2022 AAHA Canine Vaccination Guidelines (2024 Update)

John Ellis, DVM, PhD, DACVP, DACVM[†], Elizabeth Marziani, DVM[†],
Chumkee Aziz, DVM, DABVP (Shelter Medicine Practice), Catherine M. Brown, DVM, MSc, MPH,
Leah A. Cohn, DVM, PhD, DACVIM, Christopher Lea, DVM, DABVP (Canine and Feline Practice),
George E. Moore, DVM, PhD, DACVIM, DACVPM, Neha Taneja, MBA, MSHCM, LVT

— **ABSTRACT** —

Vaccination is a cornerstone of canine preventive healthcare and one of the most cost-effective ways of maintaining a dog's health, longevity, and quality of life. Canine vaccination also serves a public health function by forming a barrier against several zoonotic diseases affecting dogs and humans. Canine vaccines are broadly categorized as containing core and noncore immunizing antigens, with administration recommendations based on assessment of individual patient risk factors. The guidelines include a comprehensive table listing canine core and noncore vaccines and a recommended vaccination and revaccination schedule for each vaccine. The guidelines explain the relevance of different vaccine formulations, including those containing modified-live virus, inactivated, and recombinant immunizing agents. Factors that potentially affect vaccine efficacy are addressed, including the patient's prevaccination immune status and vaccine duration of immunity. Because animal shelters are one of the most challenging environments for prevention and control of infectious diseases, the guidelines also provide recommendations for vaccination of dogs presented at or housed in animal shelters, including the appropriate response to an infectious disease outbreak in the shelter setting. The guidelines explain how practitioners can interpret a patient's serological status, including maternally derived antibody titers, as indicators of immune status and suitability for vaccination. Other topics covered include factors associated with postvaccination adverse events, vaccine storage and handling to preserve product efficacy, interpreting product labeling to ensure proper vaccine use, and using client education and healthcare team training to raise awareness of the importance of vaccinations. (*J Am Anim Hosp Assoc* 2024; 60:■■■–■■■. DOI 10.5326/JAAHA-MS-7468)

AFFILIATIONS

University of Saskatchewan, Department of Veterinary Microbiology, Saskatoon, Saskatchewan (J.E.); Hillside Animal Hospital, St. Louis, Missouri (E.M.); Massachusetts Department of Public Health, Boston, Massachusetts (C.M.B.); Association of Shelter Veterinarians, Houston, Texas (C.A.); University of Missouri, Columbia, Missouri (L.A.C.); Auburn University, Auburn, Alabama (C.L.); Purdue University, College of Veterinary Medicine, West Lafayette, Indiana (G.E.M.); A Paw Partnership, Veterinary Well-being Advocate, Centreville, Virginia (N.T.).

CONTRIBUTING REVIEWERS

Brett Sargent, DVM, DABVP (Front Range Veterinary Clinic, Lakewood, Colorado); Jason Stull, VMD, MPVM, PhD, DACVPM (The Ohio State University, College of Veterinary Medicine, Department of Veterinary Preventive Medicine, Columbus, Ohio)

Correspondence: guidelines@aaha.org

† J. Ellis and E. Marziani were cochairs of the AAHA Canine Vaccination Guidelines Task Force.

These guidelines include updates made in 2024.

These guidelines were prepared by a task force of experts convened by the American Animal Hospital Association. This document is intended as a guideline only, not an AAHA standard of care. 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 limitations unique to each individual practice setting. Evidence-based support for specific recommendations has been cited whenever possible and appropriate. Other recommendations are based on practical clinical experience and a consensus of expert opinion. Further research is needed to document some of these recommendations. Because each case is different, veterinarians must base their decisions on the best available scientific evidence in conjunction with their own knowledge and experience.

Bb (*Bordetella bronchiseptica*); CAV-1 (canine adenovirus type 1); CAV-2 (canine adenovirus type 2); CDV (canine distemper virus); CFIA (Canadian Food Inspection Agency); CIRD (canine infectious respiratory disease); CIV (canine influenza virus); CPIV (canine parainfluenza virus); CPV (canine parvovirus); CPV-2 (canine parvovirus type 2); DA2PP (distemper, canine adenovirus type 2, parvovirus, parainfluenza combination vaccine); DOI (duration of immunity); ELISA (enzyme-linked immunosorbent assay); HI (hemagglutination inhibition); IN (intranasal); MDA (maternally derived antibodies); MLV (modified-live virus); VN (virus neutralization); USDA (United States Department of Agriculture).

Introduction

Vaccination is an essential component of preventive pet healthcare and an important pathway to nurturing a long-term veterinarian-client-patient relationship. Universal, routine vaccination for high-morbidity or high-mortality diseases such as canine distemper, canine parvovirus enteritis, and rabies is necessary for individual health and to maintain herd immunity to these infections, thereby reducing the risk for disease spread and outbreaks. Recognizing that there is hesitancy and skepticism in the human population to vaccination, client education can play a key role in helping pet owners understand that vaccination is a safe, effective, and necessary part of their pet's healthcare plan and that it acts as a barrier to zoonotic diseases that can affect client households. All members of the veterinary healthcare team should be able to communicate a consistent, unified message to clients about the importance of immunization against preventable infectious diseases. Protocols for baseline and individualized vaccination plans are useful tools not only for implementing vaccination practices but also for client education.

These guidelines include updated vaccination recommendations and dosing schedules for canine vaccines licensed in the United States. These recommendations are presented in easy-to-reference tables, categorized by core and noncore vaccine antigens. Core vaccines are defined as those recommended for all dogs irrespective of lifestyle, e.g., rabies. Noncore vaccines are those recommended for some dogs based on their risk of exposure when factors such as lifestyle, geographic location, and endemic conditions are considered, e.g., Lyme disease (*Borrelia burgdorferi* infection). Because animal shelters represent one of the most challenging environments for the prevention of canine infectious disease, these guidelines include a detailed discussion of current recommendations for vaccination of shelter dogs—at presentation, as resident animals, or in case of a disease outbreak. A simplified approach to determining the role of patient serologic titers as indicators of the need for primary or repeat vaccination is also described.

Licensed canine vaccines have a high degree of proven safety and efficacy. For this reason, dogs that present with an incomplete or ambiguous vaccination or health history can still be vaccinated with the expectation of a protective immune response and a low risk of serious postvaccination adverse effects. Stated another way, veterinarians can assume that the benefits of vaccination far outweigh the risks in cases of dogs with unknown immune status or vaccination history—a common occurrence in veterinary practice. Examples of these real-world scenarios include the possibility of recent natural exposure, absence of serologic data to guide a vaccination decision, or suitability for noncore vaccines such as Lyme disease. Thanks to the reliability of the licensed vaccine armamentarium, a good rule of thumb is, "When in doubt, vaccinate."

Vaccine Overview and Types

Vaccines are one of the medical and public health successes of the 19th and 20th centuries. Their use has reduced morbidity and mortality more than any other intervention in human and veterinary medicine. Vaccination of companion animals protects the health of the individual animal, improves animal welfare in community settings (e.g., shelters), protects public health (e.g., rabies and leptospirosis), and reduces the occurrence of infectious diseases that transmit mainly within a species (e.g., canine variants of rabies virus, canine distemper, and canine parvovirus). Vaccines have mitigated the impact of infectious diseases on populations through herd immunity so successfully that some dog owners may hold the perception that vaccination is no longer necessary. Although individual dogs with low-risk lifestyles (i.e., minimal exposure to other animals) may benefit from herd immunity, unvaccinated individuals are still more vulnerable to infection, and reductions in population-level vaccination rates without eradication of the pathogen will inevitably result in a recurrence of disease at outbreak levels. This has been clearly demonstrated by recurrent canine distemper and parvovirus outbreaks in shelters, and by recent outbreaks of measles in human populations where reduced vaccine coverage exists.

Vaccine efficacy, assessed during product development, is measured as the proportionate reduction of disease in vaccinated groups compared with unvaccinated groups. Although necessary for the purposes of licensing, vaccine efficacy calculated under these controlled settings may not equate to the population impact of the vaccine in real-world settings. This impact, known as vaccine effectiveness, is more difficult to quantify, especially in veterinary medicine, which lacks the robust surveillance systems for monitoring the numbers of individuals vaccinated and disease cases. Vaccination failures, namely, the occurrence of disease in an animal that has received an appropriately administered vaccine against that disease, are rare but should be expected because no vaccine achieves 100% effectiveness. Vaccination failures can occur for many reasons including:

- Failure of the vaccinated patient to mount an adequate immune response.
- Exposure to the infection before being fully vaccinated.
- Interference of maternal antibodies.
- Improper storage or handling of the vaccine, including inappropriate administration.
- Waning immunity (e.g., immunosenescence, or age-related deterioration of the immune system).

- Vaccine manufacturing errors, such as lack of potency due to instability, expiration, or improper storage.

Vaccination failures should be promptly reported to the manufacturer. These reports are essential for detecting changes in product performance due to defects in particular lots of vaccine. In the United States, if a veterinarian is unable to report to the manufacturer, reports can be made directly to the United States Department of Agriculture (USDA) Center for Veterinary Biologics. More information and instructions on reporting are available online from the USDA at https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/adverse-event-reporting/ct_vb_adverse_event.

Although no vaccine produces complete immunity or protection, the term duration of immunity (DOI) is commonly used for the length of time a vaccine is expected to produce a robust immune response and protection against illness following exposure. DOI data, unlike vaccine efficacy (the reduction in disease in vaccinated animals compared with unvaccinated animals) data, are not required for licensure by the USDA. Exceptions to this include rabies vaccines and, recently, new vaccines for which no pre-existing products are available. Vaccine labels historically recommend booster doses every year. Increasingly, data are available from postlicensing studies demonstrating that the effect of many vaccines persists for extended periods. In some cases, DOI data have been submitted to the USDA to update vaccine labels. These data have also been considered in vaccine guidelines developed by various stakeholder groups. Because data also reveal differences in serologic titers following administration of different vaccine formulations for the same pathogen, extrapolation about efficacy and DOI between products may not always be appropriate.[1–11]

Table 1 lists the characteristics of the four general categories of canine vaccines based on the physical attributes of the vaccine immunizing antigen.

Recommendations for Core and Noncore Canine Vaccines

Based on existing data and Task Force expertise, the AAHA Canine Vaccination Task Force has separated vaccines into two categories, core and noncore. Core vaccines are those defined by the Task Force as vaccines recommended for all dogs irrespective of lifestyle, unless there is a specific medical reason not to vaccinate. Examples of core vaccines include canine distemper virus, canine adenovirus type 2, canine parvovirus type 2, leptospirosis and rabies. Noncore vaccines are those recommended for some dogs based on lifestyle, geographic location, and risk of exposure. Canine Bordetella vaccine, canine Lyme vaccine, canine influenza vaccine, and the Western diamond-back rattlesnake toxoid are considered noncore.

In 2023, the American College of Veterinary Internal Medicine (ACVIM) updated their consensus statement on leptospirosis with the recommendation that all dogs over 12 weeks of age, regardless of breed, geography, or lifestyle, should receive the leptospirosis vaccination annually. Rationale for this decision included the zoonotic nature of leptospirosis and the risk of significant illness and/or fatality even with treatment. In response to this decision, AAHA convened a committee composed of original task force members to review the updated recommendations and evidence. This task force unanimously determined that leptospirosis should be recategorized as a core vaccine, and these guidelines reflect this update.

Sykes JE, Francey T, Schuller S, Stoddard RA, Cowgill LD, Moore GE. Updated ACVIM consensus statement on leptospirosis in dogs. *J Vet Intern Med*. 2023;37(6): 1966–1982.

Table 2 lists core and noncore vaccines as determined by the Task Force and their dosing recommendations. The designation of a core vaccine was unanimously supported by all members of the Task Force, but there was not always consensus regarding noncore vaccines. Some members preferred to leave this decision up to the veterinarian. For regions where noncore pathogens are endemic, such as canine Lyme disease, these traditionally noncore vaccines may be considered a core vaccine by veterinary practices in those locations. As travel with pets becomes more popular and vector-borne diseases spread, patients should be carefully assessed at least annually to determine their vaccine requirements. These should be considered general rather than universally prescriptive recommendations. Veterinarians have the discretion to administer vaccines off-label when scientific data, local circumstances, or evolving standards of care support that decision. In those situations, informed consent from the client is still an important consideration.[12]

These guidelines have been revised from prior versions to provide consolidated and updated clinical information, allowing the veterinarian to select the best vaccines and protocols to fit individual patient needs. The guidelines are to be considered discretionary recommendations, and the Task Force emphasizes that practitioners should be aware of the importance of reviewing and following manufacturer's label instructions for specific vaccines, including instructions on proper mixing and use of diluents. Different types of vaccines for the same pathogen may induce different immunologic responses

TABLE 1

Categories of Canine Vaccines Based on Physical Type of Immunizing Antigen

TYPE	ALTERNATIVE NAMES	DESCRIPTION	EXAMPLES*
Attenuated	• Live • Modified live • Live attenuated	• Immunogenic with long duration of immunity; induces both cellular and humoral immunity • More likely to prevent both infection and disease • Certain vaccines may result in a transient period of viral shedding of the attenuated/modified virus • Reversion to virulence theoretically possible but unlikely in appropriately tested and licensed vaccines • Requires careful storage (usually refrigeration) and handling (administer promptly after reconstitution)	• Most canine distemper virus and parainfluenza virus vaccines • All canine parvovirus and adenovirus-2 vaccines

Inactivated	• Killed	• Stable products that cannot induce disease in the animals
		• Less immunogenic and with shorter duration of immunity than attenuated products
		• Generally require an adjuvant to induce sufficient immunity; may require more frequent administration
		• May be more associated with adverse reactions
		• May not protect against infection (instead protect against disease)
			• Canine rabies and influenza vaccines
			• Whole cell bacterin vaccines
			  • Some canine Lyme disease vaccines
			  • Some canine leptospirosis vaccines
			• Parenteral *Bordetella bronchiseptica* vaccine

Recombinant	• Subunit • Polysaccharide • Conjugate • Chimeric • Viral-vectored	• Uses a gene of the pathogen inserted into a virus or bacterial plasmid, or a single protein, alone or in combination with other antigens • Significant variability in this category in terms of immunogenicity and frequency of booster doses	• Canarypox virus-vectored canine distemper vaccine • Some canine Lyme disease vaccines • Plasmid-expressed or engineered antigens
Toxoid		• Creates immunity to the toxin produced by the organism rather than the organism itself • Generally the shortest duration of immunity of vaccine types	• Western diamondback rattlesnake (*Crotalus atrox*) toxoid vaccine

*A list of licensed veterinary biologics is available at www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/ct_vb_licensed_products.

depending on vaccine technology, formulation, route of administration, and patient factors.

Key Vaccination Considerations by Antigen

Canine Distemper Virus, Canine Adenovirus, and Canine Parvovirus

Canine Distemper Virus (CDV)

Canine distemper virus can infect many species including domestic dogs, wolves, coyotes, foxes, ferrets, skunks, and raccoons. Although relatively unstable in the environment, the wide host range and worldwide disease distribution allow for increased risk of virus exposure for free-roaming dogs.

CDV vaccines are considered core vaccines, recommended for all dogs regardless of geographical location. CDV vaccines contain modified-live virus (MLV), high-titer, low-passage (less attenuated) modified-live virus, or a (recombinant) canarypox vector with targeted CDV genes. The minimum age to begin the primary vaccination protocol in puppies is 6–8 wk. MLV vaccines can be blocked, however, by maternally derived antibodies (MDA) against CDV, which decline exponentially over time and are usually absent by 12–14 wk of age. Revaccination is therefore recommended at 2 to 4 wk intervals until greater than 16 wk old; 18–20 wk of age may be preferred particularly in areas of high CDV risk.

TABLE 2

2022 AAHA Core and Noncore Vaccines for Dogs[*†]

CORE VACCINES: Recommended for all dogs irrespective of lifestyle, unless there is a specific medical reason not to vaccinate.			
ANTIGEN	**INITIAL VACCINATION**		**REVACCINATION**
	Dogs ≤16 Weeks of Age	**Dogs >16 Weeks of Age**	
Distemper **Adenovirus** **Parvovirus** **+/- Parainfluenza**	At least 3 doses of a combination vaccine between 6 and 16 weeks, 2-4 weeks apart.	2 doses of a combination vaccine, 2-4 weeks apart.	• A single dose of a combination vaccine within 1 year following the last dose in the initial vaccination series. • Administer subsequent boosters at intervals of 3 years.
Leptospira (killed) 4-serovar	Two doses, 2-4 weeks apart, starting at 12 weeks of age.	Two doses, 2-4 weeks apart, regardless of dog's age.	• A single dose within 1 year following the last dose in the initial vaccination series. • Administer subsequent boosters annually.
Rabies	As required by law.		

NONCORE VACCINES: Recommended for some dogs based on lifestyle, geographic location, and risk of exposure.			
ANTIGEN	**INITIAL VACCINATION**		**REVACCINATION**
	Dogs ≤16 Weeks of Age	**Dogs >16 Weeks of Age**	
Borrelia burgdorferi (canine Lyme disease)	Two doses, 2-4 weeks apart.	Two doses, 2-4 weeks apart, regardless of dog's age.	• A single dose within 1 year following the last dose in the initial vaccination series. • Administer subsequent boosters annually.
Bordetella bronchiseptica & canine parainfluenza virus	A single (IN) dose is indicated for dogs at risk of exposure.		• Administer subsequent boosters annually.
Bordetella bronchiseptica only	Parenteral (SQ): Two doses, 2-4 weeks apart. IN: Administer a single dose intranasally. Oral: Administer a single dose into the buccal pouch.		• Administer subsequent boosters annually.
Canine influenza virus-H3N8/H3N2	Two doses, 2-4 weeks apart.		• A single dose within 1 year following the last dose in the initial vaccination series. • Administer subsequent boosters annually.
Crotalus atrox (Western diamondback rattlesnake)	Dosing requirements and frequency of administration vary among dogs depending on body weight and exposure risk.		

OVERDUE VACCINES AND UNKNOWN VACCINE HISTORY	
Core and Noncore Vaccines	The benefits of vaccination far outweigh the risks in cases of dogs with unknown immune status or vaccination history. In cases of overdue vaccinations, consult specific vaccine manufacturers for instructions. A good rule of thumb is: When in doubt, vaccinate.
Rabies	Follow local laws and consult the state veterinarian as needed.

IN, intranasal; SQ, subcutaneous.
*For dogs in shelter environments, see narrative for additional recommendations.
†Updated in 2024

After the primary puppy series of vaccinations, a booster should be administered within 1 yr. Thereafter, interval boosters every 3 yr are recommended; annual boosters are not necessary. Longer (>3 yr) duration of immunity after vaccination has been suggested[11] but is largely unsubstantiated in the peer-reviewed literature.

Detection of CDV antibodies after vaccination can be performed by hemagglutination inhibition (HI), virus neutralization (VN), or enzyme-linked immunosorbent assay (ELISA). (See the guidelines section on Utilization and Interpretation of Serologic Titers).

Canine Parvovirus (CPV)
Canine parvovirus type 2 (CPV-2) is the most common cause of viral enteritis in dogs. Three antigenic canine variants, CPV-2a, CPV-2b, and CPV-2c, have been identified, but they are 99% genetically similar.[12]

Domestic and wild canids are susceptible to CPV-2, but risk of infection is most likely from virus particles shed by other domestic dogs. The virus is relatively stable in the environment. CPV is transmitted by oronasal exposure, but CPV MLV vaccines are currently registered for parenteral administration and are generally highly effective once maternal antibody concentrations fall below inhibitory levels.

CPV MLV vaccines are considered core vaccines, recommended for all dogs regardless of geographical location, and are currently considered protective against the three known variants.[13] The minimum age to begin the primary vaccination protocol in puppies is 6–8 wk. However, MLV vaccines can be blocked by MDA against CPV, which decline exponentially over time and may persist for 13–15 wk or possibly longer.[2,14] Revaccination is therefore recommended at 2 to 4 wk intervals until greater than 16 wk old; 18–20 wk old is preferred particularly in areas of high CPV risk.

In spite of the core vaccination recommendation for CPV, CPV diagnoses in young dogs (<1 yr old) continue owing to a lack of protective antibodies, particularly in dogs presenting to animal shelters.[15] Although host-related factors may play a role, failure to complete primary vaccine schedules or vaccine storage or administration errors may account for many or most "vaccine failures."[16,17]

After the primary puppy series of vaccinations, a booster should be administered within 1 yr. Thereafter, interval boosters every 3 yr are recommended; annual boosters are not necessary. Longer (>3 yr) duration of immunity after vaccination has been suggested[11] but is largely unsubstantiated in the peer-reviewed literature.

Detection of CPV antibodies after vaccination can be performed by HI, VN, or ELISA diagnostic tests. (See section on Utilization and Interpretation of Serologic Titers.)

Canine Adenovirus (CAV)
Canine adenovirus type 2 (CAV-2) is considered a core vaccine, primarily because it is necessary for the prevention of canine adenovirus type 1 (CAV-1) (against which it cross-protects),[18] the cause of infectious canine hepatitis, historically recognized as a severe and often fatal disease of canids. Although uncommon, sporadic cases of CAV-1 infection are still reported.[19] Vaccination schedules for parenteral CAV-2 vaccines follow the recommendations for CDV and CPV, and CAV-2 is usually a component of combination vaccines.

CAV-2 can also cause tracheobronchitis and is part of the canine infectious respiratory disease (CIRD) complex. Given in combination with canine parainfluenza virus (CPIV) and *Bordetella* vaccines, MLV CAV-2 vaccine can be administered intranasally (IN) to puppies as young as 3 wk of age, as mucosal immunity is not blocked by MDA.

Rabies
In the United States, stray dog control programs initiated in the 1940s, combined with routine rabies vaccination of owned dogs, eliminated the canine rabies virus variant (strain) from circulation by 2008. The elimination of this variant of an almost uniformly fatal virus from a domestic animal species that lives as a companion in close contact with humans has saved both canine and human lives. Today, in the United States and Canada, dogs (and humans) remain at risk from host-adapted rabies virus variants in wildlife reservoir species such as skunks, raccoons, foxes, and bats. The extent of spillover from wildlife is driven by the wildlife reservoir in the endemic area, with spillover most common in areas with the raccoon variant, somewhat less with skunk variants, and least common in areas where only bat variants occur. The US CDC publish an annual rabies surveillance summary that includes useful maps illustrating the distribution of terrestrial rabies virus variants as well as spillover events into dogs. Links to recent publications on rabies and rabies epidemiology are available at https://www.cdc.gov/rabies/resources/publications/index.html. The Canadian Food Inspection Agency (CFIA) also compiles rabies statistics at https://inspection.canada.ca/animal-health/terrestrial-animals/diseases/reportable/rabies/rabies-in-canada/eng/1356156989919/1356157139999.

Because of the high fatality rate and public health risk posed by rabies infection, administration of rabies vaccine to dogs is legally mandated in many jurisdictions. Age at initial vaccination, timing of booster doses, vaccine formulation, response to overdue booster doses, and whether rabies vaccine exemptions are permitted may all be stipulated in laws or regulations. Mandates can exist at the local, state, and provincial levels, and veterinarians should be aware of all applicable requirements in their area. Veterinarians that serve clients in multiple jurisdictions with variable requirements should generally apply the requirements of the jurisdiction where the animal resides. Local and state health departments (https://www.cdc.gov/rabies/resources/contacts.html) and state public health veterinarians (listed

at http://nasphv.org/Documents/StatePublicHealthVeterinariansBy State.pdf) are important sources of information about vaccine requirements, local rabies epidemiology, animal rabies testing, and risk assessments following a possible rabies exposure.

Rabies vaccines are highly immunogenic and effective. Vaccine failures are rarely reported. In jurisdictions where it is not mandated, rabies is recommended as a core vaccine, used in accordance with the most current recommendations in the Compendium of Animal Rabies Prevention and Control (http://www.nasphv.org/documents Compendia.html). Currently, all licensed rabies vaccines for dogs are inactivated (killed) with 1 and 3 yr DOI formulations available. All licensed products are labeled for puppies 3 mo of age and older. A booster dose is recommended 1 yr following the initial vaccination regardless of the formulation or age at initial vaccination. The booster's purpose is to immunize any animals that failed to respond to the initial dose. At this time, there are no published data supporting the efficacy of half-doses of rabies vaccine.

Legal exemptions from rabies vaccination requirements are only available in certain jurisdictions. Because exposure to rabies poses a risk to both animal and human health in unvaccinated or undervaccinated dogs, possible exemptions should be discussed with the owner in the context of the animal's health and lifestyle (i.e., risk of exposure). Veterinarians should document these discussions in the medical record. Antibody titer levels as correlates of protection have not been established for rabies, and serologic testing is not considered a substitute for vaccination.[20–25]

Leptospirosis

Vaccination for the prevention of leptospirosis should be considered a core vaccine for dogs in North America as the disease can be life-threatening, is endemic in much of the continent, and is zoonotic. In addition to protection from disease, vaccination may be necessary to meet state or international requirements for importation and transport of dogs and is often required by boarding facilities. Leptospirosis is a bacterial infection caused by spirochetes in the genus *Leptospira*, including *L interrogans* and *L kirschneri*. Surface antigens delineate multiple different serovars, with the predominant disease-associated serovars varying with geographic location and over time. *Leptospira* can be subdivided into >250 serovars falling into 30 serogroups. This antigenic system of classification into serovars is distinct from genomic classifications systems or sequence type and overlap between the systems is imperfect.

Vaccine strains have varied over time and by geography. In the past, *L interrogans* serovars Canicola and Icterohemorrhagiae were predominant in North American dogs, and vaccines for these serovars have been available since the 1960s.[26] In more recent years, additional serovars have emerged as important canine pathogens.[27]

Quadrivalent vaccines for use in North America now include the addition of *L. kirschneri* serovar Grippotyphosa and *L. interrogans* serovar Pomona bacterins. In Europe, quadrivalent vaccines are the same with the exception that Pomona is replaced by serovar Australis (both *L. interrogans*). Titers in unvaccinated dogs to *L. interrogans* serovar Autumnalis are likely due to cross-reactivity rather than infection, as there has been insufficient evidence (isolation or molecular identification) to warrant inclusion of this serovar in canine vaccines in the US. Although monovalent, bivalent, or trivalent vaccines remain available in various locations, the Task Force recommends the use of the 4-serovar vaccines for protection against the most relevant pathogens because vaccines induce only partial or no immunity to heterologous serogroups.[28,29]

Most leptospiral vaccines are adjuvanted, killed whole-cell bacterins, but nonadjuvanted bacterin vaccines have been marketed more recently.[28,30] As is typical for bacterin vaccines, annual boosters are required, with DOI shown for various vaccine serovars ranging from 12 to 18 mo.[30–35] All dogs in North America should be considered at risk of leptospirosis. Historically, the disease was most common in large breed dogs with rural outdoor exposure. This is no longer true. Small-breed dogs are frequently infected, perhaps because of urban and suburban exposure of dogs to wildlife reservoirs including rodents.[36,37] Dogs of any age, breed, or sex can be infected.[38] Leptospirosis occurs throughout North America, and while often associated with exposure to water, infection is well documented in arid regions such as Arizona.[38] Risk factors for leptospirosis include dogs spending any time outdoors (including urban, suburban, and rural environments), exposure to rodents, and time in kennels or dog daycares.[37–39]

Vaccination against leptospirosis can induce antibodies that may lead to false-positive serologic tests meant for disease diagnosis. Both microscopic agglutination tests and point-of-care serologic assays are impacted by this effect.[40–45] Fortunately, this becomes less important in light of the fact that clinical disease is unlikely in fully vaccinated dogs. Vaccination does not result in positive real-time polymerase chain reaction test results.[43]

Leptospira spp are important zoonotic pathogens.[46] Although there is little evidence of direct human infection from dogs, greater canine exposure to contaminated environments and close contact with people may link environmental sources to humans.[47–49] Newer vaccines have been documented to dramatically reduce or prevent renal carriage and urinary shedding of leptospires from exposed dogs, potentially protecting humans even if indirectly.[32,35,50,51]

Historically, veterinarians have been concerned about adverse reactions to leptospiral vaccines.[52–54] Vaccine formulations have now been altered to minimize the likelihood of such reactions. In the most recent large study of vaccine safety, odds of an adverse event following leptospirosis vaccination were less than with DA2PP or

rabies vaccinations.[55] Most adverse reactions are minor, and can include pain at injection site, malaise, anorexia, and mild fever, as can occur with many vaccines. Serious anaphylactic reactions were reported no more often for dogs given leptospiral vaccines than for other vaccine antigens. Nevertheless, adverse reactions of any type are more likely in smaller and younger dogs.[53] For this reason, the Task Force suggests that the initial dose be administered at or after 12 wk of age. Other measures to mitigate adverse reactions include minimizing the number of different vaccines administered at a single visit and following manufacturers recommendations, such as allowing a vaccine to reach room temperature before injection.[54]

Borrelia (Lyme Disease)

Vaccination for Lyme borreliosis should be considered for dogs that live within or travel to regions with emerging or endemic Lyme disease. Lyme disease is caused by infection with tick-transmitted borrelial pathogens. Although at least 21 species of borrelial pathogens can cause Lyme disease, in North America disease is due almost exclusively to Borrelia burgdorferi.[56,57] In 2014, species in the B burgdorferi sensu lato complex were awarded a new genus designation, Borreliella. However, this nomenclature is not yet routinely used by veterinarians and B burgdorferi refers to either.[57]

Lyme disease is transmitted by the bite of Ixodid ticks.[56] In the northeastern, mid-Atlantic, and north-central United States and eastern Canadian provinces, the primary vector is Ixodes scapularis (black-legged tick, or deer tick), whereas on the Pacific coast, the primary vector is Ixodes pacificus (western black-legged tick). Although the geographic expansion of endemic areas may well occur, currently infections are largely restricted to clusters of states where these ticks, and appropriate mammalian disease hosts, are abundant.

Dogs that spend time outdoors in endemic regions are most likely to benefit from vaccination. Vaccination should be complemented with an ectoparasite control program as prevention of tick feeding prevents disease transmission.[58,59] For dogs with travel planned to an endemic area, both initial vaccinations should be completed 2 to 4 wk before travel. In a recent large dataset (2013–2019), states with ≥5% seroprevalence in tested dogs included (in order of highest to lowest prevalence) Connecticut (15.5% seroprevalence), Massachusetts, Vermont, Maine, Pennsylvania, New Hampshire, Rhode Island, New York, New Jersey, West Virginia, Minnesota, Virginia, Maryland, Delaware, Wisconsin, and District of Columbia.[60] In Canada, the disease is endemic in portions of Manitoba, eastern Ontario, southern Quebec, Nova Scotia, and New Brunswick.[61,62] Dogs can serve as sentinels for infection in humans for this zoonotic disease, and regions with the greatest canine seroprevalence mirror regions with more human infections.[60,63] Fortunately, although

Lyme disease is zoonotic, there is no direct transmission from infected dogs to people, and infection in either species depends on vector transmission.[64]

Most dogs infected with B burgdorferi remain healthy.[64] Only ≤10% develop a polyarthritis that is responsive to antimicrobial therapy.[64] The most important potential consequence of infection is protein-losing nephropathy. For the estimated 1 to 5% of infected dogs that develop Lyme nephritis, the outcome is often fatal despite antimicrobial therapy.[64–66] Predisposition to Lyme nephritis has been suggested for retriever breeds, perhaps warranting additional consideration for vaccination in these breeds.[64,65,67]

There are four types of Borrelia vaccines approved for use, each of which has been proved safe and efficacious. Vaccines for prevention of Lyme disease exert their protective effect in an unusual way. All available vaccines can induce canine antibodies that bind borrelial outer surface proteins that are expressed while the pathogen is in the tick (OspA). Having only OspA in a vaccine has been shown to be effective.[68] It is also known that lipidation is a determinant of immunogenicity, and the lipidated recombinant OspA-only vaccine elicits a robust immune response.[69] Some vaccines can also induce antibodies to an antigen that is expressed shortly after transmission to the dog (OspC).[57,70,71] When the tick ingests antibodies to OspA from the vaccinated dog while feeding, the bacteria are killed before transmission. Antibodies to OspC extend protection against any bacteria that were not successfully killed inside the tick, thus acting synergistically with antibodies to OspA.[70,71]

Antibodies induced through vaccination may or may not result in positive serologic tests depending on test methodology.[64,72–74] It is important to understand the impact of vaccination on tests used for either screening or disease diagnosis. Differentiation of vaccination from infection is possible for B burgdorferi.

Bordetella, Canine Parainfluenza, and Canine Influenza

Previously evaluated[75] challenge of immunity studies in Bordetella bronchiseptica (Bb)-seronegative beagle puppies have provided variably convincing evidence of the efficacy of inactivated injectable, modified-live combination IN and single-component oral vaccines for Bb. More recently, current combination IN and single-component oral vaccines for Bb have been directly compared.[76,77] Data from these studies[76,77] are conflicting concerning the equivalency of the oral versus IN route in conferring immunity; one showed no difference between routes,[76] whereas the other demonstrated superior clinical efficacy of the IN route.[77] Altogether, available data indicate that commercial vaccines for Bb all "work" at some level, regardless of the route of administration.[75–77] However,

in general, the IN (versus oral) route of administration is preferable for respiratory pathogens. This is because it has been recognized that the common mucosal immune system, as originally conceptualized, was an oversimplification and that there is compartmentalization of mucosal immune responses, at least to some extent, making IN delivery of antigen more effective than oral at stimulating responses in the respiratory tract.[78–84]

There may be an immunological benefit in combining different vaccines and routes of administration in a primary series. This strategy is called "heterologous prime-boost" and involves administering different forms of an antigen by different routes to broaden and extend a response.[84] Although little studied in small animal veterinary medicine, there is an extensive comparative literature,[79] including a dog-relevant *Bordetella pertussis* murine model,[85] supporting this approach. Currently, heterologous prime-boost is being widely investigated in an effort to improve responses to vaccines for COVID-19.[86] One study using a combination of IN and injectable (whole-cell bacterin) *Bb* vaccines demonstrated a significant clinical benefit to this approach versus either vaccine alone.[87] However, this strategy has not yet been evaluated with current canine vaccines for *Bb* or other pathogens.

Concerning boosting of *Bb* vaccines, current combination IN and single-component acellular injectable *Bb* vaccines have been shown to induce equivalent anamnestic (memory) *Bb*-specific IgG and IgA responses when used as booster vaccines in previously immunized adult household dogs.[88] There are no similar published studies concerning the use of the single-component oral vaccine for this purpose or any use in household dogs.

Dogs that are at risk for *Bb* are also at risk for canine parainfluenza virus (CPIV) and canine adenovirus virus-2 (CAV-2) and should be vaccinated for all three pathogens.[89,90] Only the current combination IN and injectable (core) vaccines contain these pathogens. Therefore, the use of single-component oral and injectable *Bb* vaccines is not recommended. Exceptions include dogs that cannot be vaccinated IN, or in the case where the injectable *Bb* vaccine is used simultaneously with the injectable core vaccines as a booster for IN primed responses in a puppy series.[86,87] If an IN (modified-live) *Bb* vaccine is inadvertently administered by injection, the vaccine package insert or manufacturer should be consulted, as resulting inflammatory reactions can be serious.[91]

Duration of immunity and related recommendations for annual vaccination for *Bb* and CPIV are largely based on experimental infections in seronegative laboratory beagle puppies.[75,92,93] Such studies, usually conducted at peak immune response after vaccination, can generally accurately assess the ability of a vaccine to reduce disease. However, the validity of using such studies employing group-housed, genetically similar subjects to determine DOI conferred by vaccines

to household dogs is questionable. It is difficult to model heterogeneous household conditions comprising the plethora of the host, environmental and pathogen cofactors that can contribute to the brevity or longevity of protective clinical immunity. The latter endeavor requires well-designed and well-conducted field trials, including disease reporting; however, these types of studies are rare. One seminal study of the natural history of *Bb* indicated that the duration of clinical immunity (reduction of disease) may be as short as ~6 mo.[94] The duration of clinical immunity to CPIV in household dogs is unknown.[92] Therefore, for patients at high risk for CPIV and *Bb*, it may be advantageous to use IN combination *Bb* and CPIV vaccines more frequently than annually, for example, before boarding. In addition to boosting adaptive immune responses, the latter practice may better ameliorate disease through stimulation of the local innate immune response (type 1 interferon),[95] although this is poorly documented in small animals.

Canine influenza virus (CIV) serotypes H3N8 and H3N2 have been documented in North America and other parts of the world.[96] Disease caused by these viruses is usually indistinguishable from that caused by other respiratory pathogens associated with canine infectious respiratory disease (CIRD), although severe and sometimes fatal disease can occur in CIV-infected dogs. In contrast to CPIV, which tends to be endemic, or at least prevalent, in canine populations,[89,90] CIV infections and clinical disease to date have occurred as multicentric nonsustaining outbreaks.[96] Therefore, the routine use of CIV vaccines in all dogs is currently not recommended. Etiologic diagnoses of CIRD cases using quantitative polymerase chain reaction respiratory pathogen panels, together with monitoring of the current circulation of CIV (https://www.vet.cornell.edu/animal-health-diagnostic-center/news/canine-influenza-civ-updates), should be used to determine whether CIV vaccination is warranted in individual dogs, especially in dogs that are boarded and otherwise commingled at dog daycare, dog parks, dog shows and agility events, and in dogs who travel. Although immunity to influenza viruses is primarily serotype-specific, the use of bivalent CIV vaccines may avoid skewing of responses to one serotype.[97] This could broaden protective immunity and is therefore recommended.

Rattlesnake Toxoid

Currently, there are no published data documenting the efficacy of the western diamondback rattlesnake (*Crotalus atrox*) venom toxoid in dogs.[98–100] In a published experimental challenge study,[101] mice were vaccinated with 50- to 1500-fold (by volume) higher doses of toxoid than recommended in dogs and were subsequently challenged intraperitoneally with high doses (twice the LD_{50}) of venom. This protocol and challenge are of questionable relevance to rattlesnakebitten dogs.

In addition, although vaccinated mice had an increased survival time, a cohort of vaccinees died or required euthanasia earlier than unvaccinated controls following exposure to venom. Similarly, adverse reactions, including anaphylaxis, in previously vaccinated, then envenomated, dogs have been reported.[100]

The venom of pit vipers including the *Crotalidae* is antigenically heterogeneous.[102] Despite the manufacturer's claims of crossprotection against envenomation by pit vipers other than *C atrox*, there are no published data to support this in dogs. Veterinarians choosing to use this toxoid should be aware of the lack of peer-reviewed published data. Polyvalent antivenin therapy is an alternative to vaccination in suspect cases of rattlesnake bite.[99]

Vaccination of Shelter Dogs and Puppies

Increased opportunities for disease exposure and transmission, heightened animal stress, and high population turnover rates contribute to an elevated risk for infectious disease in dogs housed in high-density environments such as animal shelters. In addition, dogs entering shelters are less likely to be immune against CPV and CDV than owned dogs.[103–105] Of equal importance, infectious diseases are detrimental for individual animals, entire shelter populations, and community animals if an outbreak occurs. These increased environmental and patient risk factors inherent to shelter populations warrant more stringent vaccination requirements than those for owned dogs. Accordingly, all dogs, unless severely ill and unable to be housed within the shelter, should be vaccinated upon shelter entry. With the exception of leptospiral antigen, MLV vaccines should be used (as opposed to inactivated vaccines) owing to the possibility of more rapid onset of immunity. The DA2PP vaccination schedule in puppies should be started at a younger age, have shorter intervals between vaccinations, and end at an older age than that in owned puppies.

Core vaccines for dogs in shelter environments include parenteral MLV DA2PP, inactivated quadrivalent leptospira, IN *Bb* and CPIV, and parenteral rabies. Additional high-density or high-risk environments, including foster homes, foster-based rescues, breeding facilities, sanctuaries, boarding kennels, and pet stores, should consider following the same vaccination protocol.

Unless sufficient and reliable documentation of current vaccination status is presented, all dogs and puppies 4 wk of age and older should receive an MLV DA2PP vaccine at or before shelter entry and receive boosters at 2 to 3 wk intervals until they reach 18–20 wk of age. In addition, exposure to infectious disease should be physically avoided for puppies, ideally through placement in foster care until adoption or upon reaching 18–20 wk of age. Puppies should not be vaccinated for leptospirosis until at least 12 weeks of age.

Dogs and puppies older than 12 weeks should ideally receive a quadrivalent vaccine for leptospirosis on intake, with a booster administered 3 weeks later. For the initial vaccine, a combination of *Leptospira spp* with distemper, adenovirus, parvovirus, and parainfluenza (i.e., DA2LPP) is reasonable after 12 weeks of age, then boostering 3 weeks later with leptospira quadrivalent alone.

All dogs older than 18–20 wk of age at time of entry should receive an initial dose of MLV DA2LPP vaccine followed by a booster vaccine 2–3 wk later, administered either within the shelter, if the dog remains in care, or by their owner's veterinarian after adoption. When dogs are housed in shelters for prolonged periods of time, they should receive booster vaccinations as recommended for owned dogs.

All puppies and dogs older than 3 wk of age should receive an IN *Bb* and CPIV vaccine with or without CAV-2 at or before entry to mitigate CIRD. Although not documented in dogs, IN administration probably stimulates a local, rapid innate (interferon) response in addition to mucosal IgA. In puppies, this immune response avoids interference from maternal antibodies.[90,106,107] Single-component mucosal vaccines that contain only *Bb* should be avoided because dogs that are deemed at risk for *Bb* should be vaccinated against CPIV as well. Injectable *Bb* vaccines should be avoided in shelter environments owing to a delayed onset of immunity, including little stimulation of the local immune responses in the upper respiratory tract. This leads to reduced efficacy in limiting CIRD compared with IN vaccines. Oral or injectable single-component *Bb* vaccines are only recommended when it is not possible to administer a two-way IN vaccine.

A single dose of a rabies vaccine should be administered parenterally to all dogs older than 12 wk of age before release from the shelter. Rabies vaccination is not required upon shelter entry, as risk of exposure to rabies within the shelter environment is limited. However, if a long-term stay is anticipated, rabies vaccine should be administered on entry with the other core vaccines. Local legal mandates regarding the level of veterinary supervision required for rabies vaccination should be considered when developing shelter protocols. Rabies vaccination is acceptable even if additional vaccines may have been administered to the patient within the past 2 wk. Conclusive evidence is lacking that concurrent vaccination against multiple pathogens will impair the expected immune response to any individual component. Ensuring shelter dogs are vaccinated against rabies upon release from the shelter provides a significant public health benefit and outweighs any theoretical risk of vaccine interference.

Routine vaccination of shelter-housed dogs against *B burgdorferi* (Lyme disease), and canine influenza virus (CIV; H3N8 or H3N2 serotypes) is not recommended because these infections usually pose a minimal risk within the shelter environment. However, local

endemic or epizootic infections, such as in CIV outbreaks with potential for shelter exposure, as well as available shelter resources, legal requirements, and the risks and benefits of vaccines should be considered if adopting these noncore vaccinations in a shelter protocol.[108] Shelters should advise owners to discuss an individually tailored vaccination program with their veterinarian after adoption.

Pregnancy and mild illness or injury are not contraindications to administering core vaccines (CDV, CPV, CAV-2, *Leptospira spp*) to shelter-housed dogs. The overall benefits of MLV vaccination in a high-risk environment outweigh the potential risks posed by vaccination.[109] If a dog is mildly ill when vaccinated on entry to the shelter and the immune response to vaccination is of concern, then boostering the MLV DA2LPP vaccine in 2–3 wk (or after the animal has recovered) will likely provide additional protection. Shelters that vaccinate all animals on entry provide optimum herd immunity within their population. Conversely, shelters that do not vaccinate on entry or do not vaccinate all dogs are at higher risk for an infectious disease outbreak.

Infectious Disease Outbreak Management in Shelters

An infectious disease outbreak is one of the more daunting challenges in the high-risk animal shelter setting. Temporary cessation of animal intakes is a helpful initial approach to an outbreak. Appropriate vaccination of resident or incoming dogs is a crucial strategy when an infectious disease outbreak occurs in the animal shelter population. A proper vaccination strategy in the face of an outbreak is dependent on the pathogen involved, its route of transmission (oral vs. respiratory), the stage of the outbreak, effectiveness of local sanitation practices, and the vaccine formulations being used. Unfortunately, there are virtually no published data from controlled studies in dogs that address these issues, relegating decisions to clinical judgments.

Serological testing offers shelters an effective tool to help manage disease outbreaks, particularly in the case of CDV and CPV, as opposed to depopulation or prolonged lockdown of the shelter. Although additional host, pathogen, and environmental cofactors that contribute to disease outbreaks must also be taken into account during the outbreak management process, serological testing can provide supplemental insights. Serological testing, by providing individual risk assessment, can assist in population flow decision making during an outbreak. In general, healthy, seropositive dogs, especially those with high titers, are likely resistant to disease and can be considered low risk. They can be adopted with appropriate waivers. Healthy, seronegative dogs, who are potentially susceptible to disease and considered high risk, should be quarantined and separated from the rest of the population (ideally, placed in foster care outside of the shelter). They should be revaccinated, observed for development of

clinical signs throughout the anticipated incubation period of the disease, and serologically retested 10–14 days later. Puppies, especially those ≤4 mo of age, require additional management during an outbreak. Serological testing and risk assessment of dogs in this age group can be misinterpreted because of the potential presence of transient maternal antibodies.

Cessation of intake into the shelter is critical for effective outbreak management. If temporary cessation of intake is not possible, then housing newly admitted dogs in a completely segregated area of the shelter (with infection control practices, including designated staff and equipment) is required to prevent disease transmission.

Utilization and Interpretation of Serologic Titers

In human medicine, the efficacy of modern vaccines is established and monitored primarily on the basis of standardized serology ("titers") in conjunction with large-scale clinical trials and usually substantial centralized disease-reporting processes from vaccinated populations.[112] A similar approach has been applied to some extent in livestock medicine. This has been facilitated by large vaccinated populations and driven by economic imperatives; immunity favorably affects production parameters. Data deriving from such studies are nearly absent in canine populations.

Studies of experimental infections to determine vaccine efficacy in dogs generally involve small numbers of animals and may use challenge organisms and methods that do not reproduce naturally occurring diseases. In addition, vaccine efficacy and licensing studies generally use purebred beagles with limited genetic heterogeneity. There are relatively few studies conducted in household dogs. Understanding these limitations, as well as the biological reality that vaccines almost never protect 100% of the population 100% of the time, is essential to convey reasonable expectations of vaccine efficacy to clients.

"Protective titers" for CDV, CPV, and to a lesser extent CAV-1 have been of most interest to general practitioners. These viruses often cause lethal infections in naïve dogs and comprise the core antigens for which there are very effective vaccines. Generally, laboratories determining titers have used VN tests for CDV and HI tests for CPV.[113–115] Both are bioassays and report results as titers, which are dilutions of antibody. Both VN and HI tests measure antibodies to viral surface proteins that directly relate to neutralization of the virus (VN) or are a surrogate for actual neutralization (HI). In contrast, depending on how the test antigen is prepared, ELISA tests can measure antibody responses that are not involved in protection, such as responses to internal nuclear proteins. Results are generally reported as "units," not titers.

Interpretation of titers can be difficult for several reasons. First, by their nature, they are subject to intralaboratory and interlaboratory variation. This issue was at least implied in seminal studies.[113,114] Second, there is no readily available documentation of standardization or comparative results of these or other tests when performed in different laboratories. This makes it difficult to interpret a titer, especially if it is not very low or very high. Lastly, at best, the determination of "protective titers" has been based on limited data. These data were thoroughly reviewed 20 years ago.[113] Nothing more substantive has become available since then. ELISA-based inclinic antibody detection tests have been available for CPV and CDV for more than 20 years.[116,117] HI and VN tests, respectively, were used as "gold standards" to determine their sensitivity and specificity, as it relates to a "protective titer."[116–118] Commercial ELISAs have been applied in shelter populations outside of the laboratory and further compared with HI and VN tests.[118,119] Such applications have provided no further basis for a determination of "protective titers," primarily because the titers or amounts of antibody were not correlated with clinical outcomes. Recognizing these limitations, no values for "protective titers" are indicated in these guidelines, although some commercial laboratories will provide them.

After the disappearance of maternal antibodies, the presence of any detectable antibody (a titer) indicates, by definition, that an immune response to vaccination or exposure to an antigen involving at least B and helper (CD4+) T cells has occurred.[95] The presence, or absence, of antibody is not necessarily indicative of coincident cell-mediated immune responses, or their absence.[95] Altogether, a titer, almost regardless of the amount, is not necessarily indicative of protection or susceptibility. Rather, it is more complicated than that.[120] Disease in the individual animal results from the interaction of host, pathogen, and environmental cofactors. It can be misleading to forecast an outcome on the basis of one cofactor: a titer.

Routine administration of commonly used vaccines has been associated with uncommon to rare adverse events in dogs.[52,121] Currently, for the core DA2PP antigens, most practicing veterinarians have adopted a 3 yr protocol. Unlike in human medicine, it is based on very limited population-based data involving disease reportage, and experimental challenge studies directly comparing the responses in annually versus triennially (or any other interval) vaccinated dogs are lacking. Altogether, routine "titer testing" to ascertain the necessity to revaccinate at currently recommended intervals is not usually advised, except in cases in which dogs have a history of adverse responses to vaccination, there is a suspicion of vaccine-related autoimmune disease, or when owners express resistance or hesitancy to having their dogs vaccinated or boostered—in which case client communication and education may help overcome this hesitancy.

Postvaccination Adverse Events and Reactions

Undesired or unexpected consequences after vaccination include failure to provide protection from disease and adverse reactions associated with vaccine administration. Failure to provide protective immunity is primarily of concern in very young or very old dogs. Young dogs most commonly fail to mount a sufficient immune response following vaccination because of the presence of MDA from colostrum. Puppies in some breeds, e.g., Doberman pinschers and rottweilers, have been purported to be immune nonresponders to a standard initial vaccination series, but definitive evidence of this characteristic is lacking.

Questions are sometimes raised about whether multiple vaccines, simultaneously administered, diminish or overwhelm the immune response. Although antibody responses can vary after administration of different vaccines and antigens, there is no evidence of a lack of protective immunity following concurrent administration of multiple antigens or vaccines.

Vaccine efficacy in older dogs is typically related to concerns of immunosenescence, an age-related decline in the function of the immune system. Although geriatric dogs may have a relative diminution of naïve T cells to confront new antigens, these patients generally do not lack memory cells created from previous exposure to antigens in early or mid-life.[122]

Adverse postvaccination reactions may be (1) caused by inappropriate administration of a modified-live product, (2) secondary to innate immune responses to the vaccine, (3) specific cell-mediated or humoral immune responses to vaccine components, or (4) induced by vaccine antigens that return to virulence (unlikely in appropriately tested and licensed vaccines).

Localized cell-mediated immune reactions or generalized systemic responses can occur after vaccination. Type I hypersensitivity reactions have been linked to vaccination, but vaccine associations with other immune-mediated diseases, e.g., immune-mediated thrombocytopenia, immune-mediated hemolytic anemia, and immunemediated polyarthritis, are less consistent.[123–127] This may indicate that factors besides vaccine antigens are responsible for immune disease sequelae following vaccination.

Adverse reactions, as well as desirable immune responses, are genetically influenced in some cases. Immunogenetics is a developing investigative field for adverse drug and vaccine reactions in people[128,129] but is basically unexplored in veterinary medicine. Although some breeds have been identified as at increased risk of vaccine reactions,[52] breed (a phenotype) is a crude indicator of genetics. More likely, genetic predisposition for individuals exists within some family lines, thus selectively increasing risk overall for

some breeds. Owners should be informed that adverse event risk occurs at the individual patient level.[130]

In genetically predisposed individuals, undesirable immune responses can be triggered by various vaccine antigens.[124,131] In dogs, IgE reactivity has been detected against components of cell culture media used to propagate vaccinal viruses and other pathogens. Mostly, the offending substances are xenogeneic (to dogs) proteins, such as in fetal calf serum, e.g., bovine serum albumin, gelatin and casein.[132] In other words, the antigens of concern are typically vaccine components that are *not* the label (pathogen) antigens. Thus, identification and quantity of these antigens are not part of manufacturer labels.

Although genetic predisposition cannot be altered, adverse event risk can be diminished by reducing the quantity of vaccine antigens presented to the patient's immune system. Because antigens of concern are not the label antigens, combination vaccines containing multiple pathogens do not inherently carry more adverse event risk than single-component vaccines. Because of the way rabies vaccine virus is propagated, single-component rabies vaccines may have more adverse event risk, as they have a more diverse array of proteins than combination vaccines containing other viruses that are propagated similarly, or other single-component vaccines.[133]

Reducing antigenic stimuli can be achieved by reducing the number of vaccines administered at a single office visit. This is a particularly useful approach in small dogs.[52] Reducing the administered volume ("split dosing") for any vaccine below the manufacturer's recommended volume is *not* advised, because the USDA and manufacturer have not approved such reductions. Therefore, this practice could involve the assumption of liability.[12]

Reducing the number of vaccines administered at a single office visit may necessitate additional office visits in order to provide necessary vaccine coverage and complete protection. Although comparison studies have not been performed, at least 2 wk is recommended between vaccines to allow the heightened immune response from the most previous vaccination to subside.

If possible within guidelines and manufacturer recommendations, administering vaccines nonparenterally, e.g., mucosally or IN, can also reduce adverse event risk.

A common question is whether at-risk patients should be pretreated with diphenhydramine before vaccination. If the risk is hypothetical, i.e., involving an at-risk breed but in cases in which no previous reactions have occurred, pretreatment as a precaution is generally not recommended. Although prevaccination administration of diphenhydramine may prevent type I hypersensitivity reactions, the lack of any subsequent reaction does not actually prove the pretreatment was beneficial or necessary.

If the vaccination risk involves a dog with a history of previous vaccine reaction, one cannot presume reactions will automatically recur. Precautions such as limiting the number of vaccines administered are prudent, as is prevaccination administration of diphenhydramine. Single anti-inflammatory doses of glucocorticoids, if administered, do not impair humoral responses to vaccination.[134,135] If the vaccination risk involves a patient with an existing immunemediated disease, consideration should be given to the stability and condition of the patient, the need for vaccination, and prudent ways to minimize adverse event risk.

If vaccines are administered to patients with existing medical conditions or health concerns, clients should sign an informed consent statement as increased risk of disease may result if the dog's immunocompetence is compromised. When a dog experiences a possible adverse event, the veterinary team should report the specific patient and vaccine information to the vaccine manufacturer and/or the USDA. (https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/adverse-event-reporting/ct_vb_adverse_event).

Vaccine Storage and Handling

Vaccines are among some of the most important resources used to protect animals' health. However, they are only effective if they are stored and handled correctly. Improper handling and storage can decrease the efficacy of the vaccine, leaving the animal vulnerable to disease.[136] Specific details about storage and handling protocols can be found in each manufacturer package insert.

In general, storage and handling require vaccines to be kept in a temperature-controlled environment from the time they leave the manufacturer to the time of their administration, a process known as the vaccine cold chain.[136,137] The vaccine cold chain is a shared responsibility between the manufacturer, distributor, and veterinary team. The development of a standard operating procedure to ensure proper ordering, storage, and administration is essential to the vaccine protocol of a veterinary healthcare provider.

Storage and temperature monitoring equipment are critical to ensure proper vaccine potency. The CDC recommends purpose-built units (also known as pharmaceutical grade) or stand-alone household refrigeration units to properly store vaccines.[136,137] Either purpose-built or stand-alone units can be compact size or larger. A high-quality thermometer should be kept in the center of the refrigerator. Temperatures should be monitored and recorded per the veterinary team's standard operating manual.

Refrigerated vaccines should be stored at temperatures between 2°C and 8°C (36°F and 46°F).[136,137] The thermostat should be set at midrange to achieve a temperature of ∼5°C (40°F), which will decrease the likelihood of temperature fluctuations.[136,137] Vaccines should be organized and placed centrally in the refrigeration unit to promote proper airflow, typically 2–3 inches from the walls and doors.[136,137] Remove deli, fruit, and vegetable drawers, as these areas

have unstable temperatures and are unsuitable for storage. Vaccines should be kept in their original packaging with lids closed until ready to open.[136,137] The refrigerated vaccine storage unit should be designated for only vaccines.

Single-dose vaccines (both freeze-dried and liquid forms) should not be removed from the refrigerator until the time of administration.[136,137] A new, sterile syringe and needle should always be used for proper vaccine administration. A delay in vaccine reconstitution and administration could decrease the efficacy of the vaccine owing to the fragility of the vaccine and temperature fluctuations.[136,137] Multidose vaccines typically have preservatives to allow prolonged storage once the seal has been opened.[136,137] See the vaccine package insert for manufacturer recommendations and directions for proper storage and handling.

Interpreting Vaccine Labels

Labels for veterinary vaccines have recently undergone considerable changes to bring greater clarity to the user. Historically, veterinary vaccines were assigned a tier system based on the effectiveness of the protection of the vaccine.[138] The tier system was initially not well understood and led to confusion among veterinary practitioners. As a result, the USDA implemented a new rule that requires vaccine labels to contain a simple claim and provide the public the opportunity to view the relevant safety and efficacy studies online.[138,139] The new label system states: "This product has been shown to be effective for the vaccination of healthy (*name of species, weeks of age or older against name of disease*).[138] Veterinarians are encouraged to review individual manufacturer efficacy and safety data online at the Licensed Biological Product Information website: https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/CT_Vb_licensed_products.

Vaccine Licensure

In the United States, veterinary biologics include vaccines, bacterins, antisera, diagnostic test kits, and other products of biological origin acting through immunologic mechanisms to prevent disease.[140] The USDA, under the authority of the Virus-Serum-Toxin Act, governs and mandates the licensure of biologics.[140] The USDA prohibits the preparation or sale of veterinary biologics that are ineffective, contaminated, dangerous, or harmful.[141] The mandate of the Virus-Serum-Toxin Act is interpreted with the understanding that veterinary biologics should be safe, pure, potent, and efficacious.[141] Regulatory oversight through the USDA Animal and Plant Health Inspection Service is described in 9 CFR 101-124. In the United States, manufacturers are inspected before the issue of their first license for a product and then periodically inspected afterward. Not only are the

physical plants inspected, but starting materials (seed virus, bacteria, and cell lines) are also tested for purity and identification.[138] Once a license has been granted, no substantial changes in the manufacturing process are allowed to ensure a consistent product.[138]

Vaccines are granted different licenses through different categories.[138] Fully licensed products meet the requirements that establish the purity, safety, potency, and efficacy of the product. Conditional licenses are issued in order to meet an emergency condition, limited market, local situation, or other special circumstance under expedited procedures that ensure purity, safety, and a reasonable expectation of efficacy. Imported products can be permitted for distribution and sale and must meet the same standards as fully licensed products. This scenario is typically associated with factors such as a lack of USDA-licensed products and a viable threat of emerging infectious animal disease.[138]

The licensure standards for veterinary vaccines in Canada are similar to those required in the United States for fully licensed products. 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. Product labeling must be compliant with Canadian requirements, including the use of metric units and complete information available in both English and French. The CFIA, under the legislative authority of the Health of Animals Act and Regulations, is responsible for regulating veterinary biologics in Canada.[142] Responsibilities of the CFIA in licensing vaccines include verification of products (master seeds), licensing of the manufacturing facilities, and issuance of import and/or export permits.[142] 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.[142]

Client Education and Training the Healthcare Team

Creating a well-defined vaccination protocol with consistent messaging serves as a framework for the veterinary team to reference during patient visits. This reinforces the importance of vaccines for the veterinary team and ensures that a consistent message is communicated between the healthcare team and clients. A protocol also helps the healthcare team follow a consistent vaccination schedule, especially when starting an initial series of vaccines, while concurrently considering the lifestyle, geographical location, and risk factors for each

individual pet. At a minimum, a vaccination schedule should consist of the following information:

- Anatomical location of vaccine administration
- Route of administration
- Age requirements and/or restrictions
- Frequency of administration

A vaccination protocol should be created with the patient's needs and lifestyle in mind, with buy-in from the client through education explaining the importance of vaccines.

The Need for Consistency

Creating consistency across the healthcare team builds a strong practice culture, decreases confusion about recommendations, assists with training team members, and increases compliance. This better enables all team members to educate clients about vaccination schedules, disease prevention, and what to expect following vaccination. Client education materials can support practices by educating clients about vaccinations, vaccine reactions, and disease processes.

Wellness plans prove to be advantageous by creating consistency within a practice and providing a standard for quality pet care. Wellness plans often include the recommended vaccinations for pets and help the healthcare team deliver a clear message when it comes to the health of the dog. They can also reduce redundancy in delivering key points about certain vaccines, vaccination protocols, and the importance of vaccination.

Developing Client Education Materials

Client education continues even after a dog presents to a practice for vaccination. Developing client education materials and creating a practice library can provide a ready resource to clients about why, what, and when vaccines should be given to their pet. The more clients understand the reasons for vaccination, the more likely they will see the importance of adhering to an individualized vaccination schedule for their dog. Each practice should consider creating a source (online or physical copies) of educational material for clients, discharge instructions for practice teams, and short blurbs of 1–2 sentences about each vaccine and the disease(s) it prevents. More comprehensive educational material can be stored in a repository and used as requested or needed.

Determining the Best Communication Approach

In order to determine how to best communicate with clients, it is important to assess client communication preferences. A survey or questionnaire can be used to ask clients about their preferred contact methods or whether they would like to receive specific additional material. Client preferences can then be noted in the patient's history.

This allows information to be relayed in a way the client understands. With electronic medical record systems now in veterinary practices, documenting and finding client information has simplified. Some electronic medical record systems can even connect with mobile applications where clients and hospital teams can communicate.

Summary

Regular vaccination of canine patients is a central component of preventive healthcare, as well as an opportunity for the practice to engage with clients to discuss the importance of disease prevention. These vaccination guidelines provide a current and comprehensive resource for making informed decisions when designing vaccination protocols for dogs. Vaccination best practices are based on individualized needs determined by the patient's history and risk of disease exposure. Whereas core vaccines are recommended for every dog regardless of lifestyle, noncore vaccine recommendations are determined by assessing the likelihood of a dog's exposure to a given infectious disease. Licensed canine vaccines have a high degree of safety and efficacy, and in most cases, the benefits of vaccination far outweigh the risks. Dogs presented at, residing in, or originating from animal shelters are in a high-risk setting for infectious disease exposure and outbreaks, and shelter-specific vaccination protocols seek to mitigate that risk.

It is important that the entire healthcare team be well versed on the practice's vaccination philosophy and protocols. The practice team is then prepared to deliver a consistent and unified message to clients on the importance and role of vaccination in patients' healthcare plans. Improper vaccine storage and handling and failure to adhere to label recommendations are the principal reasons for the occasional incidence of vaccination failure. Periodic staff training can minimize these procedural shortfalls and help ensure that vaccination is a reliable and useful tool for delivering optimum pet healthcare. ■

REFERENCES

1. 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.
2. Decaro N, Buonavoglia C, Barrs VR. Canine parvovirus vaccination and immunisation failures: are we far from disease eradication? *Vet Microbiol* 2020;247:108760.
3. Decaro N, Crescenzo G, Desario C, et al. Long-term viraemia and fecal shedding in pups after modified-live canine parvovirus vaccination. *Vaccine* 2014;32(30):3850–3.

4. Day MJ. Companion animal vaccines. In: Ettinger SJ, Feldman EC, eds. *Textbook of veterinary internal medicine*. 8th ed. St. Louis: Elsevier-Saunders; 2017:895.

5. Francis MJ. Recent advances in vaccine technology. *Vet Clin North Am Small Anim Pract* 2018;48(2):231–41.

6. Gaskell RM, Dawson S, Radford AD. Duration of immunity (DOI) – the regulatory issues. *Vet Microbiol* 2006;117(1):80–5.

7. 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. *Int J Appl Res Vet Med* 2004;2(4):227–34.

8. 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* 2007;8(4):305–10.

9. Meeusen ENT, Walker J, Peters A, et al. Current status of veterinary vaccines. *Clin Microbiol Rev* 2007;20(3):489–510.

10. 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.

11. 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.

12. Miranda C, Thompson G. Canine parvovirus: the worldwide occurrence of antigenic variants. *J Gen Virol* 2016;97:2043–57.

13. Decaro N, Buonavoglia C, Barrs VR. Canine parvovirus vaccination and immunisation failures: Are we far from disease eradication? *Vet Microbiol* 2020;247:108760.

14. Pollock RV, Carmichael LE. Maternally derived immunity to canine parvovirus infection: transfer, decline, and interference with vaccination. *J Am Vet Med Assoc* 1982;180:37–42.

15. Lechner ES, Crawford PC, Levy JK, et al. Prevalence of protective antibody titers for canine distemper virus and canine parvovirus in dogs entering a Florida animal shelter. *J Am Vet Med Assoc* 2010;236: 1317–21.

16. Altman KD, Kelman M, Ward MP. Are vaccine strain, type or administration protocol risk factors for canine parvovirus vaccine failure? *Vet Microbiol* 2017;210:8–16.

17. Kelman M, Barrs VR, Norris JM, et al. Canine parvovirus prevention and prevalence: veterinarian perceptions and behaviors. *Prev Vet Med* 2020;174:104817.

18. Bass EP, Gill MA, Beckenhauer WH. Evaluation of a canine adenovirus type 2 strain as a replacement for infectious canine hepatitis vaccine. *J Am Vet Med Assoc* 1980;177(3):234–42.

19. Hornsey SJ, Philibert H, Godson DL, et al. Canine adenovirus type 1 causing neurological signs in a 5-week-old puppy. *BMC Vet Res* 2019; 15:418.

20. Brown CM, Slavinski S, Ettestad P, et al. Compendium of animal rabies prevention and control, 2016. *J Am Vet Med Assoc* 2016;248(5):505–17.

21. 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.

22. Ma X, Monroe BP, Cleaton, JM, et al. Public Veterinary Medicine: Public Health: Rabies surveillance in the United States during 2018. *J Am Vet Med Assoc* 2020;256:195–208.

23. Moore SM. Rabies: Current preventive strategies. *Vet Clin North Am Small Anim Pract* 2019;49(4):629–41.

24. Moore MC, Davis RD, Kang Q, et al. Comparison of anamnestic responses to rabies vaccination in dogs and cats with current and outof-date vaccination status. *J Am Vet Med Assoc* 2015;246:205–11.

25. Murray KO, Holmes KC, Hanlon CA. Rabies in vaccinated dogs and cats in the United States, 1997-2001. *J Am Vet Med Assoc* 2009;235: 691–5.

26. Srinivas GB, Walker A, Rippke B. USDA regulatory guidelines and practices for veterinary *Leptospira* vaccine potency testing. *Biologicals* 2013;41:298–302.

27. Wilson S, Stirling C, Thomas A, et al. A new multivalent (DHPPi/L4R) canine combination vaccine prevents infection, shedding and clinical signs following experimental challenge with four *Leptospira* serovars. *Vaccine* 2013;31:3131–4.

28. Eric Klaasen HL, Adler B. Recent advances in canine leptospirosis: focus on vaccine development. *Vet Med (Aukl)* 2015;6:245–60.

29. Sonrier CB, Michel V, RuvoeÈn-Clouet N, et al. Evidence of cross-protection within *Leptospira* interrogans in an experimental model. *Vaccine* 2001;19:86–94.

30. Grosenbaugh DA, Pardo MC. Fifteen-month duration of immunity for the serovar Grippotyphosa fraction of a tetravalent canine leptospirosis vaccine. *Vet Rec* 2018;182:665.

31. Klaasen HL, Molkenboer MJ, Vrijenhoek MP, et al. Duration of immunity in dogs vaccinated against leptospirosis with a bivalent inactivated vaccine. *Vet Microbiol* 2003;95:121–32.

32. Minke JM, Bey R, Tronel JP, et al. Onset and duration of protective immunity against clinical disease and renal carriage in dogs provided by a bi-valent inactivated leptospirosis vaccine. *Vet Microbiol* 2009;137: 137–45.

33. Schreiber P, Martin V, Grousson D, et al. One-year duration of immunity in dogs for *Leptospira* Interrogans serovar Icterohaemorrhagiae after vaccination. *Int J Appl Res Vet Med* 2012;10:305–10.

34. Wilson S, Stirling C, Thomas A, et al. Duration of immunity of a multivalent (DHPPi/L4R) canine vaccine against four *Leptospira serovars*. *Vaccine* 2013;31:3126–30.

35. Bouvet J, Cariou C, Valfort W, et al. Efficacy of a multivalent DAPPi-Lmulti canine vaccine against mortality, clinical signs, infection, bacterial excretion, renal carriage and renal lesions caused by *Leptospira* experimental challenges. *Vaccine Rep* 2016;6:23–8.

36. Lee HS, Guptill L, Johnson AJ, et al. Signalment changes in canine leptospirosis between 1970 and 2009. *J Vet Intern Med* 2014;28:294–9.

37. Ricardo T, Previtali MA, Signorini M. Meta-analysis of risk factors for canine leptospirosis. *Prev Vet Med* 2020;181:105037.

38. Iverson SA, Levy C, Yaglom HD, et al. Clinical, diagnostic, and epidemiological features of a community-wide outbreak of canine leptospirosis in a low-prevalence region (Maricopa County, Arizona). *J Am Vet Med Assoc* 2021;258:616–29.

39. Azocar-Aedo L, Monti G. Meta-analyses of factors associated with leptospirosis in domestic dogs. *Zoonoses Public Health* 2016;63:328–36.

40. Martin LE, Wiggans KT, Wennogle SA, et al. Vaccine-associated *Leptospira* antibodies in client-owned dogs. *J Vet Intern Med* 2014;28: 789–92.

41. Kodjo A, Calleja C, Loenser M, et al. A rapid in-clinic test detects acute leptospirosis in dogs with high sensitivity and specificity. *Biomed Res Int* 2016;2016:3760191.

42. Lizer J, Grahlmann M, Hapke H, et al. Evaluation of a rapid IgM detection test for diagnosis of acute leptospirosis in dogs. *Vet Rec* 2017; 180:517.

43. Midence J, Leutenegger C, Chandler A, et al. Effects of recent *Leptospira* vaccination on whole blood real-time PCR testing in healthy client-owned dogs. *J Vet Intern Med* 2012;26:149–52.

44. Stokes W, Srinivas G, McFarland R, et al. Report on the international workshop on alternative methods for *Leptospira* vaccine potency testing: state of the science and the way forward. *Biologicals* 2013;41:279–94.

45. Troia R, Balboni A, Zamagni S, et al. Prospective evaluation of rapid point-of-care tests for the diagnosis of acute leptospirosis in dogs. *Vet J* 2018;237:37–42.

46. Mwachui MA, Crump L, Hartskeerl R, et al. Environmental and behavioural determinants of leptospirosis transmission: a systematic review. *PLoS Negl Trop Dis* 2015;9:e0003843.

47. Martins G, Penna B, Lilenbaum W. The dog in the transmission of human leptospirosis under tropical conditions: victim or villain? *Epidemiol Infect* 2012;140:207–8; author reply 208–9.

48. Major A, Schweighauser A, Francey T. Increasing incidence of canine leptospirosis in Switzerland. *Int J Environ Res Public Health* 2014;11:7242–60.

49. Gay N, Soupé-Gilbert M-E, Goarant C. Though not reservoirs, dogs might transmit *Leptospira* in New Caledonia. *Int J Environ Res Public Health* 2014;11:4316–25.

50. Klaasen HL, van der Veen M, Molkenboer MJ, et al. A novel tetravalent *Leptospira* bacterin protects against infection and shedding following challenge in dogs. *Vet Rec* 2013;172:181.

51. Bouvet J, Lemaitre L, Cariou C, et al. A canine vaccine against *Leptospira* serovars Icterohaemorrhagiae, Canicola and Grippotyphosa provides cross protection against *Leptospira* serovar Copenhageni. *Vet Immunol Immunopathol* 2020;219:109985.

52. Moore GE, Guptill LF, Ward MP, et al. Adverse events diagnosed within three days of vaccine administration in dogs. *J Am Vet Med Assoc* 2005;227:1102–8.

53. Yao PJ, Stephenson N, Foley JE, et al. Incidence rates and risk factors for owner-reported adverse events following vaccination of dogs that did or did not receive a *Leptospira* vaccine. *J Am Vet Med Assoc* 2015;247:1139–45.

54. Robbins H. Adverse events in dogs given *Leptospira* vaccine. *Vet Rec* 2017;180:257.

55. Moore GE, Morrison J, Saito EK, Spofford N, Yang M. Breed, smaller weight, and multiple injections are associated with increased adverse event reports within three days following canine vaccine administration. *J Am Vet Med Assoc*. 2023 Jul 14;261(11):1653–1659.

56. Eisen L. Vector competence studies with hard ticks and *Borrelia burgdorferi* sensu lato spirochetes: a review. *Ticks Tick Borne Dis* 2020;11:101359.

57. O'Bier NS, Hatke AL, Camire AC, et al. Human and veterinary vaccines for Lyme disease. *Curr Issues Mol Biol* 2021;42:191–222.

58. Honsberger NA, Six RH, Heinz TJ, et al. Efficacy of sarolaner in the prevention of *Borrelia burgdorferi* and *Anaplasma phagocytophilum* transmission from infected *Ixodes scapularis* to dogs. *Vet Parasitol* 2016;222:67–72.

59. Kräamer F, Huüsken R, Kruüdewagen EM, et al. Prevention of transmission of *Borrelia burgdorferi* sensu lato and *Anaplasma phagocytophilum* by *Ixodes* spp. ticks to dogs treated with the Seresto® collar (imidacloprid 10%+ flumethrin 4.5%). *Parasitol Res* 2020;119:299–315.

60. Little S, Braff J, Place J, et al. Canine infection with *Dirofilaria immitis*, *Borrelia burgdorferi*, *Anaplasma* spp., and *Ehrlichia* spp. in the United States, 2013–2019. *Parasit Vectors* 2021;14:1–16.

61. Herrin BH, Peregrine AS, Goring J, et al. Canine infection with *Borrelia burgdorferi*, *Dirofilaria immitis*, *Anaplasma* spp. and *Ehrlichia* spp. in Canada, 2013–2014. *Parasit Vectors* 2017;10:1–9.

62. Evason M, Stull JW, Pearl DL, et al. Prevalence of *Borrelia burgdorferi*, *Anaplasma* spp., *Ehrlichia* spp. and *Dirofilaria immitis* in Canadian dogs, 2008 to 2015: a repeat cross-sectional study. *Parasit Vectors* 2019;12:64.

63. Liu Y, Nordone SK, Yabsley MJ, et al. Quantifying the relationship between human Lyme disease and *Borrelia burgdorferi* exposure in domestic dogs. *Geospatial Health* 2019;14:111–20.

64. Littman MP, Gerber B, Goldstein RE, et al. ACVIM consensus update on Lyme borreliosis in dogs and cats. *J Vet Intern Med* 2018; 32:887–903.

65. Dambach D, Smith C, Lewis R, et al. Morphologic, immunohistochemical, and ultrastructural characterization of a distinctive renal lesion in dogs putatively associated with *Borrelia burgdorferi* infection: 49 cases (1987–1992). *Vet Pathol* 1997;34:85–96.

66. Borys MA, Kass PH, Mohr FC, et al. Differences in clinicopathologic variables between *Borrelia* C6 antigen seroreactive and *Borrelia* C6 seronegative glomerulopathy in dogs. *Vet Intern Med* 2019;33:2096–104.

67. Purswell EK, Lashnits EW, Breitschwerdt EB, et al. A retrospective study of vector-borne disease prevalence in dogs with proteinuria: Southeastern United States. *J Vet Intern Medicine* 2020;34:742–53.

68. Conlon JA, Mather TN, Tanner P, Gallo G, Jacobson RH. Efficacy of a nonadjuvated, outer surface protein A, recombinant vaccine in dogs after challenge by ticks naturally infected with *Borrelia burgdorferi*. *Vet Ther.* 2000;1(2):96–107.

69. Grosenbaugh DA, De Luca K, Durand PY, et al. Characterization of recombinant OspA in two different *Borrelia* vaccines with respect to immunological response and its relationship to functional parameters. *BMC Vet Res.* 2018;14(1):312.

70. Marconi RT, Garcia-Tapia D, Hoevers J, et al. VANGUARD (R) crLyme: A next generation Lyme disease vaccine that prevents *B. burgdorferi* infection in dogs. *Vaccine X* 2020;6:100079.

71. Camire AC, Hatke AL, King VL, et al. Comparative analysis of antibody responses to outer surface protein (Osp)A and OspC in dogs vaccinated with Lyme disease vaccines. *Vet J* 2021;273:105676.

72. Stillman BA, Thatcher B, Beall MJ, et al. *Borrelia burgdorferi* antibody test results in dogs administered 4 different vaccines. *Top Companion Anim Med* 2019;37:100358.

73. Moroff S, Woodruff C, Woodring T, et al. Multiple antigen target approach using the Accuplex4 BioCD system to detect *Borrelia burgdorferi* antibodies in experimentally infected and vaccinated dogs. *J Vet Diagn Invest* 2015;27:581–8.

74. Marques AR, Martin DS, Philipp MT. Evaluation of the C6 peptide enzyme-linked immunosorbent assay for individuals vaccinated with the recombinant OspA vaccine. *J Clin Microbiol* 2002;40:2591–3.

75. Ellis JA. How well do vaccines for *Bordetella bronchiseptica* work in dogs? A critical review of the literature 1977-2014. *Vet J* 2015;204:5–16.

76. Scott-Garrad MM, Chiang Y-W, David F. Comparative onset of immunity of oral and intranasal vaccines against challenge with *Bordetella bronchiseptica*. *Vet Rec Open* 2018;5e000285.

77. Ellis JA, Gow SP, Waldner CL, et al. Comparative efficacy of intranasal and oral vaccines against *Bordetella bronchiseptica* in dogs. *Vet J* 2016; 212:71–7.

78. Ellis JA. Canine IgA and IgA deficiency: implications for immunization against respiratory pathogens. *Can Vet J* 2019;60:1305–11.

79. Karkani K, Bolhassani A, Shahbazi S. Prime-boost vaccine strategy against viral infections: Mechanisms and benefits. Vaccine 2016;34:413–23.

80. McDermott MR, Bienenstock J. Evidence for a common mucosal immunologic system. I. Migration of B immunoblasts into intestinal, respiratory, and genital tisssues. *J Immunol* 1979;122:1892–8.

81. Moldoveanu Z, Russell MW, Wu HY, et al. Compartmentalization within the common mucosal immune system. In: Mestecky J, Russell MW, Jackson S, et al., eds. *Advances in mucosal immunology. advances in experimental medicine and biology.* Vol. 371. Boston: Springer; 1995: 97–101.

82. Wu HY, Russell MW. Nasal lymphoid tissue, intranasal immunization, and compartmentalization of the common mucosal immune system. *Immunologic Res* 1997;16:187–201.

83. Czerkinsky C, Holmgren J. Mucosal delivery routes for optimal immunization: targeting immunity to the right tissues. In: Kozlowski P, ed.

Mucosal vaccines. current topics in microbiology and immunology. Vol. 354. Berlin, Heidelberg: Springer; 2010:1–18.

84. Brandgzaeg P. Potential of nasopharynx-associated lymphoid tissue for vaccine responses in airways. *Am J Respir Crit Care* 2011;183: 1595–604.

85. Feunou PF, Kammoun H, Debrie AS, et al. Heterologous prime-boost immunization with live attenuated *B. pertussis* vaccine in mice. *Vaccine* 2014;32:4281–8.

86. He Q, Mao Q, An C, et al. Heterologous prime-boost: breaking the protective immune response bottleneck of COVID-19 vaccine candidates. *Emerg Microbes Infect* 2021;10(1):629–37.

87. Ellis JA, Haines DM, West KH, et al. Effect of vaccination on experimental infection with *Bordetella bronchiseptica* in dogs. *J Am Vet Med Assoc* 2001;218:367–75.

88. Ellis JA, Gow SP, Lee LB, et al. Comparative efficacy of intranasal and injectable vaccines in stimulating *Bordetella bronchiseptica*-reactive anamnestic antibody responses in household dogs. *Can Vet J* 2017;58: 809–15.

89. Joffe DJ, Lelewski R, Weese JS, et al. Factors associated with development of canine infectious respiratory disease complex (CIRDC) in dogs in 5 Canadian small animal clinics. *Can Vet J* 2016;57:46–51.

90. Maboni G, Seguel M, Lorton A, et al. Canine infectious respiratory disease: new insights into the etiology and epidemiology of associated pathogens. *PLoS One* 2019;14(4):e0215817.

91. Toshach K, Jackson MW, Dubielzig RR. Hepatocellular necrosis associated with subcutaneous injection of an intranasal *Bordetella bronchiseptica*-canine parainfluenza vaccine. *J Am Anim Hosp Assoc* 1997; 33: 126–8.

92. Ellis JA, Krakowka GS. A review of canine parainfluenza virus infection in dogs. *J Am Vet Med Assoc* 2012;240:273–84.

93. Hainer N, Velineni S, Bowers A, et al. Oral vaccination of dogs with a monovalent live-avirulent vaccine confers 1 year of immunity against *Bordetella bronchiseptica* challenge. *Vet J* 2021;278:105775.

94. Bemis DA, Greisen HA, Appel MJG. Pathogenesis of canine bordetellosis. *J Infect Dis* 1977;135:753–62.

95. Ellis JA. Another look at the "dismal science" and Jenner's experiment. *Vet Clin North Am Small Anim Pract* 2018; 48:243-255.

96. Parrish CR, Voorhees IEH. H3N8 and H3N2 canine influenza viruses: understanding these new viruses in dogs. *Vet Clin North Am Small Anim Pract* 2019;49:643–9.

97. Monto AS, Malosh RE, Petrie JG, et al. The doctrine of original antigenic sin: separating good from evil. *J Infect Dis* 2017;215:1782–8.

98. Leonard MJ, Bresee C, Cruikshank A. Effects of the canine rattlesnake vaccine in moderate to severe cases of canine crotalid envenomation. *Vet Med (Aukl)* 2014;5:153–8.

99. Witsil AJ, Wells RJ, Woods C, et al. 272 cases of rattlesnake envenomation in dogs: demographics and treatment including safety of F(ab')2 antivenom use in 236 patients. *Toxicon* 2015;105:19–26.

100. Petras KE, Wells RJ, Pronko J. Suspected anaphylaxis and lack of clinical protection associated with envenomation in two dogs vaccinated with *Crotalus atrox* toxoid. *Toxicon* 2018;142:30–3.

101. Cates CC, Valore EV, Couto MA, et al. Comparison of the protective effect of a commercially available western diamondback rattlesnake toxoid vaccine for dogs against envenomation of mice with western diamondback rattlesnake (*Crotalus atrox*), northern Pacific rattlesnake (*Crotalus oreganus oreganus*), and southern Pacific rattlesnake (*Crotalus oreganus helleri*) venom. *Am J Vet Res* 2015;76:272–9.

102. Chippaux JP, Williams V, White J. Snake venom variability: methods of study, results and interpretation. *Toxicon* 1991;29:1279–303.

103. Lechner ES, Crawford PC, Levy JK, et al. Prevalence of protective antibody titers for canine distemper virus and canine parvovirus in dogs entering a Florida animal shelter. *J Am Vet Med Assoc* 2010;236:1317–21.

104. Litster A, Nichols J, Volpe A. Prevalence of positive antibody test results for canine parvovirus (CPV) and canine distemper virus (CDV) and response to modified live vaccination against CPV and CDV in dogs entering animal shelters. *Vet Microbiol* 2012;157:86–90.

105. Spindel ME, Krecic MR, Slater MR, et al. Evaluation of a community's risk for canine parvovirus and distemper using antibody testing and GIS mapping of animal shelter intakes. *J Appl Anim Welf Sci* 2018;21: 362–74.

106. Gore T, Headley M, Laris R, et al. Intranasal kennel cough vaccine protecting dogs from experimental *Bordetella bronchiseptica*. *Vet Rec* 2005; 156:482–3.

107. Kontor E, Wegrzyn R, Goodnow R. Canine infectious tracheobronchitis: effects of an intranasal live canine parainfluenza-*Bordetella bronchiseptica* vaccine on viral shedding and clinical tracheobronchitis (kennel cough). *Am J Vet Res* 1981;42:1694–8.

108. Miller L, Zawistowski S, eds. *Shelter medicine for veterinarians and staff.* 2nd ed. Ames (IA): Wiley-Blackwell; 2013.

109. Miller L, Hurley K, eds. *Infectious disease management in animal shelters.* Ames (IA): Wiley-Blackwell; 2009.

110. Andrukonis A, Brown KM, Hall NJ, et al. Intake vaccinations reduced signs of canine respiratory disease during an outbreak at an animal shelter. *Front Vet Sci* 20921;8:627580.

111. Newbury S, Blinn MK, Bushby PA, et al. *Guidelines for standards of care in animal shelters.* Corning (NY): Association of Shelter Veterinarians; 2010.

112. World Health Organization. *Guidelines on clinical evaluation of vaccines: regulatory expectations.* WHO Technical Report Series 1004; 2017.

113. Coyne MJ, Burr JHH, Yule TD, et al. Duration of immunity in dogs after vaccination or naturally acquired infection. *Vet Rec* 2001;149:509–15.

114. Appel M, Robson DS. A microneutralization test for canine distemper virus. *Am J Vet Res* 1973;34:1459–63.

115. Carmichael LE, Joubert JC, Pollock RV. Hemagglutination by canine parvovirus: serologic studies and diagnostic applications. *Am J Vet Res* 1980;41:784–91.

116. Waner T, Naveh A, Wudovsky I, et al. Assessment of maternal antibody decay and response to canine parvovirus vaccination using an enzyme-linked immunosorbent assay. *J Vet Diag Invest* 1996;8:426–32.

117. Waner T, Naveh A, Schwarz Ben Meir N, et al. Assessment of immunization response to canine distemper virus vaccination in puppies using a clinic-based enzyme-linked immunosorbent assay. *Vet J* 1998;155:171–5.

118. Gray LK, Crawford PC, Levy JK, et al. Comparison of two assays for detection of antibodies against canine parvovirus and canine distemper virus in dogs admitted to a Florida animal shelter. *J Am Vet Med Assoc* 2012;240:1084–7.

119. Litster A, Nichols J, Volpe A. Prevalence of positive antibody test results for canine parvovirus (CPV) and canine distemper virus (CDV) and response to modified live vaccination against CPV and CDV in dogs entering animal shelters. *Vet Microbiol* 2012;157:86–90.

120. Rothman KJ. Causes. *Am J Epidemiol* 1976;104:587–92.

121. Valli JL. Suspected adverse reactions to vaccination in Canadian dogs and cats. *Can Vet J* 2015;56:1090–3.

122. Pawelec G. Age and immunity: what is "immunosenescence"? *Exp Gerontol* 2018;105:4–9.

123. Siegrist CA. Mechanisms underlying adverse reactions to vaccines. *J Comp Pathol* 2007;137 suppl 1:S46–50.

124. Gershwin LJ. Adverse reactions to vaccination: from anaphylaxis to autoimmunity. *Vet Clin North Am Small Anim Pract* 2018;48:279–90.

125. Moon A, Veir J. Vaccination and associated adverse events in dogs previously treated for primary immune-mediated hemolytic anemia. *J Am Anim Hosp Assoc* 2019;55:29–34.

126. Stone CA Jr, Rukasin CRF, Beachkofsky TM, et al. Immune-mediated adverse reactions to vaccines. *Br J Clin Pharmacol* 2019;85:2694–706.

127. Moore GE, HogenEsch H. Adverse vaccinal events in dogs and cats. *Vet Clin North Am Small Anim Pract* 2010;40:393–407.

128. Poland GA, Ovsyannikova IG, Jacobson RM. Application of pharmacogenomics to vaccines. *Pharmacogenomics* 2009;10:837–52.

129. Whitaker JA, Ovsyannikova IG, Poland GA. Adversomics: a new paradigm for vaccine safety and design. *Expert Rev Vaccines* 2015;14:935–47.

130. Poland GA, Ovsyannikova IG, Kennedy RB. Personalized vaccinology: a review. *Vaccine* 2018;36:5350–7.

131. Kang SM, Compans RW. Host responses from innate to adaptive immunity after vaccination: molecular and cellular events. *Mol Cells* 2009;27:5–14.

132. Ohmori K, Masuda K, Maeda S, et al. IgE reactivity to vaccine components in dogs that developed immediate-type allergic reactions after vaccination. *Vet Immunol Immunopathol* 2005;104:249–56.

133. Moore GE, Franco J, Aryal U, et al. Proteomic analysis of canine vaccines (abstr). *J Vet Intern Med* 2020;34:2913.

134. Nara PL, Krakowka S, Powers TE. Effects of prednisolone on the development of immune responses to canine distemper virus in beagle pups. *Am J Vet Res* 1979;40:1742–7.

135. Blancou J, Milward F, Toma B, et al. Vaccination against rabies in carnivores treated with corticoids. *Rec Méd Vét* 1981;157:631–57.

136. Centers for Disease Control and Prevention. Vaccine Storage and Handling Resources. Available at: https://www.cdc.gov/vaccines/hcp/admin/storage/index.html. Accessed June 27, 2022.

137. Centers for Disease Control and Prevention. 2022 Vaccine Storage and Handling. Available at: https://www2a.cdc.gov/nip/isd/ycts/mod1/courses/sh/index.html. Accessed June 27, 2022.

138. Erdman MM, Clough NE, Hauer PJ. Review of updated regulations and product license in categories for veterinary vaccines in the United States. *J Am Vet Med Assoc* 2020;257:1142–7.

139. USDA. Product Summaries. Available at: https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/product-summaries. Accessed June 27, 2022.

140. USDA. Veterinary Biologics. Available at: https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics. Accessed June 27, 2022.

141. USDA. Common Questions About Veterinary Biologics. Available at: https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/ct_vb_pel_faqs. Accessed June 27, 2022.

142. Canadian Centre for Veterinary Biologics. The Regulation of Veterinary Biologics in Canada – Overview. Available at: https://inspection.canada.ca/animal-health/veterinary-biologics/guidelinesforms/4-10e/eng/1328215080021/1328215153251. Accessed June 27, 2022.