivity reactions are not necessarily linked to the immunizing antigen; in fact, the sensitizing protein(s) are often linked to constituent proteins associated with the manufacturing process (bovine serum albumin, tissue culture antigens). See page 19 of the guidelines for additional discussion on vaccine AEs.
51. *Can vaccines cause autoimmune diseases?*
    Vaccines themselves do not cause autoimmune disease, but in genetically predisposed dogs, vaccination may induce immune-mediated disease. *Note*: immune-mediated disease can also be linked to infection, oral or parenteral drug administration, and possibly other environmental factors.
52. *Is there any risk to clientele or veterinary staff, especially immune compromised individuals, subsequent to intranasal vaccination with an avirulent live (attenuated) Bb vaccine?*
    It is possible for transient shedding of attenuated Bb to occur following intranasal administration. There are two known reports identifying a temporal relationship between the identification of human *Bordetella* infection and exposure to attenuated live Bb canine vaccine, one of which was in an immunocompromised patient.
53. *How common are postvaccination adverse reactions?*
    There are no reliable data that provide information on the true incidence of postvaccination adverse events (reactions) in companion animals. In the US and Canada, there is no vaccine adverse event database maintained that is available for public review. Although serious postvaccinal adverse reactions among dogs are considered to be uncommon, a prior history of a known or suspected postvaccinal adverse event should be taken into consideration when recommending vaccines for individual patients
    Current studies have shown that, among dogs, the risk of an acute-onset (within 3 days) adverse reaction is greatest among small breed dogs receiving multiple vaccines at the same appointment. Such practices should be avoided (see page 22 of the guidelines).
54. *Are there dogs that cannot develop an immune response to vaccines?*
    Although uncommon, it does appear that some dogs have an inability to respond to specific vaccine antigens. Dogs vaccinated with a CDV-CPV-2-CAV-2 may respond to two of the constituent vaccines but not a third. This is attributed to a genetic trait; dogs affected in this way are called 'nonresponders'. Genetically related (same family or same breed) dogs will often share this nonresponsiveness. If the dog is a nonresponder to a highly pathogenic agent, like canine parvovirus virus (estimated at 1/1,000 dogs), the dog may die if infected. In contrast, if the individual dog is a nonresponder to a pathogen that rarely causes death (Bb), clinical signs may develop following exposure despite prior vaccination, and the dog is not likely to die, but it may become a carrier.
55. *Does the adverse reaction risk of a noninfectious (inactivated, killed) vaccine (e.g., acute hypersensitivity) persist in the individual patient for an extended period or is it of short duration?*
    Immune memory associated with acute (type I) hypersensitivity (IgE) to a leptospira bacterin may be sustained for at least 4 yr (as determined by intradermal testing) even though the protective immune response (IgG) may only last a year.
56. *Is there a vaccination program that could be recommended for those owners only wanting the least number of vaccines possible or for those dogs that are not likely to be seen again by a veterinarian?*
    The vaccination protocol that includes the minimum number of vaccines yet still provides a reasonable opportunity to immunize the dog would be: a single dose of a combined infectious (attenuated, avirulent, modified live, recombinant viral vectored) CDV, MLV CPV-2, with MLV CAV-2, administered at 16 wk of age or older, plus a rabies vaccine at the same time (but inoculated at a separate site on the body).

Questions Related to Legal Issues

57. *How should communications between the veterinarian and client associated with vaccinations differ from communications associated with other medications?*
    The issues related to consent and client discussions relative to risk/benefit profiles do not differ in their essence between vaccines and other medications. That does not mean that every practitioner must have the same level of discussion with every client for every vaccine or other medication. Wherever there are meaningful risk/benefit considerations, it is strongly recommended to include the client in the decision making process.
58. *Is it necessary to explain the risks associated with every individual vaccine during each visit in which vaccinations are administered?*
    It is advisable to have an initial vaccine discussion about vaccines with the client that is documented and more thorough, followed by periodic and less extensive discussion at subsequent vaccination. If the practitioner believes that the risk/benefit profile for the various antigens administered in a visit is essentially the same, they could be discussed as a group. If an individual antigen was considered to carry a significantly different risk/benefit profile, then it could be addressed individually. At subsequent vaccination appointments, it is a good idea to briefly remind the client of the clinical approach taken to vaccination and ask if the client has any questions. Additionally, if over time there is a change in the perceived risk/benefit profile, then additional discussion with the client is indicated. Finally, practitioners must be in a position to know their clients and identify those that will benefit from more discussion.
59. *Can a veterinarian be held legally liable for withholding a core vaccine from a dog with immune mediated disease that later succumbs to one of the diseases prevented by the core vaccines?*
    The risk should be low if the client is involved in the process and the discussion is documented in the chart. For example, a note in the chart that: (1) a discussion was held with the client regarding the relative risks of exacerbating the patient's autoimmune disease or other adverse event versus the potential for disease/death if the patient contracts a disease for which vaccination has been foregone, (2) that the client chose not to vaccinate, and (3) that the client was given an opportunity to ask questions, would go a long way to reducing legal risk.
60. *What is a reasonable degree of documentation for risk/benefit discussions with clients concerning vaccination?*
    There is no one size fits all answer to this question. The Guidelines purposefully do not say "document consent in this manner …." Why? In large measure this is opinion. The current level of legal risk relative to small animal vaccination protocols is considered low. However, whenever claims are made against veterinarians, they often include allegations that appropriate consent was not obtained. Different people have different levels of risk tolerance. One veterinarian may be very satisfied with making a note in the chart that the risks and benefits of vaccination were discussed with the opportunity for questions and/or providing a client handout. Others may not be comfortable with anything less than obtaining a client's written consent. However, given the current risk level, the recommendation is to focus on client communication with a level of documentation that does not disrupt the practice. It is also recommended that practitioners consider use of a specific client handout. If handouts are used, it is important to date or otherwise identify and archive them, such that the specific handout provided to a client can later be retrieved if necessary.

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Additional Reading

Guidelines such as these rarely have complete references and, when provided, they are limited to only a few specific references. For those wanting more general information on vaccines and vaccination and/or immunology and the immune response to vaccines, the authors suggest the following:

American Animal Hospital Association Canine Vaccine Task Force, 2003. Report of the AAHA canine vaccine task force: executive summary and 2003 canine vaccine guidelines, recommendations. *J Am Anim Hosp Assoc* 2003;39:119–131.

American Animal Hospital Association Canine Vaccine Task Force, 2006. Report of the AAHA canine vaccine task force: executive summary and 2006 canine vaccine guidelines, recommendations. *J Am Anim Hosp Assoc* 2006;42(2):80–9.

Day MJ. *Clinical Immunology of the Dog and Cat*. 2nd Ed. London, UK: Manson Publishing/The Veterinary Press; 2008.

Day MJ, Schultz RD. *Veterinary Immunology, Principles and Practice*. London, UK: Mason Publishing/The Veterinary Press; 2011.

Greene CE. *Infectious Diseases of the Dog and Cat*. 3rd Ed. St Louis, MO: Saunders/Elsevier; 2006.

Maclachlan J, Dubovi E, eds. *Fenner's Veterinary Virology*. San Diego, CA: Elsevier, Academic Press; 2011.

Miller L, Zaurstowski S (Editors), 2004. Shelter Medicine for Veterinarians and Staff. Ames, IA: Blackwell.

Miller L, Hurley K, eds. *Infectious Disease Management in Animal Shelters*. Hoboken, NJ: Wiley-Blackwell; 2009.

Pastoret PP, Blancou J, Vannier P, Verschueren C, eds. *Veterinary Vaccinology*. Amsterdam: Elsevier; 1997.

Schultz RD, ed. *Veterinary Vaccines and Diagnostics: Advances in Veterinary Medicine*. Vol 41. San Diego, CA: Elsevier, Academic Press; 1999.

Tizard IR. *Veterinary Immunology*. 8th Ed. St Louis, MO: Saunders/Elsevier; 2009.

FOOTNOTES

[a] Any relevant state law (e.g., for rabies administration) should be followed. It is also possible for vaccines, such as those used in official USDA disease eradication programs or to combat foreign diseases, to carry specific labeled restrictions on their use. Veterinarians should adhere to any such restrictions.

[b] The authors thank Douglas C. Jack, Solicitor, for providing the Canadian perspective included in this section of the Guidelines.

[c] It does not appear that CVB has taken an enforcement action against a small animal veterinarian relative to their exercise of professional judgment in the discretionary use of a vaccine for at least 30 years. It is believed they have never done so. The most likely reason for any such action would be a significant safety issue.

[d] *See* 811 IAC 12.2(169) (IA—a board rule titled "extra-label use of veterinary drugs and immunization products" specifies one of the requirements for extra-label use as: "For drugs used in animals not intended for food, there are no marketed drugs and immunization products specifically labeled for the conditions diagnosed; or in the veterinarian's clinical judgment the labeled dosage is inappropriate for the condition or the extra-label use should result in a better outcome for the patient."); Ala Admin Code r. 420-4-.02 & .07 (AL—rabies control program defines "extra label use of vaccine" as "use of an animal vaccine in a species that is not specified on the product label or product insert.")

[e] For example, Colorado is a state that provides a mechanism for waivers for rabies vaccination. *See* C.R.S. 25-4-607 (provides that with the consent of the owner, a veterinarian may issue a written waiver for rabies vaccination when following the rules of the local health department if the rabies vaccination is contraindicated due to the health of the animal.)

[f] The duty arises out of the veterinary–client–patient relationship and is typically stated as the duty to exercise reasonable care, i.e., the same level of care and competence as a reasonably prudent practitioner would, 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 and does not necessarily equate with professional practices or standards. With few exceptions, establishment of the relevant standard of care and whether a practitioner deviated from it must be established by competent expert testimony.
In practice, many medical negligence cases become a battle of experts. The plaintiff uses an expert witness to establish a standard of care and then presents the opinion that the practitioner failed to meet the standard and that such failure caused the plaintiff's injury or damages. In turn, the defense offers differing expert testimony, establishing a different standard of care, and attests that the defendant practitioner 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 arrives at a verdict on the basis of innumerable variables, including the qualifications and presentation of the various experts and the defendant.

[g] For example, Louisiana, Missouri, and Pennsylvania have administrative regulations covering this area. *See* LAC 46: LXXXV.1039 (Louisiana—must obtain written consent before general anesthesia, except in emergency); 20 CSR 2270-6.011(19) (Missouri—must obtain written informed consent before anesthesia or surgical procedure, except in emergency); and 49 Pa. Code § 31.22 (Pennsylvania—client communications relative to consent for recommended diagnostic tests, treatments, and drugs must be documented in patient record).

[h] There are two primary standards by which informed consent cases involving physicians have been evaluated, with a fairly even division between those states that use a practitioner-focused inquiry and those that use a patient-focused inquiry. In some states the standard is set by the courts and in others it is set by statute. Such statutes may or may not apply to veterinarians. In those states that would allow an informed consent case against a veterinarian to proceed, it is likely they would look to the standard used in physician cases as instructive. Under the practitioner-focused standard, the inquiry focuses on 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-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 what information a reasonable person would need to make informed, rational decisions. Regardless of which standard is used, the other elements of a negligence case, including the causal connection, must be established for a plaintiff to prevail.

[i] In Canada, it is now generally accepted that as long as the veterinary practitioner obtains the informed consent of the client to either proceed or not proceed with a particular use or nonuse of a vaccine, having explained all of the material and probable risks, then such conduct would not constitute malpractice, unless, of course, the generally accepted standard of practice was compromised by so doing.

[j] *See Lawrence v. Big Creek Veterinary Hosp., L.L.C.,* 2007 Ohio 4627 (Ohio Ct. App., Geauga County Sept. 7, 2007) ("The informed consent doctrine is not codified in Ohio. However, such practice is clearly indicative of the veterinarian's duty of care. This is an evidentiary issue that goes directly to the standard of care in a malpractice case. Finally, we note that experts should also be able

to testify regarding this standard, as it goes to the central issue of compliance with professional conduct. Informed consent is part of and necessary to a veterinarian's duty of care."); *Ullmann v. Duffus,* 2005 Ohio 6060, P27 (Ohio Ct. App., Franklin County Nov. 15, 2005). (Court found no Ohio precedent for an informed consent action against a veterinarian but did not resolve the question as the plaintiff's failure to present expert testimony was fatal to an informed consent claim under practitioner-focused standard.); *Zimmerman v. Robertson*, 259 Mont. 105 (Montana 1993) (Court did not address substantive application of informed consent claims to veterinarians holding that plaintiff had not raised the issue on a timely basis); *Emes Stable v. University of Pennsylvania*, 1988 U.S. Dist. LEXIS 2972 (E.D. Pa. Apr. 4, 1988) (The question of whether veterinarians obtained informed consent for operation was submitted to jury. It is not clear if this was contested by the defendants); *Ladnier v. Norwood*, 781 F.2d 490 (5th Cir. La. 1986). (Applied practitioner-focused standard to find veterinarian met duty to warn); *Hull v. Tate*, 1974 Okla. LEXIS 423 (Oklahoma 1974). (Court applied practitioner-focused standard to find no duty to warn of remote risk of anaphylaxis from drug injection); *Hoffa v. Bimes*, 2008 PA Super 181 (Pennsylvania Super. Ct. 2008) (Under facts of the case, the Veterinary Immunity Act dispensed with need to obtain informed consent before emergency care).

[k] *See* LAC 46:LXXXV.1039 (Louisiana—Required written anesthesia consent form must indicate that the client has been advised as to the nature of the procedures and the risks involved in performing anesthesia); Minn. R. 9100.0800 (Minnesota—client must be informed of the treatment choices and reasonable medical or surgical alternatives); Miss. Code Ann. § 73-39-53 (Mississippi—practice act uses patient/client–focused standard to define informed consent to require informing client, "in a manner that would be understood by a reasonable person, of the diagnostic and treatment options, risk assessment and prognosis…."); 20 CSR 2270-6.011(19) (Missouri—must obtain written informed consent before anesthesia or surgical procedure, except in emergency); NAC 638.0175 (Nevada—a required element for establishment of a veterinarian–client–patient relationship is obtaining informed consent before medical treatment.); American Association of Veterinary State Boards, *Veterinary Medicine and Veterinary Technology Practice Act Model with Comments*, Comments to Section 107(y), available at http://www.aavsb.org/PAM/ (recommends incorporation by board rule of requirement to obtain informed consent into code of conduct or standards of practice).

[l] If client handouts are used in connection with a note in the chart that the handout was discussed and provided to the client, the handout should be dated and archived so that if ever necessary, a copy of the specific handout provided to the client can be retrieved.

[m] The online version of this article (available at www.jaaha.org) contains supplementary data in the form of two forms.

[n] Esbilac, PetAg, Hampshire, IL

REFERENCES

1. Greene CE, Schultz RD. Immunoprophylaxis and immunotherapy. In: Greene CE, ed. *Infectious Diseases of the Dog and Cat*. 3rd ed. Philadelphia: WB Saunders; 2006:1069–119.
2. Pardo MC, Bauman JE, Mackowiak M. Protection of dogs against canine distemper by vaccination with a canarypox virus recombinant expressing canine distemper virus fusion and hemagglutinin glycoproteins. *Am J Vet Res* 1997;58(8):833–6.
3. Horzinek MC, Schijns VEC, Denis M, et al. General description of vaccines. In: Pastoret PP, Blancou I, Vannier P, et al, eds. *Veterinary Vaccinology*. Amsterdam: Elsevier; 1997:131–52.
4. Roth JA, Henderson LM. New technology for improved vaccine safety and efficacy. *Vet Clin North Am Food Anim Pract* 2001;17(3):585–97, vii.
5. Edelman R. 2000. Vaccine adjuvants: Preparation methods and research protocols. In: O'Hagan DT (ed). Clifton, NJ: Humana Press; 2000:1–28.
6. Spickler AR, Roth JA. Adjuvants in veterinary vaccines: Modes of action and adverse effects. *J Vet Intern Med* 2003;17(3):273–81.
7. Roth JA. Mechanistic bases for adverse vaccine reactions and vaccine failures. In: Schultz RD, ed. *Advances in Veterinary Medicine 41: Veterinary Vaccines and Diagnostics*. San Diego: Academic Press; 1999:681–700.
8. Dodds WJ. More bumps on the vaccine road. In: Schultz RD, ed. *Advances in Veterinary Medicine 41: Veterinary Vaccines and Diagnostics*. Vol 41. San Diego: Academic Press; 1999:715–32.
9. Hogenesch H, Azcona-Olivera J, Scott-Moncrieff C, et al. Vaccine-induced autoimmunity in the dog. In: Schultz RD, ed. *Advances in Veterinary Medicine 41: Veterinary Vaccines and Diagnostics*. Vol 41. San Diego: Academic Press; 1999:733–44.
10. Greene CE, Schultz RD, Ford RB. Canine vaccination. *Vet Clin North Am Small Anim Pract* 2001;31(3):473–92, v–vi.
11. Ford RB and Schultz RD. Vaccines and vaccination programs for the 21st century. In: Bonagura JD, ed. *Kirk's Current Veterinary Therapy XIII*. Philadephia: WB Saunders CO; 2000:250–3.
12. Frana TS, Elsken LA, Karli SA. Summary of adverse event reports for veterinary biologic products received by the USDA from 1999 through 2005. *J Am Vet Med Assoc* 2006;229(7):1100–2.
13. Frana TS, Clough NE, Gatewood DM, et al. Postmarketing surveillance of rabies vaccines for dogs to evaluate safety and efficacy. *J Am Vet Med Assoc* 2008;232(7):1000–2.
14. Schultz RD. Considerations in designing effective and safe vaccination programs for dogs. In: Carmichael, LE, ed. *Recent Advances in Canine Infectious Diseases. International Veterinary Information Service*. 2000. Available at: http://www.ivis.org/. Accessed August 2011.
15. Martinod S. In: Pastoret PP, et al. In: Pastoret P, Blancou J, Vannier P, Verschueren C, eds. *Adverse Effects of Vaccination in Veterinary Vaccinology*. Amsterdam: Elsevier; 1997:574–80.
16. Meyer EK. Vaccine-associated adverse events. *Vet Clin N Am. Small Anim Prac.* 2001;31:493–514.
17. Phillips TR, Jensen JL, Rubino MJ, et al. Effects of vaccines on the canine immune system. *Can J Vet Res* 1989;53(2):154–60.
18. Moore GE, Frana TS, Guptill LF, et al. Postmarketing surveillance for dog and cat vaccines: new resources in changing times. *J Am Vet Med Assoc* 2005a;227(7):1066–9.
19. Carmichael LE. Vaccines for dogs. In: Pastoret P, Blancou J, Vannier P, Verschueren C, eds. *Veterinary Vaccinology*. Amsterdam: Elsevier; 1997:326–35.
20. Carmichael LE. Canine viral vaccines at a turning point—a personal perspective. In: Schultz RD, ed. *Advances in Veterinary Medicine 41: Veterinary Vaccines and Diagnostics*. San Diego: Academic Press; 1999:289–307.
21. Schultz RD, Appel MJ, Carmichael LE. Canine vaccines and immunity. In: Kirk RW, ed. *Current Veterinary Therapy VI*. Philadelphia: WB Saunders Co; 1977:1271–5.
22. Schultz RD. Theory and practice of immunization. In: Kirk RW, ed. *Current 285 Veterinary Therapy VII*. Philadelphia: W.B. Saunders Co.; 1980:1248–51.

23. Schultz RD, Scott FW. Canine and feline immunization. *Vet Clin North Am* 1978;8(4):755–68.
24. Schultz R. Current and future canine and feline vaccination programs. *Vet Med* 1998;93:233–54.
25. Schultz RD, Conklin S. The immune system and vaccines. *Compend Contin Educ Pract Vet* 1998;20:5–18.
26. Day MJ, Horzinek MC, Schultz RD; Vaccination Guidelines Group. WSAVA guidelines for the vaccination of dogs and cats. *J Small Anim Pract* 2010;51(6):1–32.
27. Eschner A. Guide for dogs who are late in receiving their regularly scheduled Lyme vaccination. *Technical Service Bulletin*. Duluth, GA: Merial Limited; 2008.
28. Lehar C, Jayappa H, Erskine J, et al. Demonstration of 1-year duration of immunity for attenuated *Bordetella bronchiseptica* vaccines in dogs. *Vet Ther* 2008;9(4):257–62.
29. Jacobs AA, Theelen RP, Jaspers R, et al. Protection of dogs for 13 months against *Bordetella bronchiseptica* and canine parainfluenza virus with a modified live vaccine. *Vet Rec* 2005;157(1):19–23.
30. Appel M. Canine distemper virus. In: Appel M, ed. *Virus Infections of Carnivore*. NY: Elsevier; 1987:133–59.
31. Appel MJ. Forty years of canine vaccination. In: Schultz RD, ed. *Advances in Veterinary Medicine 41: Veterinary Vaccines and Diagnostics*. Vol 41. San Diego: Academic Press; 1999:309–24.
32. Day MJ, Horzinek MC, Schultz RD; Vaccination Guidelines Group (VGG) of the World Small Animal Veterinary Association (WSAVA); Compiled by the Vaccination Guidelines Group (VGG) of the World Small Animal Veterinary Association (WSAVA). Guidelines for the vaccination of dogs and cats. *J Small Anim Pract* 2007;48(9):528–41.
33. Povey RC, Carman PS. In: Pastoret PP, et al. Pastoret P, Blancou J, Vannier P, Verschueren C, eds. *Technical Basis of Vaccination in Veterinary Vaccinology*. Amsterdam: Elsevier; 1997:519–34
34. Chappuis G. Control of canine distemper. *Vet Microbiol* 1995;44 (2-4):351–8.
35. Audonnet J-C, Minke J, Poulet H. Veterinary applications of the canarypox vaccine vector technology–recent developments for vaccines in domestic mammalian species. In: Moingeon P, ed. *Vaccines: Frontiers in Design and Development. Wymondham*. Norfolk, UK: Horizon Bioscience; 2005:133–40.
36. Pastoret PP, Vanderplasschen A. Poxviruses as vaccine vectors. *Comp Immunol Microbiol Infect Dis* 2003;26(5-6):343–55.
37. Hageny TL, Haase CJ, Larson LJ, et al. A comparison between recombinant, naked DNA and modified live canine distemper virus (CDV) vaccines. Dept Pathobiological Sciences, UW Madison School of Vet Med, Madison, WI. Poster Presentation abstract 65: Conference of Workers in Animal Disease, November 13–16, 2004. Chicago, IL.
38. Larson L, Schultz RD. Effect of vaccination with rCDV vaccine immediately before exposure under shelter-like conditions. *Vet Ther* 2006;7(2):113–8.
39. Larson LJ, Quesada M, et al. Evaluation of a CPV-2 fecal parvovirus ELISA (SNAP fecal parvo test) from IDEXX laboratories. Poster 113. In: *Proceedings of Conference of Research Workers in Animal Disease*. Chicago, IL; Dec 2–4, 2007.
40. Larson LJ, Schultz RD. Do two current canine parvovirus type 2 and 2b vaccines provide protection against the new type 2c variant? *Vet Ther* 2008;9(2):94–101.
41. Hong C, Decaro N, Desario C, et al. Occurrence of canine parvovirus type 2c in the United States. *J Vet Diagn Invest* 2007;19(5):535–9.
42. Schultz R., Larson L.. Current canine parvovirus type 2 (CPV-2) vaccines provide excellent immunity to all genotypes of CPV-2 (eg CPV-2a, 2b, and 2c). Presented at Conference for Research Workers in Animal Diseases. Dec 7–9, 2008. Chicago, IL.
43. Schultz RD, Thiel B, Mukhtar E, et al. Age and long-term protective immunity in dogs and cats. *J Comp Pathol* 2010;142(Suppl 1):S102–8.
44. Spibey N, Greenwood NM, Sutton D, et al. Canine parvovirus type 2 vaccine protects against virulent challenge with type 2c virus. *Vet Microbiol* 2008;128(1-2):48–55.
45. Schultz RD, Appel MJ, Carmichael LE. Canine vaccines and immunity. In: Kirk RW, ed. *Current Veterinary Therapy VI*. Philadelphia: WB Saunders Co.; 1977:1271–5.
46. Larson LJ, Hageny TL, Haase CJ, et al. Effect of recombinant canine distemper vaccine on antibody titers in previously vaccinated dogs. *Vet Ther* 2006;7(2):107–12.
47. Pardo MC, Tanner P, Bauman J, et al. Immunization of puppies in the presence of maternally derived antibodies against canine distemper virus. *J Comp Pathol* 2007;137(Suppl 1):S72–5.
48. Reed TL, von Messling V, et al. A comparative study of canine distemper vaccines. Poster 87. In: *Proceedings of Conference of Research Workers in Animal Disease*, Dec 9–11, 2003.
49. Schultz RD, Appel MJ, Carmichael LE. Update on canine immunizations. In: Kirk RW, ed. *Canine Veterinary Therapy VII*. Philadelphia: WB Saunders Co.; 1980:1252–5.
50. Shroeder JP, Bordt DW, et al. Studies of canine distemper immunization of puppies in a canine distemper-contaminated environment. *Vet Med/Small Anim Clin*. 1967;62(8):782–7.
51. Larson LJ, Newbury S, Schultz RD. Canine and feline vaccinations and immunology. In: Miller L, Hurley KF, eds. *Infectious Disease Management in Animal Shelters*. Ames, Iowa: Wiley-Blackwell; 2009:61–82.
52. Larson LJ, Sawchuck S, Schultz RD. 2002. Duration of vaccinal immunity in a population of clinic dogs [abstract 75P]. In: *Proceedings 83rd Meeting, Conference Research Workers in Animal Disease*. Nov 10–12, 2002. St. Louis, MO.
53. Larson LJ and Schultz RD. Current canine parvovirus type 2 (CPV-2) vaccines provide excellent immunity to genotypes of CPV-2 (eg CPV-2, 2a, 2b, 2c). *Conference of Research Workers in Animal Disease*. Chicago IL: Dec 2–4, 2007.
54. Schultz RD. Duration of immunity for canine and feline vaccines: a review. *Vet Microbiol* 2006;117(1):75–9.
55. Gill M, Srinivas J, Morozov I, et al. Three-year duration of immunity for canine distemper, adenovirus, and parvovirus after vaccination with a multivalent canine vaccine. *J Appl Res Vet Med* 2004; 2(4):227–34.
56. Larson LJ, Schultz RD. Three-year duration of immunity in dogs vaccinated with a canarypox-vectored recombinant canine distemper virus vaccine. *Vet Ther* 2007a;8(2):101–6.
57. Larson LJ, Schultz RD. Three-year serologic immunity against canine parvovirus type 2 and canine adenovirus type 2 in dogs vaccinated with a canine combination vaccine. *Vet Ther* 2007b; 8(4):305–10.
58. Mansfield PD. Vaccination of dogs and cats in veterinary teaching hospitals in North America. *J Am Vet Med Assoc* 1996;208(8):1242–7.
59. Mouzin DE, Lorenzen MJ, Haworth JD, et al. Duration of serologic response to five viral antigens in dogs. *J Am Vet Med Assoc* 2004; 224(1):55–60.
60. Olson P, Klingeborn B, Hedhammar A. Serum antibody response to canine parvovirus, canine adenovirus-1, and canine distemper virus

in dogs with known status of immunization: study of dogs in Sweden. *Am J Vet Res* 1988;49(9):1460–6.

61. Olson P, Finnsdóttir H, Klingeborn B, et al. Duration of antibodies elicited by canine distemper virus vaccinations in dogs. *Vet Rec* 1997; 141(25):654–5.
62. Phillips TR, Schultz RD. Canine and feline vaccines. In: Kirk RW, Bonagura JD, eds. *Current Veterinary Therapy XI*. Philadelphia: W.B. Saunders Co.; 1992:202–6.
63. Prydie J. Persistence of antibodies following vaccination against canine distemper and the effect of re-vaccination. *Vet Rec* 1966; 78(14):486–8.
64. Rikula U, Nuotio L, Sihvonen. Canine distemper virus neutralizing antibodies in vaccinated dogs. *Vet Rec*. 2000;147:598–603.
65. Schultz R and Scott F. Canine and Feline Immunization. *Vet Clin N Am* 1978;8(4):755–8.
66. Twark L, Dodds WJ. Clinical use of serum parvovirus and distemper virus antibody titers for determining revaccination strategies in healthy dogs. *J Am Vet Med Assoc* 2000;217(7):1021–4.
67. Schultz RD, Ford RB, Olsen J, et al. Titer testing and vaccination: a new look at traditional practices. *Vet Med* 2002;97(2):1–13.
68. Guo Y, German T, Schultz RD. Canine parvovirus (CPV-2) antigen expression in plants. *Conference of Research Workers in Animal Disease*. St. Louis, MO: Nov 11–13, 2001.
69. Abdelmagid OY, Larson L, Payne L, et al. Evaluation of the efficacy and duration of immunity of a canine combination vaccine against virulent parvovirus, infectious canine hepatitis virus, and distemper virus experimental challenges. *Vet Ther* 2004;5(3):173–86.
70. Aubert MF. Practical significance of rabies antibodies in cats and dogs. *Rev Sci Tech* 1992;11(3):735–60.
71. Cliquet F, Aubert M, Sagné L. Development of a fluorescent antibody virus neutralisation test (FAVN test) for the quantitation of rabies-neutralising antibody. *J Immunol Methods* 1998;212(1):79–87.
72. Cliquet F, Verdier Y, Sagné L, et al. Neutralising antibody titration in 25,000 sera of dogs and cats vaccinated against rabies in France, in the framework of the new regulations that offer an alternative to quarantine. *Rev Sci Tech* 2003;22(3):857–66.
73. Moore GE, Guptill LF, Ward MP, et al. Adverse events diagnosed within three days of vaccine administration in dogs. *J Am Vet Med Assoc* 2005b;227(7):1102–8.
74. Newbury S, Larson LJ, Schultz RD. Canine Distemper Virus. In: Miller L, Hurley KF, eds. *Infectious Disease Management in Animal Shelters*. Ames, IA: Wileyand Blackwell; 2009:161–73.
75. Ford RB. Canine infectious tracheobronchitis. In: Greene CE, ed. *Infectious Diseases of the Dog and Cat*. 3rd ed. Philadelphia: WB Saunders Co.; 2006:54–61.
76. Ford RB. *Bordetella bronchiseptica*: beyond "kennel cough." In: Bonagura J, Twedt DC, eds. *Kirk's Current Veterinary Therapy XIV*. St. Louis: Saunders-Elsevier, 2009;647–50.
77. Gore T, Headley M, Laris R, et al. Intranasal kennel cough vaccine protecting dogs from experimental *Bordetella bronchiseptica* challenge within 72 hours. *Vet Rec* 2005;156(15):482–3.
78. Deshpande MS, Jirjis FF, Tubbs AL, et al. Evaluation of the efficacy of a canine influenza virus (H3N8) vaccine in dogs following experimental challenge. *Vet Ther* 2009;10(3):103–12.
79. Crawford C, Spindel M. Canine influenza. In: Miller L, Hurley K, eds. *Infectious Disease Management in Animal Shelters*. Hoboken, NJ: Wiley-Blackwell; 2009:173–80.
80. Davis R, Jayappa H, Abdelmagid OY, et al. Comparison of the mucosal immune response in dogs vaccinated with either an intranasal avirulent live culture or a subcutaneous antigen extract vaccine of Bordetella bronchiseptica. *Vet Ther* 2007;8(1):32–40.
81. Ford RB. Vaccination strategies in the shelter environment. In: Miller L, Zawistowski S, eds. *Shelter Medicine for Veterinarians and Staff*. Ames, IA: Blackwell; 2004:285–304.
82. Jacobs AA, Bergman JG, Theelen RP, et al. Compatibility of a bivalent modified-live vaccine against Bordetella bronchiseptica and CPiV, and a trivalent modified-live vaccine against CPV, CDV and CAV-2. *Vet Rec* 2007;160(2):41–5.

Adverse Event Report

Pharmacovigilance
United States Department of Agriculture
Center for Veterinary Biologics
1920 Dayton Avenue
Ames, IA 50010
Phone: (515)337-6100 FAX: (515)337-6120

*Required Fields

Product information

List ALL immunobiological products used.

*Brand Name or Generic Name	*U.S. Vet. License (ESt. No.) or Manufacturer Name	Serial (lot) Number	Type of Product[1]
1			
2			
3			
4			

1. Type of Product (select one for each product) = Viral, Bacterial, Combination, Antibody, Coccidia, Immunomodulator, Protozoa, Recombinant, Rickettsia, Other, or Do Not Know.

Administration of products

Dose	Route	Site	Needle Size	Date Reconstituted
1				
2				
3				
4				
Administered by:[2]			*Date of Product Use (MM/DD/YYYY):	
Concurrent Drugs or Procedures:				

2. Administered by (select one) = Veterinarian or Veterinary staff or Nonveterinarian

Event Information

*Event description:[3]
Explain the event description and treatment in a concise paragraph:

3. Event description (select one) = Anaphylaxis-hypersensitivity, autoimmune, birth defect, lack of expected efficacy, local, neoplasia, reproductive, systemic, other

Onset (How long after product use did the event begin?) : (Specify whether units are in mins,hrs, days, wks, mos, yrs)

Attending veterinarian's level of suspicion that product caused event: High Medium Low Not Listed	*Outcome: (Select One) Recovered without treatment Recovered with treatment Did not recover Died Other

Animal Information

Case identification number:		
*Species[4]	Breed:	Age (i.e., 2 yrs or 2 mos):
Sex: (male, female , not listed) Neutered: (yes, no, not listed)	For animals handled in a group (herd, litter, etc) Number in group: _____ Number affected:_____ Number vaccinated:_____ Number dead: _____	

4. Species (Select One) = Porcine, Bovine, Canine, Feline, Ferret, Ovine, Caprine, Equine, Exotic, Fish, Poultry, or Other

History and Enviroment (e.g., acquisition, vaccination, and medical histories; housing, diet, contacts, etc)

Personal Information

Veterinarian	Owner
*Name:	Name:
Address:	Address:
City: State Zip:	City: State: Zip:
*Phone: FAX: E-mail:	Phone: E-mail:

Submitter's information

This event has been reported to the manufacturer(s): (Select one) = yes or no	
*Submitter's first name:	*Submitter's last name:
*Submitter's phone number:	* Today's Date:
Relationship to animal:[5]	

5. Relationship to animal (select one) = veterinarian, owner, other, not listed)

For internal use:

Product Code	Other comment(s):
1.	
2.	
3.	
4.	

Canadian Food Inspection Agency | Agence canadienne d'inspection des aliments

File No. / N° de dossier

NOTIFICATION OF SUSPECTED ADVERSE EVENTS TO VETERINARY BIOLOGICS

DÉCLARATION DES ÉVÈNEMENTS INDÉSIRABLES SOUPÇONNÉS À L'ÉGARD DES PRODUITS BIOLOGIQUES VÉTÉRINAIRES

Mail notification to:
Canadian Centre for Veterinary Biologics
59 Camelot Drive
Ottawa, Ontario K1A 0Y9
Tel: 613-773-7408 Fax: 613-773-7570

Envoyer la déclaration à :
Centre canadien des produits biologiques vétérinaires
59, promenade Camelot
Ottawa (Ontario) K1A 0Y9
Tél.: 613-773-7408 Téléc.: 613-773-7570

Product Information / Information sur le produit

Assigned and Trade name of product Nom commercial et attribué au produit	Manufacturer / Fabricant	Serial number Numéro de série	Expiration date Date de péremption

Owner's name, description of animal Nom du propriétaire, description de l'animal	Clinic, address and tel. No. and name of attending veterinarian Clinique, adresse et n° de tél. et nom du vétérinaire traitant

History and Symptoms / Anamnèse et symptomatologie

Veterinarian Submitting Reports / Vétérinaire présentant le rapport

Signature _____ Date _____

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CFIA / ACIA 2205 (2011/02)

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