

Weighing the Risks and Benefits of Vaccination

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I. Defining the Problem

There is increasing concern about the safety of vaccines for companion animals. The *Journal of the American Veterinary Medical Association* recently addressed this topic in its section on Current Concepts in an article titled "Are we vaccinating too much?" (Smith, 1995). Two sides of the issue were discussed: (1) Are the currently used vaccination schedules excessive? (2) Are the adverse reactions to vaccines unacceptable? One point raised by several experts was that there is little scientific evidence to back up label claims for annual administration of most vaccines. While in the past most veterinarians believed that annual vaccination was beneficial and would do no harm, this attitude has begun to change. Several events appear to underlie increasing concern for the safety of veterinary vaccines, including a possible nationwide epidemic of postvaccinal sarcomas in cats (Hendrick and Goldschmidt, 1991) and an apparent increase in the frequency of autoimmune diseases in dogs (Dodds, 1985), one of which (e.g., im-

mune-mediated hemolytic anemia) has been associated in controlled epidemiologic studies with recent vaccinations (Duval and Giger, 1996).

While few veterinarians challenge the fact that most vaccines are highly effective and have been responsible for a marked decrease in the incidence of common infectious diseases of dogs and cats, many have proposed reducing the frequency of vaccine use by either vaccinating every other year or by performing annual antibody titer screens to determine which vaccines to administer (Smith, 1995). In essence, by only vaccinating dogs when indicated by antibody titers, veterinarians would tailor vaccination schedules to individual patients. While these approaches will no doubt continue to be debated for some time to come, the need now is for accurate quantitative estimates of the nature and frequency of adverse effects associated with vaccines (i.e., the risks) as well as the best way to vaccinate individual animals according to their age, general health, and environment. This type of information can only be ascertained through a formal process of risk assessment. Another aspect of the issue that must be considered is how to communicate risk estimates to the veterinary community and companion animal owners, so they can make informed decisions and become more involved in managing the risks posed by vaccines.

II. Vaccine Risk Assessment

Risk assessment is the use of scientific evidence to define the health effects of exposures of individuals or populations to hazardous substances and situations (National Research Council, 1983). In this context the hazard in question is the vaccine and the situation is the act of vaccination. Four steps are usually undertaken to assess risk: (1) *hazard identification*, the determination of whether a particular substance or procedure is or is not causally linked to a particular health effect; (2) *dose-response assessment*, the determination of the relation between the magnitude of the exposure (e.g., frequency or time since last vaccination) and the probability of occurrence of the health effects in question; (3) *exposure assessment*, the determination of the extent of exposure; a description of the population at risk; and (4) *risk characterization*, a description of the nature and the magnitude of risk, including the uncertainty associated with it. This last step is usually performed by combining the results of exposure and dose-response assessments. A risk assessment might stop with the first step, hazard

identification, if no adverse effect is found, or if it is decided to take action without further analysis.

This question arises: Where will the data come from for a risk assessment of individual veterinary vaccines? There is general agreement that safe vaccines are those which do not induce local or systemic adverse reactions, are not excreted or are excreted only at low levels for modified live organisms, do not revert to virulence, do not affect the fetus, and are completely inactivated for killed vaccines. However, there are few published studies specifically designed to estimate the frequency of adverse reactions following vaccination.

Clinical trials conducted to evaluate the efficacy of veterinary vaccines prior to their licensing often include less than 100 animals. While this may be sufficient for a manufacturer to demonstrate efficacy and obtain a license from the U.S. Department of Agriculture for their product, it is unlikely to reveal adverse effects even when the incidence is high. For example, if a disease like immune-mediated hemolytic anemia (IMHA) occurs at a rate of 2 per 10,000 dogs per year independent of vaccination in the general population, and if a new vaccine induces IMHA at a rate of 50 per 10,000 dogs per year, then a clinical trial of approximately 2500 dogs will be needed to have a 90% probability of detecting this adverse effect. If these two rates are lower, for example, 2 per 100,000 dogs and 50 per 100,000 dogs, respectively, then approximately 20,000 dogs will be required. Surely no studies of this magnitude are feasible or likely to be conducted in the future. Where then will accurate data come from to measure the safety of a vaccine so that any adverse effects can be detected before they occur in near-epidemic proportions following its widespread use?

III. Current Sources of Data on Adverse Reactions

The types of adverse reactions to animal vaccines have been well characterized in the veterinary literature (Brooks, 1991; Tizard, 1990). These reactions can generally be categorized as either systemic or local. Systemic reactions include type I hypersensitivity or anaphylaxis, type III complex-mediated hypersensitivity, diluent and contamination problems, and reactions due to endotoxins. Local site reactions include type I hypersensitivity, type IV cell-mediated (delayed-type hypersensitivity), reactions to adjuvants such as granulomas and possibly even cancer (Hendrick *et al.*, 1992), diluent and contamination related problems, and faulty administration techniques. The failure of a vaccine to protect against the disease for which it is intended can also

be considered an adverse consequence. Evaluating the risk of adverse reactions for an individual animal following vaccination is based on knowledge of the frequency of adverse reactions in the general population of similar animals and the host and environmental risk factors that are associated with these events.

Surveillance is defined as the continuing scrutiny of all aspects of occurrence of disease that are pertinent to effective control (Last, 1988). This approach is routinely used in human and veterinary medicine to monitor the use and untoward effects of vaccines. To be effective as a method of disease control and prevention, surveillance should involve four interrelated components, namely, data collection, analysis, interpretation, and timely dissemination. In the U.S. veterinarians are requested to voluntarily report all potential adverse reactions and vaccine failures to vaccine manufacturers. These data are collated by the manufacturers and compared with the number of vaccines of that type that were sold to determine the adverse reaction rate, usually by lot number, on a monthly or yearly basis. Inherent to this approach, however, is a marked degree of underreporting and a bias toward more severe adverse reactions. Also, since the actual number of animals that were vaccinated with the vaccine in question in a given time period is unknown, it is not possible to calculate a true adverse reaction incidence or risk rate. This method of data collection can be effective, however, for identifying changes in the frequency of adverse effects from vaccine lot to vaccine lot, epidemics of adverse reactions associated with new products (Martin, 1985), and geographic clusters of excess adverse reactions. Routinely collected veterinary health data such as that in the Veterinary Medical Data Base (Priester and McKay, 1980), and hospital or diagnostic laboratory records are also potential sources of information regarding unusual disease occurrences.

Surveillance is a form of descriptive epidemiology in that it is designed only to describe the frequency and distribution of adverse reactions without regard to predetermined causal or other hypotheses. Its main value is to reveal potential causal relationships that can be further examined in controlled analytic epidemiologic studies that attempt to quantify the association between health effects and specific exposure(s) (Last, 1988). For example, concern was first raised about possible vaccine site reactions and fibrosarcomas in cats by veterinary pathologists who regularly reviewed surgical biopsy specimens from their own teaching hospital and from regional veterinary practices (Hendrick and Goldschmidt, 1991). A clear trend of increasing vaccine site-associated fibrosarcoma prevalence was later demonstrated

among tissue specimens evaluated histologically at a state veterinary diagnostic laboratory where the vaccine site fibrosarcomas were found to differ morphologically and biologically from those occurring at non-vaccine sites (Doddy *et al.*, 1996). In a case-control study (Kass *et al.*, 1993) it was shown that the vaccine-site fibrosarcomas were significantly associated with injection of several types of inactivated vaccines. Experimental studies are currently in progress to identify the mechanisms responsible for these cancers so that preventive action can be taken. Great uncertainty remains, however, regarding the actual risk of fibrosarcoma attributable to feline vaccines, with estimates ranging from as little as 1 per 10,000 vaccinated cats (Burton and Mason, 1997) to as high as 1.3 per 1000 cats (Lester *et al.*, 1996). This illustrates the inadequacy of currently used passive surveillance systems in veterinary medicine for accurately estimating vaccine-associated risks.

Most surveillance efforts are designed to relate specific adverse reactions to recently administered vaccines, that is, to vaccination in the previous few hours, days, or even months. However, in the past few years, there appears to be a considerable increase in the number of dogs and cats recognized to have immune-mediated diseases with onset in middle and older ages. While a variety of causes or predisposing factors are known or thought to precipitate immune-mediated diseases, it has been suggested that some of these can be triggered by frequent exposure to modified live vaccines (Dodds, 1985). The longer the latency period between vaccination and disease, the less likely it is that the relationship will be detected by routine postmarketing vaccine surveillance.

Most reports of an association between vaccination and autoimmune disease in animals are anecdotal in nature such as "A number of cases (10) have come to my attention over the last 2–3 years which appear to have an autoimmune–vaccination relationship. Specifically, a number of dogs have been observed to develop conditions which appear to be immune-mediated, following annual vaccination, at an incidence which is greater than that which has been observed in previous years" (Albritton, 1996). A controlled epidemiologic study of this possible relationship found that, when compared with a randomly selected hospital control group of dogs, dogs with IMHA were more likely to have been vaccinated within the previous month ($p < 0.0001$) and the dogs with IMHA that had been vaccinated in the previous month had more severe disease than those with IMHA that had been vaccinated more than 1 month previously (Duval and Giger, 1996). All of the recently vaccinated dogs with IMHA in the study had received combination

vaccines from various manufacturers against canine distemper, adenovirus type 2, leptospirosis, parainfluenza, and parvovirus.

While a single epidemiologic study does not by itself establish a cause-and-effect relationship between vaccination and autoimmune disease, it indicates a need to develop better reporting systems and for experiments to define possible underlying immunologic mechanisms. In such a recent experiment, a group of Beagle dogs vaccinated with a commercial multivalent canine vaccine at 8, 10, 12, 16, and 20 weeks of age, and with a rabies vaccine at 16 weeks of age, developed a significant rise of IgG autoantibodies against fibronectin, laminin, cardiolipin, sphingomyelin, DNA, and collagen compared with a group of unvaccinated control dogs (HogenEsch *et al.*, 1998). Because all of the dogs were euthanatized at 22 weeks of age, it was not possible to determine the clinical significance of these postvaccinal autoantibody responses. However, many of these autoantibodies and in particular anti-fibronectin, are present in elevated concentration in humans with systemic lupus erythematosus and rheumatoid arthritis (Henane *et al.*, 1986; Girard *et al.*, 1995). Another interesting finding in this study was that the autoantibody response appeared to have a genetic basis, in that it was more pronounced in dogs from some litters than others.

IV. Suggested Improvements in Postmarketing Surveillance

Reports are received by vaccine manufacturers by telephone and in writing from animal owners and veterinarians concerning health problems that appear to be temporally associated with vaccination of their animal(s). These contacts may be handled by veterinarians or by trained veterinary technicians who record the facts, usually on standardized forms. Data from these forms are often coded and entered into a computerized database. The data are periodically analyzed and reports generated showing adverse reaction rates by vaccine lots over time. Often, the reaction rates are categorized as to local or systemic, allergic, lethal, lack of efficacy, etc. No industry-wide standard currently exists for characterizing adverse reactions or for determining what constitutes an excess adverse reaction rate for a particular vaccine. Also, since the number of animals that were actually vaccinated with the vaccine is unknown, adverse reaction rates are calculated based on the number of vaccines sold and distributed over a given time period, rather than by the actual population at risk.

The present system of post-marketing surveillance for veterinary vaccines can be improved considerably if industry-wide standards are

adopted for characterizing and counting adverse reactions and if individual manufacturers consider the following:

1. Increase ascertainment of adverse reactions by encouraging more complete reporting by veterinarians. This can be accomplished by supplying prestamped postcards with all vaccines sold, so that veterinary practices can more easily record and report adverse reactions. The postcard should provide a place to record the species, breed, age, sex, and health of the animal; the type and lot number of the vaccine; route of administration; time from vaccination to clinical signs; clinical signs; outcome; and name, address, and telephone number of the reporting person. For food animal vaccines the postcard should also record herd information such as number of animals in the herd, number vaccinated, and number affected; and changes in productivity and feed consumption. More complete reporting will facilitate the interpretation of clusters of adverse events by time and place that may be artifacts of incomplete or sparse data. Also, a method is needed to score the reliability of each report that is received based on supporting documentation such as laboratory and pathologic findings, follow-up investigation, and qualifications of the reporting party.

2. Vaccine manufacturers should standardize their reporting systems to be consistent with each other in terms of the type and severity of adverse reactions. This standardization requires the training of veterinary paraprofessionals to collect and code adverse reaction reports.

3. Criteria should be developed for analyzing and reporting adverse reaction data on a regular basis. This should include establishing statistical methods to determine when an adverse reaction rate exceeds the expected value, which is the fundamental definition of an epidemic.

No universal criteria can necessarily be applied to determine the excess number of adverse reactions sufficient to warrant further investigation. The decision to investigate is influenced by factors such as the severity of the health consequences and the particular circumstances of the events. This analysis may exclude reports thought to be invalid, because they are either incomplete or unreliable. Also, a standard needs to be established for defining what goes into the denominator when calculating adverse reaction rates (e.g., total number of a vaccine lot sold, number of a vaccine lot sold in the previous month or the current month, etc.).

In addition to improvements in current postmarketing surveillance systems, new approaches should be developed to measure more accu-

rately the risk of vaccine-associated adverse reactions. The following should be considered:

1. Manufacturers need to decide when surveillance data indicate the need for additional investigation. Procedures have been described to investigate outbreaks of disease in animals (Kahrs, 1978) as well as geographic clusters of health-related events (Fiore *et al.*, 1990). Veterinary epidemiologists should lead these investigations of adverse reactions and, therefore, need to be part of the professional and technical services teams in industry. In some instances, confirmation of the occurrence of a vaccine-associated epidemic should be followed by analytic epidemiologic studies (e.g., case-control) so that multiple etiologic hypotheses can be tested concurrently using appropriate field investigations. This is particularly true where the population at risk cannot be unequivocally defined and or fully enumerated (Dwyer *et al.*, 1994).

2. Because postmarketing surveillance is likely to reveal apparent space-time clusters of adverse reactions, increasing use should be made of statistical software such as CLUSTER in interpreting the patterns observed and in deciding whether further investigation is warranted (Aldrich and Drane, 1990).

3. Special postmarketing surveillance systems need to be established that are capable of defining the population at risk in order to determine true adverse reaction incidence rates. One possible method is to prospectively monitor over a specified time period all animals in selected veterinary practices that are vaccinated. The growth of large corporate practices such as VetSmart, which see as many as 1 million dogs and cats yearly in multiple geographic locations and which utilize a common computerized medical record system, make such a reporting system more cost effective. Each vaccine manufacturer will need to identify a group of veterinary practices that use their products and will provide accurate information on potential adverse reactions on a regular basis. The number of animals that need to be included in such a monitoring system should be based on the statistical probability of detecting some specified minimum adverse reaction rate with a given level of confidence.

4. Existing postmarketing industry surveillance programs need to utilize individuals with expertise in database management, epidemiology, and computer programming to provide more timely analysis and dissemination of adverse reaction reports. Such individuals should work with industry and practicing veterinarians to improve data collection procedures and with the U.S. Department of Agriculture to

make current surveillance programs more suitable for analytic studies, while at the same time retaining their administrative value.

V. Risk Management and Risk Communication

Risk assessment is designed to draw extensively on scientific evidence linking specific exposures and health effects. However, as indicated earlier, the available information may be incomplete and lacking in quality such that there is uncertainty in the nature and magnitude of health effects associated with vaccination. This problem has no immediate solution. Nevertheless, decisions regarding the use of certain vaccines still must be made by veterinarians, animal owners, and governmental agencies in the face of this uncertainty. The process of evaluating alternative strategies and selecting among them has been termed risk management. Risk management entails consideration of not only the scientific facts regarding vaccine safety and efficacy, but also political, social, economic, and technical concerns.

A decision to vaccinate companion animals against a particular disease may involve consideration of the efficacy of the vaccine, the likelihood of the animal being exposed to the disease-causing agent, the age and health of the animal, and the probability of side effects. However, veterinarians might also take into account the revenue that will be lost by not including this vaccine in their routine protocol for all animals, while owners are interested in the cost to them. For example, should all cats be vaccinated yearly for rabies when there are rabies vaccines licensed that provide 3 years duration of immunity? Though the exact risk of fibrosarcoma in cats following vaccination for rabies and other infectious diseases is uncertain, repeated immunizations of cats has been associated with an increased risk of fibrosarcoma (Kass *et al.*, 1993). Does the risk of rabies and the ensuing public health threat in areas where rabies is endemic outweigh the risk of fibrosarcoma from yearly rabies vaccination? Yearly vaccination of cats against rabies is required by law in some states, despite the fact that no formal risk assessment was ever done justifying this regulation in light of rabies vaccines that provide 3 years of protection. Similar issues can be raised about vaccines for Lyme disease and for vaccines currently being developed for heart worm infection, *Toxoplasma*, *Giardia*, etc. Who will do the risk assessments for these vaccines and how will they be done?

Veterinarians are increasingly expected to discuss the benefits and risks of vaccination with their clients and this topic is frequently highlighted in newspapers and magazines. The animal-owning public de-

depends on their veterinarians to interpret the results of scientific studies and to share with them their opinions. This is made more difficult when the public's perception of the risk is disproportionate to the scientific facts, that is, the client overestimates the risk to their animal. Effective risk communication is not something veterinarians are taught in school.

Several guidelines for risk communication have been developed for epidemiologists (Sandman, 1991) and most of these could benefit veterinarians. These include:

1. Tell people who are most affected what you know—and tell them first.
2. Make sure people understand what you are telling them and what you think its implications are.
3. Acknowledge uncertainty promptly and thoroughly.
4. Seek advice from experts in the field when you have questions.
5. Show respect for public concerns even when they are not “scientific.”
6. Decide that risk communication is part of your job, and learn its rudiments—it is easier than dealing with disgruntled clients. Poor communication may compromise even the best trained veterinarian.

VI. Summary

The following summarizes this author's current thoughts regarding veterinary vaccines and their safety:

1. Every licensed animal vaccine is probably effective, but also produces some adverse effects.
2. Prelicensing studies of vaccines are not specifically designed to detect adverse vaccine reactions.
3. An improved system of national postmarketing surveillance is required to identify most adverse vaccine reactions that occur at low and moderate frequency.
4. Even a good postmarketing surveillance system is unlikely, however, to detect delayed adverse vaccine reactions, and the longer the delay the less likely they will be associated with vaccination.
5. Analytic epidemiologic (field) studies are the best way to link vaccination with delayed adverse reactions, but these are often hindered by incomplete vaccination histories in medical records in veterinary practice and by a lack of veterinarians in industry trained in epidemiologic methods.

6. Each licensed veterinary vaccine should be subjected to a quantitative risk assessment, and these should be updated on a regular basis as new information becomes available.
7. Risk assessment should be used to identify gaps in information regarding the safety and efficacy of vaccines, and appropriate epidemiologic studies conducted to fill these gaps that contribute to the uncertainty in risk estimates.
8. Risk assessment is an analytical process that is firmly based on scientific considerations, but it also requires judgments to be made when the available information is incomplete. These judgments inevitably draw on both scientific and policy considerations.
9. Representatives from industry, government, veterinary medicine, and the animal-owning public should be involved in risk management, that is, deciding between policy options.

The controversy regarding vaccine risks is intensifying to the point that some animal owners have stopped vaccinating their animals. They offer as justification the belief that current vaccines are "just too dangerous." Some owners report that since they completely stopped vaccinating their animals, they have been healthy. What they fail to realize is that a high percentage of animal owners are responsible and do vaccinate their animals, thus providing "herd immunity" protection to the unvaccinated animals whom they contact. The solution to the vaccine controversy is not to abandon vaccination as an effective means of disease prevention and control, but rather to encourage vaccine research to answer important questions regarding safety and to identify the biological basis for adverse reactions. Key questions to be answered include these: What components of vaccines are responsible for adverse reactions? What is the genetic basis for susceptibility to adverse health effects in animals? How can susceptible individuals be identified? Do multivalent vaccines cause a higher rate of adverse reactions than monovalent vaccines? Is administration of multiple doses of monovalent vaccines really any safer than administering a single multivalent vaccine? These and other vaccine-related questions deserve our attention as veterinarians so we can fulfill our veterinary oath to relieve animal suffering and "above all else, do no harm."

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REFERENCES

- Albritton, A. R. (1996). Autoimmune disease and vaccination? *Vet. Allergy Clin. Immunol.* **4**, 16–17.
- Aldrich, T. E., and Drane, J. W. (1990). "CLUSTER: User's Manual for Software to Assist Investigators with Investigations of Rare Health Events." Agency for Toxic Substances and Disease Registries, Atlanta, GA.
- Brooks, R. (1991). Adverse reactions to canine and feline vaccines. *Aust. Vet. J.* **68**, 342–344.
- Burton, G., and Mason, K. V. (1997). Do postvaccinal sarcomas occur in Australian cats? *Aust. Vet. J.* **75**, 100–106.
- Dodds, W. J. (1985). Immune-mediated blood diseases. *Dog News*, June, pp. 8–26.
- Doddy, F. D., Glickman, L. T., Glickman, N. W., and Janovitz, E. B. (1996). Feline fibrosarcomas at vaccination sites and non-vaccination sites. *J. Comp. Pathol.* **114**, 165–174.
- Duval, D., Giger, U. (1996). Vaccine-associated immune-mediated hemolytic anemia in the dog. *J. Vet. Intern. Med.* **10**, 290–295.
- Dwyer, D. M., Strickler, H., Goodman, R. A., and Armenian, H. K. (1994). Use of case-control studies in outbreak investigations. *Am. J. Epidemiol.* **16**, 109–123.
- Fiore, B. J., Hanrahan, L. P., Anderson, H. A. (1990). Public health response to reports of clusters. *Am. J. Epidemiol.* **132**, S14–S22.
- Girard, D., Raymond, Y., Labbe, P., and Senecal, J.-L. (1995). Characterization of a novel human antibody xenoreactive with fibronectin. *Clin. Immunol. Immunopathol.* **77**, 149–161.
- Henane, T., Tigel, D., and Monier, J. C. (1986). Anti-fibronectin autoantibodies in systemic lupus erythematosus, rheumatoid polyarthritis, and various viral or bacterial infectious diseases. *Pathol. Biol.* **34**, 165–171.
- Hendrick, M. J., and Goldschmidt, M. H. (1991). Do injection site reactions induce fibrosarcomas in cats? Letter to the editor. *J. Am. Vet. Med. Assoc.* **199**, 968.
- Hendrick, M. J., Goldschmidt, M. H., Shofer, F. S., Wang, Y., and Somlyo, A. P. (1992). Postvaccinal sarcomas in the cat: Epidemiology and electron probe microanalytical identification of aluminum. *Cancer Res.* **52**, 5391–5394.
- HogenEsch, H., Azcona-Oliveira, J., Scott-Moncrieff, C., Snyder, P. W., and Glickman, L. T. (1998). Vaccine-induced autoimmunity in the dog. *Adv. Vet. Sci. Comp. Med* (in press).
- Kahrs, R. F. (1978). Techniques for investigating outbreaks of livestock disease. *J. Am. Vet. Med. Assoc.* **173**, 101–103.
- Kass, P. H., Barnes, W. G., Spangler, W. L., Chomel, B. B., and Culbertson, M. R. (1993). Epidemiologic evidence for a causal relation between vaccination and fibrosarcoma tumorigenesis in cats. *J. Am. Vet. Med. Assoc.* **203**, 396–405.
- Last, J. M. (1988). "A Dictionary of Epidemiology." Oxford University Press, New York.
- Lester, S., Clemett, T., and Burt, A. (1996). Vaccine site-associated sarcomas in cats: Clinical experience and a laboratory review (1982–1993). *J. Am. Anim. Hosp. Assoc.* **32**, 91–95.
- Martin, M. L. (1985). Canine coronavirus enteritis and a recent outbreak following modified live virus vaccination. *Compend. Contin. Educ. Comp. Anim.* **7**, 1012–1017.
- National Research Council (1983). "Risk Assessment in the Federal Government: Managing the Process." National Academy Press, Washington, DC.
- Priester, W. A., and McKay, F. W. (1980). "The Occurrence of Tumors in Domestic Ani-

mals," Natl. Cancer Inst. Monogr. No. 54. U.S. Dept. of Health and Human Services, Washington, DC.

Sandman, P. M. (1991). Session III: Ethical considerations and responsibilities when communicating health risk information. *J. Clin. Epidemiol.* **44**(Suppl. I), 41S-50S.

Smith, C. (1995). Are we vaccinating too much? *J. Am. Vet. Med. Assoc.* **207**, 421-425.

Tizard, I. (1990). Risks associated with the use of live vaccines. *J. Am. Vet. Med. Assoc.* **196**, 1851-1858.