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CURRENT VETERINARY THERAPY

XI

SMALL ANIMAL PRACTICE

W.B. SAUNDERS COMPANY
A Division of Harcourt Brace & Company
Philadelphia London Toronto Montreal Sydney Tokyo

CANINE AND FELINE VACCINES

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Vaccination is a common procedure. Virtually every puppy or kitten that enters a veterinary hospital receives an initial series of vaccinations that continue, in the form of "boosters," for the duration of the animal's life. It is a testament to the overall quality of our commercial vaccines that few directly observable detrimental effects occur from immunization. Thus, it is no wonder that vaccination is frequently believed to be an innocuous procedure. However, it is important to recognize that although vaccination is an important weapon in preventing infectious disease, immunization, like any therapeutic procedure, does have limitations and can cause adverse reactions. This article describes potential problems associated with immunization, as well as when, where, and what type of vaccine should be used in various situations.

MODIFIED LIVE VACCINES, KILLED VACCINES, AND SUBUNIT VACCINES

Three types of vaccines are currently used in veterinary medicine: modified live (attenuated), killed (inactivated), and subunit vaccines. In modified live vaccines, the microorganisms are altered in such a way that they are no longer virulent to the majority of the host species yet retain the antigenic properties that induce a protective immune response. Modified live vaccines may be given locally or parenterally. Local administration of certain modified live vaccines to the mucous membranes of the eyes, nose, and mouth produces not only a strong systemic immunity but also a local immune response. Local immunity is important when the point of entry of the microorganism and the target organ of the disease are the same (e.g., feline calicivirus). An effective local immune response requires a live replicating vaccine and usually cannot be produced by noninfectious vaccines (killed or subunit). Some live vaccines are not fully attenuated and may require inoculation by an unusual route to produce immunity without causing disease (e.g., feline rhinotracheitis via a parenteral route). Care must be taken when immunizing with this type of vaccine, because aerosolization or environmental contamination may expose susceptible animals, resulting in the development of a mild form of the disease. Modified live vaccines must replicate after inoculation to produce enough antigen to induce an immune response. Thus, any inactivation of a modified live vaccine before or immediately after inoculation will result in vaccine failure. Because modified live vaccines replicate in the host, they more closely resemble virulent viral infections and generally produce a stronger and more durable protective immune response than the noninfectious vaccines (killed and subunit). Modified live vaccines may also induce interferon in the first few days after immunization, providing additional early protection against some virulent viral infections. However, this "better" immune response has a cost: a decrease in vaccine safety. Certain modified live vaccines can induce immunosuppression, may be shed into the environment, and may revert to virulence or cause vaccine-induced disease. Thus, even though modified live vaccines generally provide a better immune response that more closely resembles the natural infection, they are not always the best vaccine on all occasions or for all animals.

Killed vaccines are safer than modified live vaccines because they cannot replicate and are unable to cause infectious diseases. However, to induce a protective immune response, killed vaccines require a large antigenic dose, multiple immunizations, and often the use of adjuvants. These factors substantially increase the cost of inactivated vaccines and the probability of local and systemic vaccine reactions. Also, killed vaccines generally produce weaker immune responses with a shorter duration than the immune response produced by modified live vaccines.

Subunit vaccines are not infectious. Thus, subunit vaccines and killed vaccines have some of the same advantages and disadvantages. However, instead of containing the complete microorganism as found in the modified live and killed vaccines, the subunit vaccine theoretically contains only the components of the microorganism that are necessary to produce a protective immune response. The risk of developing an allergic reaction to nonessential vaccine

elements is thus reduced. At present, subunit vaccines are not frequently used in veterinary medicine because of their higher cost and lack of proven efficacy. However, with the advent of recombinant DNA technology and the recent improvements in adjuvants, effective subunit vaccines may become more common (see this volume, p. 457).

PROPER USE, STORAGE, AND ADMINISTRATION

All vaccines should be stored according to the manufacturer's recommendations. Lyophilized products should be used immediately after reconstitution and not stored for prolonged periods in the reconstituted form. Modified live vaccines are particularly sensitive to improper storage. This type of vaccine relies on vaccine virus replication to generate enough antigen to induce an immune response. Thus, improper storage conditions may result in the inactivation of modified live vaccines and thus cause vaccine failures. Although modified live vaccines are more sensitive to improper storage, exposing killed and subunit vaccines to excessive heat or light may also result in reduced immunogenicity. To ensure proper immunization, careful attention should be given to the vaccine storage conditions.

It is important that a new needle and syringe be used to administer each vaccine. Reused syringes and needles may contain contaminants that inactivate the vaccine or interfere with immunization. Vaccines should only be administered at the manufacturer's recommended concentration and reconstituted using the diluent provided with the vaccine. Vaccine products from the same or different manufacturers should never be mixed together in one syringe unless specified in the package insert. Vaccine components from different products may interfere with or inactivate each other, resulting in improper immunization.

Adherence to the recommended route of administration is essential. A rabies vaccine labeled "for intramuscular inoculation only" should not be given subcutaneously. For successful immunization to occur, many modified live rabies vaccines require a well-innervated tissue (i.e., muscle). Nerves serve as a target for rabies virus replication. Viral replication is necessary for the production of enough antigen to induce a protective immune response. Thus, inoculation into the subcutaneous connective tissue (low in nerve endings) often leads to vaccine failure unless the vaccine is specifically approved for subcutaneous inoculation.

It is important for veterinarians to follow vaccine recommendations not only to ensure successful immunization but also to limit their liability should an adverse reaction or vaccine failure occur.

MATERNAL ANTIBODY

One of the most common problems associated with vaccination is maternal antibody interference with active immunization. Maternal immunity, a form of passive immunity, has a vital role for neonates. It helps to protect neonates during the critical transition from the protected uterine environment of the fetus to the hostile external environment of the newborn. This transition occurs not only at a time when a neonate's immune system is not fully developed but also when a neonate's immune system is naive to virtually all pathogens. Without the acquisition of maternal immunity, a neonate's chances of survival are greatly reduced. However, maternal immunity is not without its negative effects. Maternal antibody interference with immunization is the most common cause of vaccine failure, particularly in weanling and postweanling animals. It is generally believed that when this interference occurs maternal antibody binds to the vaccine in such a way that the vaccine is cleared from the body before it is able to stimulate an immune response. Because maternal antibody is acquired exogenously and is not actively being replaced, it is gradually depleted as the animal matures.

Maternal antibody is degraded at a *constant* rate. Its retention time in the animal is largely dependent on the class and quantity of antibody acquired at birth. The level of maternal immunity obtained at or around the time of birth is dependent on a number of factors: the immune state of the dam, the amount of colostrum produced, the immunoglobulin (antibody) content of the colostrum, the amount of colostrum ingested and absorbed, and the age of the neonate at the time of ingestion. These factors can cause substantial variation in the amount of maternal antibody that is transferred to newborn animals, even among littermates.

Because of these factors, it is difficult to accurately predict the level of maternal antibody for a specific puppy or kitten at the time of immunization. It is possible to obtain a serum sample from a given animal and determine the level of maternal antibody to each pathogen. From this information, the most appropriate immunization time for each agent can be determined. However, the cost and time requirements of such determinations would be prohibitive. The most successful and cost-effective approach to immunizing animals with unknown amounts of maternal antibody is based on multiple vaccinations, with the last immunization occurring at approximately 22 weeks of age for a puppy and approximately 16 weeks of age for a kitten.

By the time an animal reaches these ages, the vast majority (>95%) of animals no longer have levels of maternal antibody sufficient to interfere with active immunization. It is important to note

that many of the previous puppy immunization schedules recommend that the last immunization in the series occur at 12 to 16 weeks of age. New information on maternal antibody to canine parvovirus demonstrates the need to extend the last immunization in the series to 20 to 22 weeks of age, so a greater percentage of puppies can be effectively immunized. As many as 20% of dogs at 18 weeks of age have enough maternal antibody to prevent successful canine parvovirus (CPV) immunization. Thus, it is important to recognize that unless the last immunization is given at 22 weeks of age or later that a certain percentage of the animals will remain unprotected until the next immunization, probably at the yearly booster vaccination. It is possible that under certain conditions, the level of maternal antibody at 20 weeks of age for a puppy and 14 weeks of age for a kitten may also interfere with the immunization of other canine and feline pathogens. Thus, for this reason, we recommend that the last immunization of the initial vaccination series occur at 22 weeks of age for puppies and 16 weeks of age for kittens. Various immunization programs have recommended initial vaccination ages of 6, 8, or 9 weeks with repeat immunizations at 2-, 3-, 4-, or 6-week intervals. The program that is correct for your practice largely depends on your philosophy and the incidence of disease within your community. Certainly, the more vaccinations an animal receives, within reason, the more likely it will become actively immunized at the earliest possible age and the less likely it will be susceptible when exposed to virulent agents. However, one must weigh the possible risk of infection versus the cost to the client and possible risks to the patient. We believe that a reasonable compromise for puppies would be three to four immunizations given at regular intervals between the ages of 6 and 22 weeks and for kittens two to three immunizations given at regular intervals between the ages of 6 and 16 weeks. Veterinarians frequently blame a vaccine failure on a "bad vaccine." However, it is more likely that the vast majority of vaccine failures, between the ages of 4 months and 1 year, occur as the result of giving the last vaccination when the maternal antibody levels are sufficient to prevent active immunization.

A substantial problem, especially for CPV, is that virulent virus is able to infect and cause severe disease in animals with levels of maternal antibody that prevent active immunization. There is a 2- to 5-week window of vulnerability when an animal can be infected with virulent virus but cannot be successfully immunized. This is of particular concern in some breeding kennels where the level of environmental contamination with CPV is so high that virtually every puppy born within the kennel contracts CPV disease before it can be successfully immunized. In kennels with this problem, the best solution, although often difficult to implement, is to totally remove the puppies from the kennel at 4 to 6 weeks of age and not allow them to return until they have completed their full immunization program, at approximately 6 months. It is important that these isolated puppies not have direct or indirect contact with persons or equipment from the contaminated kennel until their immunization program is complete, because CPV is very stable and can persist on fomites for weeks.

Maternal antibody interference with canine distemper virus (CDV) immunization is overcome by a unique approach: the development of heterotypic immunity. Heterotypic immunity is the production of an immune response to one microorganism by immunizing with a different but antigenically related microorganism. Measles virus (MV) is antigenically related to CDV. When MV is inoculated into a puppy with moderate levels of CDV maternal antibody, an immune response is produced that protects the puppy from CDV disease. It is important to realize, when considering the use of MV, that high levels of CDV maternal antibody will also prevent immunization with MV. For this reason, it is not advisable to vaccinate with MV before 6 weeks of age. MV vaccination should be given only once early in the immunization schedule. Multiple immunizations given to older animals may result in high MV maternal antibody titers, which will limit the effectiveness of MV as a heterotypic vaccine for the next generation. MV may be given alone or in combination with CDV vaccine. However, MV is more effective when inoculated alone. Another important and poorly understood aspect of MV vaccine is that MV should always be given *intramuscularly*.

MV vaccination does not prevent infection with CDV but does prevent the development of clinical CDV disease. This is accomplished by MV vaccination inducing a cross-reactive T-helper immunity to CDV. When MV-vaccinated dogs are exposed to CDV, through vaccination or virulent virus, they produce a rapid anamnestic antibody response to CDV. It is this rapid antibody response that prevents clinical CDV disease from developing.

VACCINATION AND IMMUNOSUPPRESSION

We recently reported that certain polyvalent vaccines cause immunosuppression, as measured by a significant decrease in an *in vitro* immune function assay, the lymphocyte blastogenesis test (Phillips et al., 1989). When the individual components of the immunosuppressive polyvalent vaccines were inoculated alone into dogs, the immunosuppression did not occur, leading us to believe that the suppression was caused by an interaction between two or more components of the vaccine. We were able to reproduce the suppression of the polyvalent vaccine by

combined inoculations of the CDV component and the canine adenovirus type 1 (CAV-1) or canine adenovirus type 2 (CAV-2) components from various immunosuppressive polyvalent vaccines.

Although the degree of suppression induced by some of the polyvalent vaccines was significant (>80% suppression), it was transitory, persisting for 7 to 10 days. Generally, for immunosuppression to be clinically apparent, it must persist for weeks or months. Thus, vaccination by itself is unlikely to cause detectable adverse effects in an animal. However, under unusual circumstances, even this relatively short duration of lymphocyte suppression may become clinically important, especially if an animal is already in a partially immunosuppressed condition (e.g., nutritional deficiency). Also, it is possible that vaccine-induced immunosuppression may potentiate the severity of a concurrent disease or allow an inapparent infection to become evident.

It is important that results of our study not be misinterpreted. Our results do not suggest that polyvalent vaccines should not be used. All vaccines must be demonstrated safe and efficacious to be licensed. Polyvalent vaccines are efficacious and convenient for both veterinarians and clients. However, vaccination should not be viewed as an innocuous procedure and should be performed in accordance with a manufacturer's recommendations: that is, only *healthy, clinically normal* animals should be vaccinated. It should also be understood that adverse reactions can and will occur regardless of the type of vaccine used.

POLYVALENT VS. MONOVALENT VACCINES

Concern has been expressed about the frequent use of polyvalent vaccines in veterinary medicine. This concern primarily deals with the presumed problems of vaccine interference and antigen overload. Antigen overload occurs when the amount of antigen exceeds the ability of the immune system to respond, and vaccine interference occurs when the inoculation of one vaccine prevents the immune response to another vaccine. There is no scientific evidence that either problem occurs with the currently available canine or feline vaccines. However, as discussed earlier, some polyvalent vaccines have been shown to cause transitory immunosuppression and should be avoided when there is a high potential for concurrent immunosuppression. With monovalent vaccines, concerns about antigen overload, vaccine interference, and vaccine-induced immunosuppression are alleviated but at the expense of convenience and cost.

IMMUNIZATION OF HOSPITALIZED PATIENTS

All animals entering the hospital for elective procedures, boarding, or grooming should have a current vaccination history. If not, they should be immunized at least 10 days before admission. However, an acutely ill patient that requires immediate hospitalization but does not have a vaccination history, in most cases, should *not* be vaccinated for the following reasons: (1) vaccination is not likely to be effective until at least 3 to 7 days after immunization, (2) the immunosuppression of certain polyvalent vaccines may contribute to the current admitting illness, and (3) if the admitting illness has an immunosuppressive component, vaccination may not result in effective immunization or, worse, may result in postvaccinal disease (i.e., postvaccinal distemper encephalitis). Furthermore, if the animal has previously been immunized, it is likely that protective immunity remains. An exception to the foregoing counsel would be an outbreak of a new epizootic disease. In an epizootic outbreak, an acutely ill animal without a vaccination history should be immunized against the agent causing the disease, because the chances of exposure are greatly increased.

ANNUAL VACCINATIONS

A practice that was started many years ago and that lacks scientific validity or verification is annual revaccinations. Almost without exception there is no immunologic requirement for annual revaccination. Immunity to viruses persists for years or for the life of the animal. Successful vaccination to most bacterial pathogens produces an immunologic memory that remains for years, allowing an animal to develop a protective anamnestic (secondary) response when exposed to virulent organisms. Only the immune response to toxins requires boosters (e.g., tetanus toxin booster, in humans, is recommended once every 7 to 10 years), and no toxin vaccines are currently used for dogs or cats. Furthermore, revaccination with most viral vaccines fails to stimulate an anamnestic (secondary) response as a result of interference by existing antibody (similar to maternal antibody interference). The practice of annual vaccination in our opinion should be considered of questionable efficacy unless it is used as a mechanism to provide an annual physical examination or is required by law (i.e., certain states require annual revaccination for rabies).

IMMUNIZATION OF ANIMALS ON CORTICOSTEROIDS

The common use of glucocorticosteroids for various chronic inflammatory diseases raises a question about how affected animals should be immunized. It seems logical that suspected immunosuppressive agents should be avoided when attempting to in-

duce a primary immune response. Interestingly, although glucocorticosteroids are frequently thought of as immunosuppressive agents, there are no data to suggest that they interfere with canine or feline immunization. On the contrary, the available studies suggest that they do not adversely affect immunization (Nara et al., 1979). However, if possible, prudence would suggest that glucocorticosteroid therapy gradually be reduced or eliminated a week before and for 2 weeks after primary vaccination. Animals with seasonal allergies should probably be vaccinated at the time of year when glucocorticosteroid therapy is not required. However, the available evidence suggests that vaccination will likely be successful whether the glucocorticosteroid dose is reduced or not.

VACCINE REACTIONS

It is common for an animal receiving its first immunization to have a mild vaccine reaction. At the site of inoculation, a local reaction consisting of a painful inoculation, pruritus, swelling, redness, or abscess formation can occur. These local reactions are more common with inactivated vaccines, because this type of vaccine often contains adjuvants (local irritants) and also a greater amount of antigen than the modified live vaccines. Mild systemic reactions occur, particularly with modified live vaccines, because these vaccines have virus that replicates after immunization. Vaccine virus replication may be viewed as a mild infection that can result in temperature elevation, decreased activity, or increased irritability.

It is important that pregnant animals not be inoculated with a modified live vaccine unless the vaccine has been approved for this use, because fetal resorptions, abortions, or birth defects may result. Inactivated vaccines have been reported to cause problems when given to pregnant dogs, possibly from the stress associated with vaccination or adverse reactions sometimes resulting from these products. Similarly, animals younger than 3 weeks should not receive a modified live vaccine, unless the vaccine has been shown to be safe at this early age.

An occasional dog develops an immune complex disease after being administered CAV-1 vaccine. This condition is called "blue eye," because the affected eye develops a bluish cast in the cornea. The blue is the result of corneal edema, occurring from the deposition of antigen-antibody complexes. This is an immune-mediated (type III hypersensitivity) reaction. The dog usually regains full vision in the affected eye. Because of this adverse reaction, we recommend that dogs be immunized only with CAV-2. CAV-2 vaccine does not appear to cause blue eye and effectively protects against both virulent CAV-1 and CAV-2.

On rare occasions, anaphylaxis (type I hypersensitivity) may occur after immunizations. Anaphylaxis usually develops within an hour after immunization, presenting as weakness, dyspnea, vomiting, mucous membrane pallor, collapse, or death. The vaccine component that is most commonly associated with this reaction is the leptospirosis bacterin, although any component of the vaccine can cause anaphylaxis. Animals that develop anaphylaxis should never be reimmunized with the same vaccine until the causative component has been identified. Problem animals should be observed at the veterinary clinic for 1 hr after immunization with all vaccines.

Incomplete vaccine attenuation or vaccination of an immunosuppressed host can result in modified live vaccines causing the disease they are designed to prevent. Examples of this problem are feline respiratory vaccines causing a mild upper respiratory tract disease after immunization and the development of postvaccinal encephalitis subsequent to canine distemper vaccination. An even more alarming example is vaccine induction of clinical rabies (Esh et al., 1982; Pedersen et al., 1978). The reasons why vaccines become virulent are not always known. However, it is important that veterinarians be familiar with these possible outcomes of immunization and give modified live vaccines only to approved animals that are in good general health and have no indication of immunosuppression.

Most infectious diseases of dogs and cats have been controlled through the use of conventional vaccines. Although not perfect, these vaccines are exceptionally safe and effective. The future challenge will be to continue to improve the safety and efficacy of our current vaccines and to develop new vaccine approaches for diseases that have thus far been resistant to immunization.

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