Vaccination of dogs and cats: General principles and duration of immunity

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Vaccination of dogs and cats has recently become a topic of concern for veterinarians and pet owners, as questions have arisen regarding vaccine safety and duration of immunity (1). Emerging data indicate that we may be vaccinating too frequently against some pathogens, and, although infrequent, serious complications can be associated with vaccination. In addition, there are questions regarding vaccine efficacy and whether or not it is appropriate to vaccinate all animals with all types of vaccines available. Recommendations that include significant changes to current vaccination practices are being made by various individuals and groups. The Canadian Veterinary Medical Association recently published its action plan to address the issue of vaccine protocols, including a Public Statement on Vaccines (2).

This commentary has been written to assist the practitioner with vaccine-related decision making, by describing the principles of vaccination and reviewing the issue of duration of immunity. A follow-up commentary will review safety concerns and suggest a rational approach to making decisions regarding vaccination protocols for dogs and cats.

Vaccine design

Vaccines can be made from viruses, bacteria, fungi, protozoa, or helminths. Vaccines are either attenuated ("modified live virus (MLV)") by serial passage through culture or inactivated ("killed"). *Attenuated* products infect the animal and replicate to a limited extent, inducing humoral, cell-mediated, and mucosal immunity. These vaccines tend to "break-through" maternally-derived immunity at an earlier age than do inactivated products and induce immunity more rapidly than do inactivated products, and they induce protective immunity after only one dose (assuming maternal immunity has waned). Because attenuated products are living organisms, they can be inactivated through improper storage or administration. A concern of less frequency but greater consequence is that these vaccines may not be adequately attenuated and thus may cause disease. For example, ascending paralysis was associated with attenuated rabies vaccines in cats. Another problem is that of contamination with other pathogens, as was reported in 1994, when a combination canine vaccine was contaminated with a bluetongue virus, causing the death of several pregnant bitches (3). Further, attenuated vaccines can cause fetal injury and should not be given to pregnant animals.

Safety and stability are the major benefits of *inactivated* products; however, they do not mimic natural infection, and thus may not engender adequate cell-mediated or mucosal immunity. Inactivated products often contain adjuvants, chemicals that induce a (usually) mild inflammatory response, which is necessary to recruit cells associated with the immune response. Aluminum hydroxide, mycobacterial cell wall extracts, and Quil A are examples of adjuvants; some others are proprietary and their composition is not described in detail on the label.

For some pathogens, such as rabies virus, *Leptospira* spp., *Borrelia* sp., and feline leukemia virus (FeLV), only inactivated products are available. For other pathogens, such as canine distemper virus, measles virus, canine adenoviruses 1 and 2, parainfluenza virus, and feline coronavirus, only attenuated products are available. Both types of products are available for some pathogens, such as canine parvovirus, *Bordetella* sp. (attenuated bacterins are given intranasally, inactivated products are given parenterally), canine coronavirus, feline calicivirus, herpesvirus, parvovirus, and *Chlamydia psittaci.*

For convenience, many vaccines contain antigens from multiple pathogens. Product licensing agencies require that multiple-antigen products have the same efficacy as vaccines containing each antigen alone; however, there is data suggesting that, in some cases, multiple antigens may actually interfere with the immune response to the vaccine. On the other hand, one could argue that the use of combination vaccines in cats is associated with less adjuvant being administered, which might reduce the likelihood of induction of postvaccinal sarcomas in susceptible animals. These concerns have not yet been resolved.

Vaccines also contain diluents, which include water for suspension, buffers, indicator dyes, and preservatives. Diluents are designed for specific products, so one brand of diluent should not be used with another brand of vaccine.

Newer vaccine technologies are designed to make products safer; they include "extracted" bacterins (which

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contain only bacterial surface antigens, without bacterial endotoxin) and "sub-unit" products, such as one of the FeLV vaccines containing unassembled FeLV virus produced by transformed cell lines. Vaccines based upon recombinant DNA technology are also entering the market, and include products in which the gene(s) encoding antigen(s) associated with the induction of protective immunity is/are cloned and expressed in *Escherichia coli,* for example, a *Borrelia burgdorferi* vaccine. A high concentration of antigen is thus obtained in a nonvirulent product. However, it is not known if the presentation of an isolated antigen to the immune system is as effective in the induction of protective immunity as is presenting the antigen in the context of the infectious agent. The answer will likely vary from pathogen to pathogen. Another recombinant DNA approach is to delete virulence genes from the agent, leaving the protection-inducing antigens in place. There are no products of this type for use in dogs and cats yet, although a swine pseudorabies virus vaccine and a human hepatitis B virus vaccine have been licensed. A third recombinant DNA approach is the *"vectored"* vaccine, in which a gene(s) encoding an antigen known to induce protective immunity is spliced into an unrelated virus that serves to deliver (vector) the gene of interest into host cells. An example of this approach is a canarypox vector canine distemper virus vaccine, which will be available in Canada soon. Vaccines based upon recombinant technology are probably safe in that they are not virulent and may not require adjuvants, but it remains to be shown if they are as effective as vaccines made by more traditional methods.

Response to vaccination

The goal of *vaccination* is to induce protective immunity (*immunize* the animal) by engendering a broad immune response, including humoral immunity, cell-mediated immunity, and mucosal immunity. Ideally, protective immunity will occur at the initial site of exposure to the pathogen and will prevent infection. Failing this, the concept is that an immune response will prevent the development of serious clinical disease. Antibodies delivered to the young animal via colostrum can bind vaccine antigens and may prevent an immune response to the vaccine. The initial exposure to an antigen, or *primary immunization,* of a puppy or kitten is designed to overcome this maternally derived immunity. In the case of inactivated vaccines, primary immunization protocols usually include a second dose of vaccine to induce an anamnestic or "boosted" response. Regardless of the type of product used, a protective immune response will not be present in young animals in which maternally derived antibody has waned, until approximately 2 wk following primary immunization. Theoretically, if the animal is exposed later to the specific pathogen, the infection (or at least clinical signs) will be controlled by the induced immunity. As long as memory cells are present, the immune system will respond rapidly upon reexposure to the pathogen.

The protective immune response is usually directed toward multiple sites, or epitopes, on a given antigen. Switching vaccine brands at the time of revaccination does not require that one starts the immunization procedure again from the beginning, as it is highly likely that at least some epitopes are shared between products.

Failure of immunization

It is likely that the most common cause of failure of primary vaccination is interference by maternally derived immunity. Other causes of "vaccine failure" include administration of a vaccine containing a strain of pathogen that is different from the strain encountered by the animal (*Leptospira* bacterins contain only *L. canicola* and *L. icterohemorrhagiae,* which do not cross immunize against other *Leptospira* serovars), and inactivation of the product through improper storage, reconstitution, or improper route of administration. Malnutrition, debilitation, and major illness can also be associated with an inadequate response to vaccination, as can immunosuppression associated with concurrent illness or cytotoxic drug therapy. Some drugs, such as tetracycline, chloramphenicol, dapsone, clindamycin, griseofulvin, nalidixic acid, and sulfamethoxypyridazine have been associated with an inadequate response to vaccination. Vaccination of animals receiving glucocorticoids should be avoided, if practical, although challenge studies have shown that "immunosuppressive" doses of glucocorticoids given at the time of vaccination do not significantly inhibit the immune response to canine distemper virus or rabies virus vaccines (4). Similarly, anesthesia and surgery do not impair the response to canine parvovirus vaccines (5).

Apparent vaccine failure occurs when the animal is either incubating the pathogen or is exposed to it at the time of vaccination, in which case the disease may develop before an effective immune response can develop. In rare instances, a normal animal will simply not mount an adequate immune response to the vaccine antigens.

Efficacy of vaccination

Some vaccines, such as those for canine distemper and panleukopenia, are thought to induce long-lasting protective immunity in most vaccinates, although the data from challenge studies are limited. However, some attenuated vaccines used in the past performed poorly because the vaccine strains were over-attenuated. For example, it was shown that several canine parvovirus vaccines did not induce protective immunity due to over-attenuation and low antigen mass. This problem has been overcome with the development of low-passage (less attenuated), high-mass parvovirus vaccines (6).

Pathogens that are associated with chronic or latent infections are generally more difficult to vaccinate against than those that cause acute infections. The biology of feline herpesvirus, calicivirus, and FeLV infections is such that vaccination is less efficacious than in diseases such as canine distemper and panleukopenia. Vaccination alone may not control these types of pathogens, and proper husbandry needs to be emphasized for animals at high risk for these infections.

Duration of immunity

The duration of vaccine-induced immunity is variable, both among different pathogens and among individuals vaccinated against the same pathogen, and may not

last for the life of the animal. Manufacturers thus recommend *revaccination,* and as the maximum duration of immunity is not known for most products, the recommendation has been to revaccinate annually, assuming that vaccination is a safe procedure. A current concern is that, in predisposed animals, vaccination is not always safe. The corollary is that the likelihood of vaccine-associated complications might be reduced if dogs and cats were vaccinated less frequently.

The annual interval is a convenient, but arbitrary, recommendation, which is not grounded in *maximum duration of immunity* studies (the length of time a vaccine induces protective immunity, based upon challenge), as these studies are prohibitively expensive and logistically difficult for manufacturers to carry out. Some *minimum duration of immunity* studies have been published, documenting that a specific product induces immunity for at least one year (7,8). Veterinarians realize that the basic biology of the immune response of dogs and cats is probably not significantly different from that of humans, a species that does not require annual revaccination for many pathogens. Nevertheless, the benefits of a yearly physical examination associated with vaccination has been considered to partially justify this practice in companion animals.

There is now evidence that vaccination can be harmful in rare animals. For example, the development of sarcomas at vaccination sites in cats and an association between recent vaccination and immune-mediated anemia in dogs are of particular concern. Coincidentally, information is now becoming available regarding the duration of immunity for some vaccines, especially rabies vaccines, for which challenge-documented duration of immunity studies have demonstrated protection for 3 y.

The measurement of serum virus-neutralizing antibody titers is one measure of immunity, and for some infections (canine distemper, panleukopenia) correlates well with the level of immunity. Serum antibody titers may not correlate well with protective immunity for other infections (feline herpesvirus, feline calicivirus) in which cell-mediated immunity and mucosal immunity are important determinants of protection. Recently, the duration of serum virus-neutralizing antibody titers was published for feline parvovirus, herpesvirus, and calicivirus. This study documented persistence of titers considered to be protective for at least 3 y in all cats tested (9). Based upon these data, the American Association of Feline Practioners and Academy of Feline Medicine have published recommendations that cats undergo primary immunization for parvovirus, herpesvirus, calicivirus, and rabies virus as directed by the manufacturer, followed by revaccination 1 y later, then every *3 y.* The recommendation also states that veterinarians may elect to vaccinate more frequently on the basis of risk assessments of their patients (10). Parvovirus, herpesvirus, calicivirus, and rabies virus represent the *core* vaccines that all cats should receive, based upon the ubiquitous nature and seriousness of these infections, or their zoonotic potential, given that the vaccines are safe and effective. While recognizing that these recommendations are consistent with available data, it is also important to realize that (other than for rabies vaccines) they are based largely on a single study in a small number of cats; the cats were vaccinated with only one product, which might not be representative of all products on the market; and a challenge exposure was not performed. Certainly, a new product would never be licensed, based upon the strength of this data.

"Non-core vaccines" (vaccines that are only indicated for cats at demonstrable risk) include FeLV, feline coronavirus, and *Chlamydia psittaci.* The maximum duration of immunity for these vaccines has not been published, and the current American Association of Feline Practioners recommendation is to revaccinate *annually* with these products, if the cat is considered to be at risk for developing these infections.

Similar recommendations have been made for vaccination of dogs, with the "core" vaccines being canine distemper virus, adenovirus-2, parvovirus, and rabies virus. According to these recommendations, primary immunization should be performed as directed by the manufacturer, the dog should be revaccinated 1 y later, and then *every 3 y* (11). Again, although this makes biological sense in the light of serologic data, there is little published data derived from challenge studies to support this schedule (other than for rabies).

With respect to "non-core" vaccines, the utility of parenteral parainfluenza virus vaccines has not been demonstrated. Intranasal vaccination of dogs with attenuated *Bordetella bronchiseptica* and parainfluenza virus is indicated for dogs at risk, but the duration of immunity induced by these products is unknown (and may be only months). *Leptospira* vaccines have been associated with short-lived immunity (months), and do not induce protective immunity against serovars, such as *pomona* and *grippotyphosa,* which appear to be increasing in prevalence (12). There is still considerable debate over the utility of *Borrelia* sp. vaccines (13,14). Finally, it is difficult to document that canine coronavirus is a significant pathogen, and the need to vaccinate against it has not been proven (11).

Why not simply measure serum virus-neutralizing antibody titers and revaccinate as necessary? As already mentioned, while serum titers are reasonable indicators of protection for some infections, there are others in which cell-mediated immunity and mucosal immunity are important, and titers could give misleading information. Also, the determination of titers is not a standardized procedure, and different laboratories will report significantly different values for the same serum. For titers to be useful in predicting when revaccination is necessary, it would be critical that the assays be standardized or run by a central laboratory.

Conclusion

A basic understanding of vaccine antigens and adjuvants, as well as the relative strengths and weaknesses of attenuated and inactivated products is a necessary background for rational vaccine decision making. The design of primary immunization protocols is based upon the induction of an initial protective response, and it is not known how long protection lasts (based upon challenge studies) for each pathogen or product. It will not

be surprising to find that for some pathogens, the duration of immunity will be for years, while for others, it may only be for months (using current vaccine technologies). The decision to vaccinate should be based upon considerations including the given patient's risk of developing serious disease compared with the risk of vaccine-induced complications.

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