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CHAPTER 12

# Immunization

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## KEY POINTS

- Active immunization can partially or completely protect dogs and cats from severe consequences of infection with a variety of different pathogens, and in some cases it reduces shedding of these pathogens.
- Vaccines contain attenuated live microorganisms, inactivated microorganisms, or portions of these organisms. They also contain preservatives and adjuvants.
- Failure of immunization can occur with improper storage or administration of vaccines, a large challenge dose, host factors such as concurrent infections or disease, and interference by maternal antibody.
- Other adverse effects of vaccine administration are uncommon to rare but include hypersensitivity reactions, disease induced by live attenuated vaccine organisms, and injection-site sarcomas in cats.
- The decision to administer a vaccine should be based on discussion of risks and benefits between the veterinarian and pet owner. This should be documented in the medical record.
- Guidelines for vaccine selection and administration have been published by a number of veterinary bodies, such as the AAFP, AAHA, AVMA, and WSAVA; suggestions can also be found in Appendix I.

## INTRODUCTION

Immunization refers to artificial induction of immunity or protection from infectious disease and may be *active* or *passive*. *Active immunization* involves administration of vaccines that stimulate cell-mediated or humoral immunity, or both, to a specific pathogen. *Passive immunization* refers to the administration of antibodies in order to provide temporary protection from disease and can occur through acquisition of maternally derived antibody (MDA) transplacentally, in colostrum, or milk; or treatment with preparations that contain specific or nonspecific immunoglobulins (see Immunomodulators, Chapter 7, and post-exposure prophylaxis for rabies, Chapter 13). Readers are referred to advanced immunology texts for detailed descriptions of the physiology of active and passive immunity.[1]

The goal of immunization is to generate a protective immune response of prolonged duration against a specific infectious disease, with minimal adverse effects. Because of the potential for adverse effects, vaccination should be performed only if there is a risk for significant morbidity or mortality from an infectious disease. Since the 1950s, a huge number of vaccines for dogs and cats have been developed and marketed worldwide, and more are in development. Nevertheless, it is estimated that even in developed countries such as the United States, only 30% to 50% of dogs are properly immunized, and possibly an even smaller proportion of cats.[2,3] Appropriate vaccination of a larger proportion of the pet population may assist in reduction of the prevalence of infectious diseases through the induction of herd immunity.

With the appearance of injection-site sarcomas in cats, increased emphasis has been placed on vaccine safety, and a change from annual to 3-yearly immunization protocols for some vaccines has been recommended, with administration of other vaccines based on exposure risk. Vaccines have had a profound influence in the control of infectious disease, and for many vaccines the benefits of vaccination outweigh the risks.

## Vaccine Composition and Types of Vaccines

A vaccine is a suspension of attenuated live or inactivated microorganisms, or parts thereof, that is administered to induce immunity. In addition to protective antigens, vaccines may contain preservatives and stabilizers as well as specific antibiotics to preserve the antigen and inhibit bacterial and fungal growth within the vaccine. Some vaccines also contain an *adjuvant* to enhance the immune response to the antigen. Although the mechanisms are not completely clear, adjuvants can delay the release of antigen from the site of injection and induce the secretion of chemokines by leukocytes.[4] The most widely used adjuvants are particulate adjuvants, such as those that contain aluminum salt precipitates such as aluminum hydroxide.[5] Other particulate adjuvants include immunostimulators such as saponin, which is present in a canine *Leishmania* vaccine.

*Attenuated live vaccines* (or modified live vaccines) contain microorganisms that are artificially manipulated so as to negate or greatly reduce their virulence, or are field strains of low virulence. Repeated passage through cell culture is the most common means of attenuation. Because they replicate in the host, organisms in attenuated live vaccines usually stimulate an immune response that most closely mimics the protection that results from natural infection. Vaccination with attenuated live canine parvovirus (CPV) and canine distemper virus (CDV) vaccines in the absence of MDA can result in protective immune responses within 3 days of a single injection, which may be followed by immunity that lasts many years, if not for life.[6-8] Partial immunity after vaccination with attenuated live CDV and feline panleukopenia virus (FPV) vaccines can occur within hours.[3,9,10] In addition, vaccine organisms that are shed can serve to immunize other animals in a population. However, the potential for reversion to virulence or vaccine-induced disease exists. Vaccine-induced disease is most likely to occur in highly immunosuppressed animals. Attenuated live vaccines also have the potential to cause some immunosuppression in their

TABLE 12-1

**Advantages and Disadvantages of Attenuated Live and Inactivated Vaccines**

| | Attenuated Live | Inactivated |
|---|---|---|
| Advantages | Rapid onset of immunity<br>Sustained immunity after single dose<br>May immunize others in populations<br>Improved breakthrough of maternal antibody interference | Safe, even in immunocompromised and pregnant animals<br>Do not interfere with development of immunity from other vaccines<br>Stable in storage |
| Disadvantages | Potential for reversion to virulence<br>Virulence in the immunocompromised<br>Contraindicated in pregnancy<br>May cause immune suppression<br>Can interfere with development of immunity if administered within days to 2 weeks of another vaccine<br>Less stable in storage<br>Potential for vaccine contamination | Slow onset of immunity<br>Multiple boosters required<br>Often highly adjuvanted, with greater potential for adverse effects<br>Reduced degree of protection compared with attenuated live vaccines<br>Poor breakthrough of maternal antibody interference |

own right,[11,12] or they may shift the balance from Th1 to Th2 immune responses.[13] Rarely, this can lead to clinical disease. For example, an outbreak of salmonellosis was reported in cats after use of a high-titered attenuated live FPV vaccine.[14] Very rarely, contamination of attenuated live vaccines has occurred with other pathogenic microorganisms present within cell cultures used to propagate the vaccine.

Generally speaking, *inactivated vaccines* are less effective than attenuated vaccines, because replication in the host does not occur. They produce weaker immune responses of shorter duration, and more frequent booster immunizations may be required. Two initial doses of vaccine 3 to 4 weeks apart are essential to produce an effective immune response, and if more than 6 weeks elapses between these doses, it has been recommended that the series should be repeated.[15] Beyond the initial vaccination series, it is not clear whether lapsed annual boosters require the series to be restarted. This is not considered necessary for human immunization[16] but has been suggested for dogs when more than 2 or 3 years elapses between boosters.[15] Inactivated vaccines usually contain adjuvant as well as a large infectious dose to improve immunogenicity. They are safer than live attenuated vaccines for use during pregnancy and in very young or debilitated animals. Although bacterins have traditionally been associated with a greater likelihood of allergic reactions than live attenuated vaccines, newer inactivated vaccines are safer and have reaction rates that more closely approach those of live attenuated vaccines. The maximum duration of immunity that is induced by commercially available bacterins for dogs and cats remains largely unknown, partly because challenge studies that evaluate long-term duration of immunity are prohibitively expensive. However, some inactivated viral vaccines have been shown to have durations of immunity in excess of 7 years in cats.[17] Caution is required when extrapolation is made from the duration of immunity for one product to that for a similar product from a different manufacturer, because it may not be equivalent. Although bacterins usually do not protect all animals from infection, they may prevent clinical illness. In some cases, natural infection of vaccinated animals serves to further boost the immune response, and this can influence duration of immunity in the field. The advantages and disadvantages of attenuated live and inactivated vaccines are shown in Table 12-1.

*Subunit vaccines* contain specific structural components of a microbe that stimulate a protective immune response, together with adjuvant. They contain reduced amounts of foreign protein, which minimizes the potential for hypersensitivity reactions.

*Recombinant DNA vaccines* are created through manipulation of the DNA of a pathogen in the laboratory, with the negation of pathogen virulence. Sometimes this also can allow diagnostic tests to differentiate naturally infected from vaccinated animals (DIVA), because of differences in the antibody response evoked by the vaccine. There are several different types of recombinant DNA vaccines:

1. Recombinant subunit vaccines. These are produced by cloning one or more genes for a protective antigen into an expression vector, such as in *Escherichia coli*. The protein expressed by the bacteria is then purified and used in the vaccine (Figure 12-1, *A*). An example of a recombinant subunit vaccine is the Lyme recombinant OspA vaccine.
2. Deletion mutant vaccines. These are produced by deleting virulence genes from a pathogen while protective antigens are left in place. There are currently no such vaccines for dogs and cats.
3. Vectored vaccines. These are produced by inserting genes for one or more protective antigens into the genome of a virus. The virus replicates in the host and expresses the antigens but is nonpathogenic (see Figure 12-1, *B*). Currently available vectored vaccines for dogs and cats use canarypox virus as a vector.
4. DNA vaccines. These consist of naked DNA that encodes the antigens required for protective immunity. The DNA is injected directly to the animal using an inoculation system. The DNA is then taken up by host cells and translated into antigen. Both humoral and cell-mediated immune responses are produced. DNA vaccines are not currently available commercially for use in dogs and cats.

## Vaccine Storage, Handling, and Administration

Vaccines should be stored and administered according to label recommendations. Inactivation of vaccines can occur if they

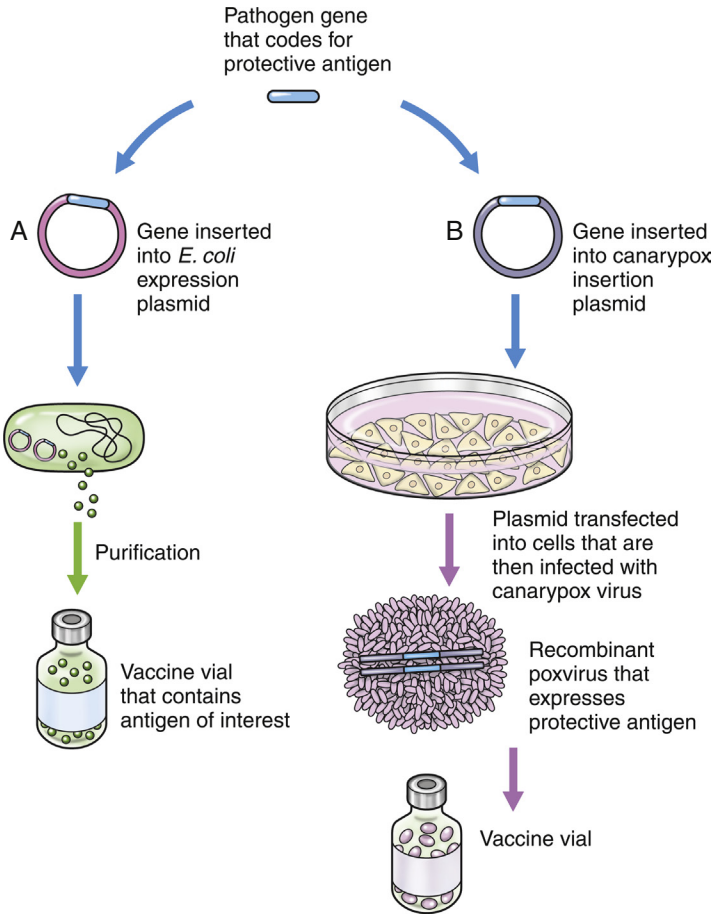


**FIGURE 12-1** Examples of recombinant DNA vaccines. **A,** Recombinant subunit vaccine. The gene of interest is inserted into an expression vector such as a plasmid taken up by *Escherichia coli,* which subsequently produces large amounts of an immunogenic protein. This is purified and used in the vaccine. **B,** Vectored vaccine. The gene or genes of interest are inserted into a canarypox or vaccinia vector, which is then inoculated into an animal. Replication of the vector within the host is followed by expression of the immunogenic protein.

are inadvertently frozen or heated to excessive temperatures, exposed to excessive amounts of light, or used beyond their expiration date. Hands should be washed before preparation and administration of the vaccine. Lyophilized products should be reconstituted with the proper diluent, and different vaccines should not be mixed in the same syringe or vial. Reconstituted products should be used immediately. It has been recommended that attenuated live vaccines be discarded if more than 1 hour has lapsed since reconstitution,[15] although no published reports exist of the viability of vaccine organisms over time after reconstitution or of the ability of stored, reconstituted vaccine to elicit an immune response. Vaccines should only be used in the animal species for which they are labeled, or serious adverse effects or failure of immunization can occur.

If vaccines for multiple different pathogens are to be administered simultaneously, they should be injected at distant sites or, if possible, a combination vaccine should be used. Simultaneous vaccination for more than one pathogen does not appear to interfere with immune responses to each component of the vaccine,[18-20] and vaccine manufacturers must demonstrate that the protection that occurs for a specific pathogen after vaccination with a combination product equals the protection that occurs when a vaccine for only that pathogen is given. In contrast, successive parenteral administration of different attenuated live vaccines at 3 to 14 day intervals has the potential to interfere with immune responses. An interval of 4 weeks is preferred for human patients.[16,21] Inactivated vaccines do not produce interference in this way.[16] If possible, administration of vaccines to animals that are under anesthesia should be avoided because adverse reactions may be difficult or impossible to recognize in this situation. It is not necessary to re-administer an intranasal vaccine if the animal coughs or sneezes after administration.

The site and route of administration, product, serial number, expiry date, and individual who administered the vaccine should be recorded for each vaccine administered.[2] Vaccine vials often possess adhesive labels that can be easily removed and applied to a paper medical record.

## Components of the Immune Response

The immune response is divided into innate and adaptive immune responses. The innate immune response is nonspecific and acts as an immediate line of defense against an infection. Components of the innate immune response consist of natural killer cells, which recognize host cells that are infected by viruses; complement, which is activated by bacterial cell wall components; and phagocytes, such as macrophages and dendritic cells. The adaptive immune response develops over several days and involves presentation of antigen by dendritic cells in association with the major histocompatibility complex and stimulation of B and T cell responses, together with the

**BOX 12-1**

**Factors That Can Affect Immune Responses to Vaccines**

Target pathogen (e.g., respiratory versus systemic pathogen)
Vaccine composition (e.g., inadequate adjuvant)
Route of administration
Young age
Breed/genetic factors
Nutrition
Pregnancy status
Concurrent moderate to severe illness
Fever
Immunosuppressive drugs
Presence of maternal antibody
Improper vaccine storage and administration
Vaccination with an attenuated live viral vaccine within last 3 days to 2 weeks
Inadequate time allowed for immunization before exposure to field organisms

formation of memory B cells. The nature of the innate response influences the subsequent adaptive response. Cells of the innate immune system possess pattern recognition receptors that can recognize patterns that are characteristic for various pathogens (pathogen-associated molecular patterns, or PAMPs), including Toll-like receptors and NOD-like receptors. PAMPs are under investigation for use as adjuvants in human and animal vaccines in order to create improved T cell immune responses.[4,22]

## Determinants of Immunogenicity

All vaccines that are available for dogs and cats induce cell-mediated immunity (CMI) with induction of immunologic memory and a booster effect on repeat administration. Although the presence of antibody correlates with protection for some pathogens, such as CDV and CPV, a lack of antibody does not infer a lack of protection, because of the presence of CMI, which is more difficult to measure.

Vaccines rarely protect all vaccinated individuals from infection and disease. In particular, vaccines for canine and feline respiratory pathogens do not prevent disease but can reduce the prevalence and severity of disease as well as reduce the number of organisms shed. Limited immunity following vaccination is especially likely for infections for which immunity after natural infection is partial or short-lived.

The ability of a vaccine to induce an immune response depends not only on the target pathogen, vaccine composition, and route of administration, but also on host factors such as age, nutrition, pregnancy status, stress, concurrent infections, and immune status, including the presence or absence of passively acquired antibody (Box 12-1). Some of these factors may also influence vaccine safety. Some animals, particularly dogs of the Rottweiler breed, may have an impaired ability to respond to vaccination. These dogs have been termed *nonresponders*.[2,23] This situation is probably rare if efficacious vaccines are used and booster vaccines are administered. Young dogs, less than 1 year of age, have a significantly reduced response to vaccination with rabies virus vaccines when compared with adult dogs.[24] Small-breed dogs have a greater serologic response to rabies vaccines than large-breed dogs.[25] Administration of vaccines to febrile animals or animals with moderate to severe illness should be avoided if possible until recovery has occurred, because the immune response to the vaccine may be suboptimal.

Failure of immunization can result from an inadequate dose of antigen. Thus, division of a single vaccine dose for administration to a larger number of dogs and cats, or small-breed dogs as opposed to large-breed dogs, may lead to failure of immunization. Veterinarians should not split vaccine doses because this shifts the liability from the vaccine manufacturer to the veterinarian if vaccine failure occurs. Immunization can also fail in the face of an overwhelming challenge dose.

The route of administration can influence the type of immune response generated. Subcutaneous administration is associated primarily with an IgG response, and rarely induces high levels of secretory IgA antibodies. In contrast, intranasal administration results in an IgA and, to a lesser extent, an IgG response. Immunogenicity and safety may be compromised when a vaccine is administered using the incorrect route.

In young animals, MDA can neutralize vaccine antigens and interfere with effective immunization. This is one of the most common reasons for vaccine failure in dogs and cats. Any MDA titer against CPV has the potential to interfere with immunization. The amount of MDA in a puppy or kitten at any one point in time cannot be predicted because it varies depending on the titer of the dam and the amount of colostrum ingested after birth. As a result, a series of vaccinations are administered in order to increase the chance that successful immunization will occur soon after the decline of MDA titers to sufficiently low concentrations (Figure 12-2). Nevertheless, a window always exists when MDA concentrations are high enough to interfere with immunization, but not sufficient to prevent natural infection. This window is known as the *window of susceptibility* or the *window of vulnerability*. The use of recombinant vectored vaccines can overcome the interference by MDA, although the extent to which this applies in animals that have passive immunity to the vector virus (i.e., immunity transferred from a dam that was immunized with a recombinant vector vaccine) requires clarification. Because replication of the vector is aborted, the immune response to the vector itself may be reduced. As a result, passive transfer of neutralizing antibody titers to the vector may not occur. Mucosal vaccines can also provide greater protection in the face of MDA; the mucosal immune system matures shortly after birth.[26,27]

Whenever possible, animals should be isolated until sufficient time has elapsed for proper immunization. For most parenteral and mucosal vaccines, this is 1 week (and at the absolute minimum, 3 days) after inoculation. Vaccine failure can also occur in animals that are incubating the disease for which vaccination is performed at the time of vaccination.

## Measurement of the Immune Response

For some vaccines, such as rabies, CDV, CPV, and FPV, the presence of circulating antibodies correlates with protection (Table 12-2). Thus, serologic assays have been used in dogs and cats to decide whether vaccination is necessary or likely to be effective. These serologic assays have also been used to clear pets for travel.

Although tests that measure antibody responses in dogs and cats have improved in recent years, different laboratories can report significantly different values for the same serum

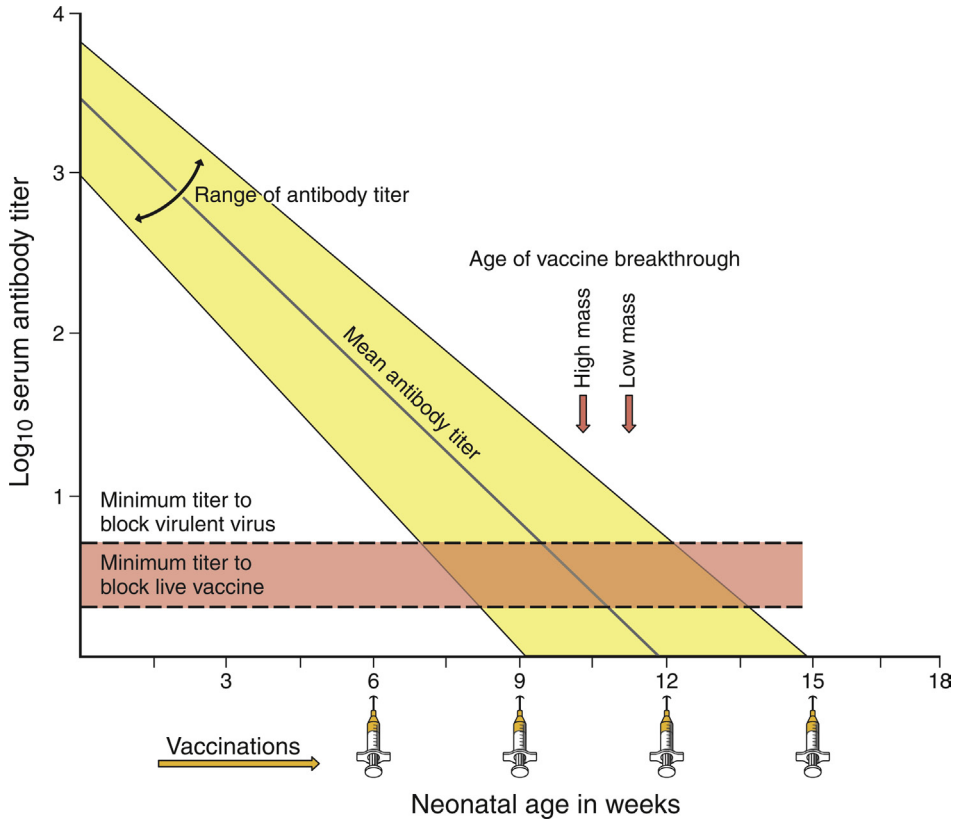


**FIGURE 12-2** Influence of maternal antibody (MDA) on immunization. Puppies and kittens acquire variable amounts of MDA transplacentally and through colostrum after birth. This binds to vaccine antigens and inhibits the immune response. A series of vaccines are administered to maximize the chance of inducing an immune response as MDA concentrations decline. The *window of susceptibility* is the period of time when MDA concentrations are high enough to interfere with immunization, but not sufficient to prevent natural infection. High antigen mass vaccines provide protection earlier than low mass vaccines. (From Greene CE, Schultz RD. Immunoprophylaxis. In: Greene CE, ed. Infectious Diseases of the Dog and Cat, 3 ed. St Louis, MO: Saunders; 2006.)

## TABLE 12-2

**Antibody Titers That Correlate with Protection against Distemper, Parvovirus, and Rabies**

| Pathogen | Minimum Protective Titer | Methodology Used |
|---|---|---|
| Canine distemper virus | ≥1:16 to 1:20 | Serum neutralization (SN) |
| Canine parvovirus | ≥1:80 to 1:100 | Hemagglutination inhibition (HI) |
| Rabies | ≥0.5 IU/mL | Fluorescent antibody virus neutralization (FAN) |

specimen, and there is a lack of validated sensitivity and specificity for these assays. Sometimes use of these assays increases costs significantly and delays immunization. In-practice assays also are available for detection of antibody responses, and these have the potential to overcome problems associated with laboratory quality control and delays in immunization. In-practice assays are generally not quantitative. Although high antibody titers are generally associated with greater protection, an animal with no titer may still be resistant to challenge because of CMI, which is not measured. Conversely, an animal with a titer that is generally regarded as protective has the potential to develop disease after challenge, possibly because of overwhelming exposure or immune suppression. Measurement of antibody titers may be considered for animals that have had previous adverse responses to vaccination, particularly susceptible breeds (e.g., Rottweilers and CPV infection). The World Small Animal Veterinary Association (WSAVA) has suggested that puppies could be tested at least 2 weeks after the final puppy vaccine to decide whether further vaccination for CDV or CPV is necessary.[2] Negative titers should prompt additional vaccination for these puppies.

Rapid in-house serologic assays have also been used to make decisions regarding isolation or euthanasia in shelter situations, through identification of immune animals.[28] Unfortunately, it is not always be possible to know if positive titers represent recent infection, and animals that test positive may still shed virus and pose a risk to other animals. In young puppies and kittens, positive results may represent persistent MDA or the presence of active immunity, and MDA does not have the same ability to protect against infection. In-house serologic assays can also be used to decide whether pregnant animals are susceptible in a shelter environment and thus minimize adverse reactions to attenuated live vaccines in this group of animals (see Appendix I). A study that evaluated the performance of one ELISA assay (Synbiotics TiterCHEK CPV/CPV) found that for CPV antibodies, the sensitivity and specificity of the assay was 92% and 94%, respectively, when compared with hemagglutination inhibition; and for CDV was 76% and 92%, respectively, when compared with serum neutralization.[29]

**FIGURE 12-3** Facial edema and hyperemia in a 4-month old intact male Chihuahua mix after vaccination with a bacterin vaccine. (Courtesy Dr. Stephen D. White, University of California, Davis Veterinary Dermatology Service.)

## Adverse Reactions to Vaccines

A vaccine is needed if an infectious disease causes significant morbidity and mortality. Vaccines should prevent more disease than they cause. In order to produce protective immunity, a vaccine *must* stimulate a reaction in an animal, both at the site of injection and systemically. This may cause clinical signs. Ideally, the signs are mild and either unnoticeable or acceptable to the pet owner. In rare situations, adverse reactions are severe enough to threaten a pet's life. Sometimes, enhanced efficacy leads to a reduction in vaccine safety. Veterinarians are encouraged to report adverse reactions to vaccines to a technical service veterinarian employed for this purpose by the vaccine manufacturer. In some countries, the drug company then reports details of the adverse reaction to drug regulatory authorities. An understanding of the true nature and incidence of adverse effects associated with vaccination has been hampered by underreporting and variable delays between vaccination and the inconsistent appearance of potential, more chronic systemic adverse effects.[30] In addition, correlation of adverse reactions to vaccine administration in young animals may be difficult because of the uniform and frequent administration of vaccines to this group. For example, it has been difficult to prove a connection between vaccination for distemper and development of hypertrophic osteopathy in Weimaraner dogs.

### Immune-Mediated Vaccine Reactions

#### Type I Hypersensitivity Reactions

Type I hypersensitivity reactions occur when allergens cross-link IgE molecules that are bound to receptors on mast cells and basophils and trigger degranulation. Clinical signs of type I hypersensitivity responses that occur after vaccine administration include facial or periorbital edema, urticaria, cutaneous hyperemia, generalized pruritus, salivation, hypotensive shock, tachypnea, vomiting, diarrhea, collapse, and even death (Figure 12-3). Vomiting and respiratory distress are common in cats. These signs generally occur within 24 hours of vaccine administration; anaphylaxis usually begins within minutes. The estimated incidence of anaphylaxis after vaccination of dogs and cats is 1 in 5000 to 1 in 50,000 and depends on the vaccines used. One retrospective study evaluated 1.23 million dogs and nearly 0.5 million cats from more than 300 Banfield hospitals in the United States in 2002 through 2005. In this study, vaccine-associated adverse effects that were listed as vaccine reactions, allergic reactions, anaphylaxis, urticaria, and/or cardiac arrest were documented within 3 days of vaccine administration in 38.2 per 10,000 dogs and 47.4 per 10,000 cats.[20,31] Reactions coded as "allergic" or "anaphylaxis" were reported in approximately 1 in 785 dogs and 1 in 1200 cats. Reactions coded as anaphylaxis constituted only 5% of these reactions. Death occurred in 1 in 400,000 dogs and 1 in 125,000 cats that received vaccines, and all 3 dogs and 1 of the 4 cats that died received four or more doses of a vaccine (i.e., more than one vaccine product administrated simultaneously). Most reactions in dogs (73%) occurred on the day the vaccine was administered (day 0), 19% occurred on day 1, 6% on day 2, and 3% on day 3. Data from the UK Veterinary Products Committee report indicated anaphylaxis in 1 in 385,000 vaccinated dogs and 1 in 555,000 cats.[23]

Vaccines that contain large amounts of adjuvant, certain preservatives, or inactivated bacteria with proinflammatory outer surface components are more likely to cause reactions. Proteins present in fetal calf serum and stabilizers such as gelatin within the vaccine may also be responsible for allergic reactions.[32] In the Banfield study, the risk of reactions increased with the number of vaccine doses (i.e., volume of vaccine in milliliters) administered per office visit.[20] Small-breed dogs, such as miniature dachshunds, pugs, Boston terriers, miniature pinschers, and Chihuahuas, were more susceptible to development of acute vaccine reactions, and the risk of a vaccine-related adverse increased as body weight decreased. The risk of vaccine-related adverse events was 4 times greater in dogs that weighed 5 kg or less than in those that weighed more than 45 kg (Figure 12-4). Adverse events increased in frequency with age up until 2 years of age in dogs and 1 year of age in cats, after which the frequency progressively declined to rates lower than that observed in animals less than 1 year of age (see Figure 12-4). The decrease in frequency with older age may have occurred because of owners' unwillingness to have their pets vaccinated if a previous reaction occurred. Sexually intact dogs were less likely to develop adverse reactions than neutered dogs, but the opposite was true for cats.[20,31] Female cats were more likely to exhibit reactions than male cats.

The treatment of choice for anaphylaxis is epinephrine, together with other supportive treatments such as intravenous fluids and supplemental oxygen if necessary. Antihistamines and corticosteroids can be administered to dogs with less severe reactions. Vaccination should be avoided in animals with a history of severe reactions. Pretreatment with an antihistamine could be considered in animals with a history of mild reactions. These animals should also be monitored closely in the hospital for several hours after vaccine administration. It has been suggested that in the future, commercial production of low-dose vaccines for small-breed dogs might be more appropriate, given their increased risk of reactions and more marked serologic responses to vaccination.[33]

#### Other Hypersensitivity Reactions, including Autoimmune Disease

Type II hypersensitivity reactions occur when IgG and IgM bind to cell surface antigens and fix complement, with target cell lysis or removal of target cells by macrophages within reticuloendothelial tissues. Concerns have been raised that vaccination may predispose certain genetically susceptible individuals to immune-mediated cytopenias, although as in human medicine, studies of dogs and cats to date have failed to conclusively document vaccines as causes of these and other chronic diseases.[21,34]

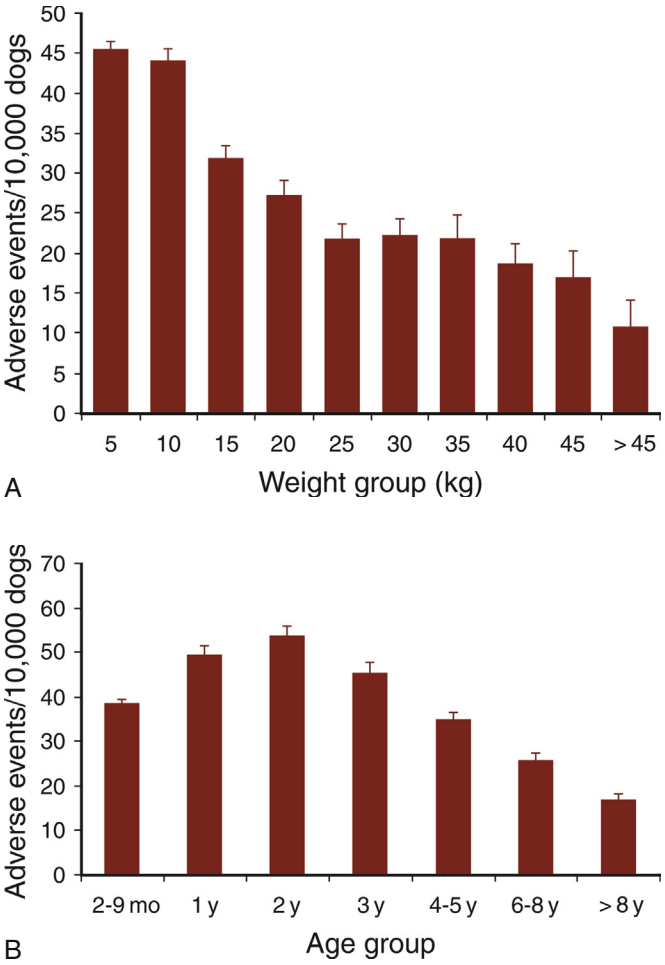


**FIGURE 12-4** Correlation between **(A)** body weight and **(B)** age and the occurrence of vaccine-associated adverse effects within 3 days of vaccination in dogs. (From Moore GE, Guptill LF, Ward MP, et al. Adverse events diagnosed within three days of vaccine administration in dogs. J Am Vet Med Assoc 2005;227(7):1102-1108.)

Immune-mediated hemolytic anemia was suspected to occur following parvovirus vaccination, possibly due to the hemagglutinating properties of the virus and the high antigen mass in some of these vaccines,[35] but a later retrospective case-control study found no association.[36] Transient thrombocytopenia can occur after vaccination in some dogs.[37] In one study, dogs developed antithyroglobulin antibodies after vaccination, although this was not associated with development of hypothyroidism.[38] Cats that are vaccinated with Crandell-Rees feline kidney (CRFK) cell-derived vaccines develop antibodies against the CRFK proteins alpha-enolase and annexin A2.[39] Whether production of these antibodies has clinical significance remains to be determined.

Type III hypersensitivity reactions are characterized by immune-complex deposition in tissues and may be a consequence of immunization with certain vaccines. For example, anterior uveitis and subclinical nephritis developed in 0.4% of dogs receiving the canine adenovirus-1 (CAV-1) vaccine. This vaccine has now been replaced by CAV-2 vaccines, which rarely produce these lesions. A cutaneous vasculitis has been described after vaccination of dogs and cats with rabies virus vaccines ("rabies vaccine-induced vasculitis")[40-42] (Figure 12-5). This can occur at the site of vaccine administration, and in some animals, a multifocal ischemic dermatopathy and myopathy that affects sites such as the pinnal margins, periocular areas, tail tip, and paw pads has been reported to occur 1 to 5 months after the appearance of the initial skin lesion.[40] The multifocal dermatopathy and myopathy has been reported to resolve after treatment with pentoxifylline and vitamin E. Additional evidence is required to strengthen the association between the multifocal condition and rabies vaccination. Similarly, concerns have been raised about a possible temporal association between vaccination and immune-mediated polyarthritis in some dogs,[43] but this association remains unproven. Immune-mediated polyradiculoneuritis, a type IV hypersensitivity reaction (delayed-type hypersensitivity), occurred after vaccination of dogs with suckling-mouse brain-derived inactivated rabies vaccines, which are no longer

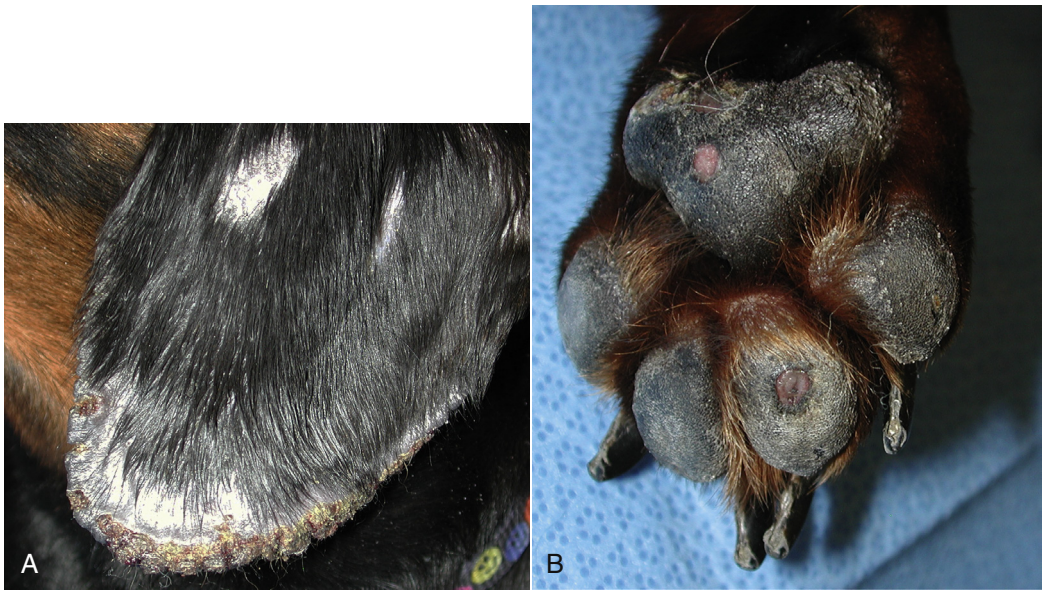


**FIGURE 12-5** Ischemic dermatopathy suspected to be associated with rabies virus vaccination that involved the pinnae **(A)** and footpads **(B)** of a 1-year-old male dachshund. The rabies vaccine was administered several months before the onset of signs. (Courtesy Dr. Stephen D. White, University of California, Davis Veterinary Dermatology Service.)

available.[44] Subsequent reexposure resulted in more severe and prolonged paralysis. Granuloma formation at the site of vaccine administration also represents a type IV hypersensitivity reaction.

Despite the lack of conclusive evidence for an association between vaccination with currently available vaccines and autoimmune disease, it is possible that vaccination may be associated with dysregulation of the immune response in predisposed individuals. Therefore, vaccination is often withheld if not absolutely necessary in dogs and cats with a history of autoimmune disease. Serum titers could also be assessed to gauge the need for specific immunization in these animals.

## Vaccine Organism-Induced Disease

Disease occasionally results from replication of microorganisms present in a vaccine, although severe disease is uncommon with currently available vaccines. Fever and lethargy are the most common adverse effects of vaccination and result from cytokine production in response to the vaccine. These are transient and usually resolve within 1 to 2 days.

In the past, the use of attenuated rabies virus vaccines resulted in ascending paralytic disease in a proportion of cats and dogs. This led to a change to inactivated, adjuvanted rabies vaccines. Administration of attenuated parvovirus vaccines to pregnant cats and dogs can lead to cerebellar disease in the fetus, and these vaccines have the potential to cause severe disease if shed vaccine virus infects colostrum-deprived neonates that are less than 2 weeks of age.[2] Some CDV vaccines have been associated with postvaccinal distemper in young puppies.[45] As a result, vaccination with live attenuated CDV and CPV (dogs) and feline panleukopenia virus (cats) vaccines should be avoided in pregnant animals, puppies and kittens less than 6 weeks of age, and animals receiving potent anticancer chemotherapy drugs. Some CDV vaccine strains, such as Rockborn-like strains, are more virulent than others, and these may continue to circulate and contribute to distemper in the dog population.[46] The safest attenuated live CDV vaccines contain the Onderstepoort strain. Vaccination of certain exotic pet, zoo, and wild animal species, such as ferrets, with any attenuated live CDV vaccine for dogs can also lead to postvaccinal distemper.[47,48] For animals with chronic immunocompromise, the use of inactivated vaccines has been recommended if immunization is deemed necessary. However, inactivated vaccines may have reduced efficacy in immunocompromised animals compared with healthy animals.

The use of mucosal (e.g., intranasal) vaccines for respiratory pathogens in dogs and cats can be followed by development of mild to moderate, transient upper respiratory tract signs. There have been concerns that mucosal *Bordetella bronchiseptica* vaccines may cause respiratory disease in immunosuppressed humans who inhale the vaccine directly during administration or who contact vaccine organisms that are subsequently shed by the vaccinated dog,[49,50] but definitive proof of this is still required. Inadvertent parenteral administration of the avirulent live intranasal *B. bronchiseptica* vaccine to dogs can lead to local injection-site reactions and, occasionally, fatal hepatic necrosis.[51] Inadvertent parenteral administration of mucosal *B. bronchiseptica* vaccines should be treated with subcutaneous fluids at the site of administration and treatment with an oral antibiotic likely to be effective against *B. bronchiseptica*, such as doxycycline. The ASPCA Poison Control Center also recommends injection of a gentamicin sulfate solution into the affected area (2 to 4 mg/kg gentamicin sulfate in 10 to 30 mL of saline).[4] Doxycycline treatment could be continued for 5 to 7 days. Dogs that develop hepatic necrosis may need more aggressive supportive care.

**FIGURE 12-6** Two-year-old female toy poodle/maltese terrier mix that developed focal alopecia at the site of vaccination followed by regrowth of hair with an altered color and texture. (Courtesy Nicole Pierce, University of California, Davis, Class of 2013.)

## Local Cutaneous Reactions and Injection-Site Sarcomas

Local cutaneous reactions are common adverse effects of vaccination, especially in cats, and include pain, swelling, irritation, and abscess formation. In dogs, focal alopecia or discoloration of the haircoat at the vaccination site can also occur (Figure 12-6). Inactivated, adjuvanted vaccines have been most commonly incriminated. Focal cutaneous granulomas and sometimes permanent focal alopecia have been most commonly reported after inactivated rabies vaccine administration to breeds such as Maltese terriers and bichon frisé.

In the late 1980s, an increase in inflammatory injection-site reactions at the site of rabies vaccine administration were noted in canine and feline biopsy specimens sent to the University of Pennsylvania. Shortly thereafter, sarcomas were observed at these sites in cats in the United States, with a 25% increase each year from 1987 to 1991 (Figure 12-7).[52] This followed (1) the change from attenuated live to inactivated rabies vaccines, (2) increased use of rabies vaccines in cats, and (3) the introduction of FeLV vaccines. The national incidence of sarcoma formation is estimated to be 0.6 to 2 sarcomas per 10,000 cats that are vaccinated.[53,54] In contrast, in the United Kingdom, it was 0.21 per 10,000 vaccine doses sold between 1995 and 1999.[22] The interval between tumor development and the last rabies vaccine typically ranges from 3 months to 3.5 years. Most tumors are fibrosarcomas, but other types of sarcomas can also occur. Although development of injection-site sarcomas is clearly linked to administration of FeLV, rabies, and other vaccines, development of sarcomas is not related to the use of specific brands or types of vaccine within an antigen class (with the possible exception of recombinant vaccines[56]), reuse of syringes, needle gauge, use and shaking of multidose vials, or concomitant viral infection.[55] There is also no evidence that aluminum-containing vaccines are associated with a higher risk of sarcoma development than aluminum-free vaccines, but there has been concern that adjuvant stimulates an inflammatory response that predisposes to sarcoma formation. A recent study showed that

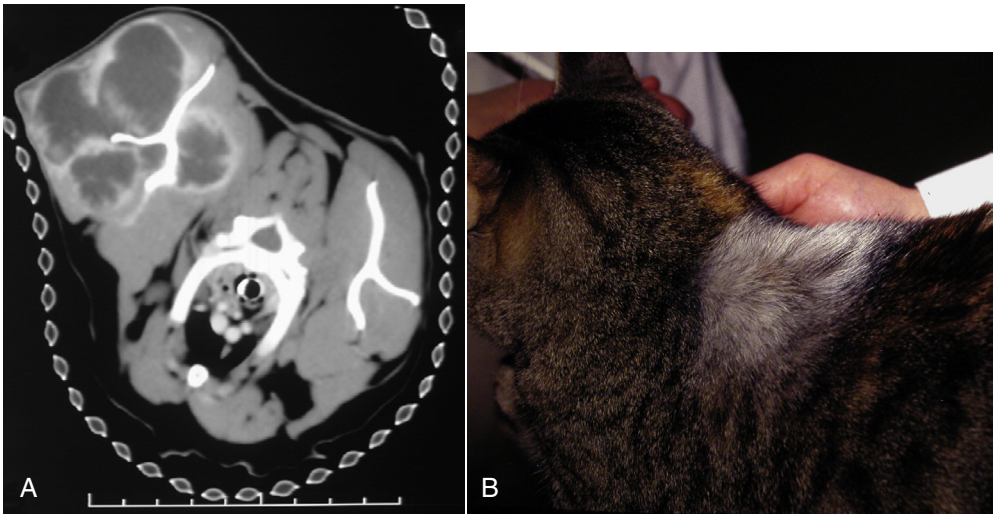


**FIGURE 12-7** **A,** Computed tomographic image of an injection-site sarcoma over the scapula of a 12-year old male neutered domestic shorthair cat. **B,** Discoloration of the haircoat after radiation therapy.

inactivated vaccines were approximately 10 times more likely to be associated with injection-site sarcomas when administered at the pelvic limb site than nonadjuvanted recombinant vaccines.[56] However, neither attenuated live, recombinant, nor inactivated vaccines are risk-free, and injection of certain long-acting injectable medications (especially glucocorticoids) can also be associated with sarcoma formation in cats years later.[56,57] There is some evidence that administration of cold vaccine may also be more likely to be associated with sarcoma formation, but this requires verification.[55] It is currently hypothesized that an individual cat's genetically programmed wound healing response is responsible for the development of injection-site sarcomas.

Treatment of injection-site sarcomas involves aggressive surgical resection followed by full-course post-operative radiation therapy, because of the high incidence of recurrence. Possible adverse effects of radiation include mild to moderate cutaneous burns, hypopigmentation of the hair in the field (see Figure 12-7, *B*), and damage to the spinal cord, lungs, and kidneys within the field, although the last is rare. In one study, the median survival time for cats treated with postsurgical curative radiation therapy was 43 months.[57] Most of these cats had clean margins after surgical resection of the tumor. In contrast, the median survival times for cats treated with coarse fractionated radiation therapy was 24 months. These cats generally had macroscopic disease or dirty margins. Adjuvant chemotherapy with carboplatin or single-agent doxorubicin also has been associated with improved outcome.[57]

In order to prevent death from sarcoma formation in cats, the Vaccine-Associated Feline Sarcoma Task Force (VAFSTF) in North America recommended that rabies vaccines be administered as distally as possible on the right pelvic limb, and leukemia vaccines be administered as distally as possible on the left pelvic limb (rabies right, leukemia left). Care should be taken not to administer the vaccine too proximally or in the flank region, because tumors in these locations cannot be resected as effectively.[58] Other core vaccines should be administered over the right shoulder. These recommendations were not adopted by the WSAVA, which suggested that the skin of the lateral thorax and abdomen be used for vaccination, and vaccination sites be rotated from year to year.[2] Both groups recommended that the interscapular region be avoided, because vaccine constituents can pool in this region and contribute to a chronic inflammatory response. In addition, both groups recommended that the sites of administration and the product and batch number be documented to facilitate the reporting of adverse events. Excessive administration of vaccines to cats should be minimized, and alternative routes, such as intranasal immunization, should be considered. Owners should be advised to monitor injection sites for 3 months after vaccines are administered. If a lump forms and increases in size 1 month after vaccination, or persists beyond 3 months, the owner should have the mass evaluated by the veterinarian.

In accordance with the VAFSTF recommendations, the anatomic location, shape, and size of masses that develop at injection sites should be documented, and an incisional or tru-cut biopsy performed. Fine-needle aspiration is not recommended. If the mass is malignant, routine laboratory tests and thoracic radiography should be performed, together with computed tomography or magnetic resonance imaging of the mass if client finances allow. A veterinary oncologist should be consulted, and if possible, referral to a specialist surgeon or oncologist is recommended. Wide excision that includes at least a 2-cm margin is necessary, and the entire piece of tissue excised should be submitted for histopathology and evaluation of surgical margins. Additional treatment, such as chemotherapy and radiation therapy, is often necessary. Cats should be reevaluated at 3-month intervals for a year after surgery.

## Interference with Diagnostic Test Results

Vaccination has the potential to interfere with the results of assays that detect the antibody response to infection or assays that detect components of a pathogen itself.

*Interference with antibody test results* can be specific or nonspecific. Nonspecific interference is rarely identified, but results from cross-reactivity between antibodies to vaccine components (such as albumin) and the reagents used in serodiagnostic tests. More commonly, specific interference with serodiagnostic tests for the infection that is targeted by the vaccine occurs. This especially problematic if (1) vaccination does not completely protect against infection, (2) the results of serologic tests are required for diagnosis, and (3) infection is chronic and persistent, and so identification of recent natural infection through seroconversion

is usually not possible. For example, the inactivated FIV vaccine does not provide 100% protection, but vaccinated cats develop antibodies to the vaccine virus. These antibodies are detected by ELISA and Western blot immunoassays used for diagnosis of FIV infection. In the absence of a history of vaccination, positive antibody test results indicate active infection.[59] PCR can be used to detect FIV infection in infected cats that have a history of vaccination with FIV vaccines, but PCR can occasionally be negative in cats with active infection, so a negative PCR result does not rule out natural infection with FIV. Vaccine interference with serodiagnosis can occur after vaccination of dogs for influenza or leptospirosis, but because both of these diseases are acute, seroconversion can be used for diagnosis of recent infection in vaccinated dogs. Some serologic assays differentiate between vaccinated and naturally infected animals (DIVA). For example, serologic assays that detect the C6 antigen of *Borrelia burgdorferi* do not detect antibodies that result from immunization with Lyme vaccines. The development of recombinant vaccines that stimulate a pattern of antibody responses that differ from those that result from natural infection can help to overcome issues related to differentiation of naturally infected and vaccinated animals.

Interference with the results of assays *that detect the pathogen itself (as opposed to the antibody response)* occurs after vaccination with attenuated live vaccines that are shed by animals after vaccination. For example, cats may test positive using ELISA assays for FPV antigen after vaccination with attenuated live FPV vaccines, although for some assays, the rate at which this occurs is very low.[60] PCR tests can be positive for extended periods after vaccination with attenuated live vaccines. In some cases, sequence analysis of the PCR product can sometimes allow differentiation between vaccine and field strains, but this is currently performed only on a research basis.[61] Rapid PCR assays have also been designed that differentiate between vaccine and field strains of some pathogens, such as CDV or *B. bronchiseptica*.[62,63] Quantification of organism numbers present in a specimen through the use of real-time PCR assays (e.g., for CDV) may shed light on whether natural infection (high organism load) or vaccination (low organism load) has occurred.

## Vaccine Selection

The advantages and disadvantages of vaccines and vaccine combinations that are currently available on the market are provided in the relevant sections of this book for each infection entitled "Immunity and Vaccination." Suggested vaccination schedules for individual pets and shelter animals that are based on recommendations provided by the American Animal Hospital Association (AAHA), the American Association for Feline Practitioners (AAFP), the European Society for Feline Medicine (ESFM), and WSAVA are summarized in tables in Appendix.[2,15,64-73]

To facilitate vaccine selection, vaccines for dogs and cats have been divided by various task forces into core vaccines, noncore vaccines, and those that are generally not recommended.

*Core vaccines* are recommended for all animals with an unknown vaccination history. The diseases involved have significant morbidity and mortality and are widely distributed, and in general, vaccination results in good protection from disease. All shelter animals should be vaccinated with core vaccines before entry to a shelter or at the time of entry if immunization ahead of time is not possible. Canine core vaccines include vaccines for CPV, CDV, CAV, and rabies for countries where rabies is endemic. The core feline vaccines are those for feline herpesvirus-1 (FHV-1), feline calicivirus (FCV), FPV, and rabies.

*Noncore vaccines* are optional vaccines that should be considered in light of exposure risk, that is, based on geographic distribution and the lifestyle of the pet. Vaccines considered as noncore vaccines for dogs are canine parainfluenza virus, canine influenza virus, *B. bronchiseptica, Leptospira* spp., and *Borrelia burgdorferi*. Optional or noncore vaccines for cats include FeLV, FIV, virulent FCV, *Chlamydia felis,* and *B. bronchiseptica* vaccines.

Several other vaccines are currently available on the market. For dogs, these are vaccines for canine coronavirus, CAV-1, and rattlesnake envenomation. The reports of the American Veterinary Medical Association (AVMA) and the AAHA canine vaccine task force have listed the first two vaccines as not generally recommended, because "the diseases are either of little clinical significance or respond readily to treatment," evidence for efficacy of these vaccines is minimal, and they may "produce adverse events with limited benefit." Currently, information regarding the efficacy of the canine rattlesnake vaccine is insufficient. For cats, the feline infectious peritonitis (FIP) vaccine is not generally recommended by the AAFP.

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