

## CLINICAL APPROACHES TO MANAGING AND TREATING ADVERSE VACCINE REACTIONS



W. Jean Dodds, DVM

HEMOPET

938 Stanford Street

Santa Monica, CA 90403

(310) 828-4804; FAX (310)-828-8251

[www.hemopet.org](http://www.hemopet.org); [hemopet@hotmail.com](mailto:hemopet@hotmail.com)

### Background

There is no doubt that application of modern vaccine technology has permitted us to protect companion animals effectively against serious infectious diseases.

Viral disease and recent vaccination with single or combination modified live-virus (MLV) vaccines, especially those containing distemper virus, adenovirus 1 or 2, and parvovirus are increasingly recognized contributors, albeit relatively rare, to immune-mediated blood disease, bone marrow failure, and organ dysfunction. Potent adjuvanted killed vaccines like those for rabies virus also can trigger immediate and delayed (vaccinosis) adverse vaccine reactions. Genetic predisposition to these disorders in humans has been linked to the leucocyte antigen D-related gene locus of the major histocompatibility complex, and is likely to have parallel associations in domestic animals.

It must be recognized, however, that we have the luxury of asking such questions today only because the risk of disease has been effectively reduced by the widespread use of vaccination programs.

### Adverse Events Associated with Vaccination

The clinical signs associated with vaccine reactions typically include fever, stiffness, sore joints and abdominal tenderness, susceptibility to infections, neurological disorders and encephalitis, collapse with autoagglutinated red blood cells and icterus (autoimmune hemolytic anemia, AIHA, also called immune-mediated hemolytic anemia, IMHA), or generalized petechiae and ecchymotic hemorrhages (immune-mediated thrombocytopenia, ITP). Hepatic enzymes may be markedly elevated, and liver or kidney failure may occur by itself or accompany bone marrow suppression.

Furthermore, MLV vaccination has been associated with the development of transient seizures in puppies and adult dogs of breeds or cross-breeds susceptible to immune-mediated diseases especially those involving hematologic or endocrine tissues (e.g. AIHA, ITP, autoimmune thyroiditis). Post-vaccinal polyneuropathy is a recognized entity associated occasionally with the use of distemper, parvovirus, rabies and presumably other vaccines. This can result in various clinical signs including muscular atrophy, inhibition or interruption of neuronal control of tissue and organ function, muscular excitation, incoordination and weakness, as well as seizures.

Certain breeds or families of dogs appear to be more susceptible to adverse vaccine reactions, particularly post-vaccinal seizures, high fevers, and painful episodes of hypertrophic osteodystrophy (HOD). Therefore, we have the responsibility to advise companion animal breeders and caregivers of

the potential for genetically susceptible littermates and relatives to be at increased risk for similar adverse vaccine reactions. In popular (or rare) inbred and linebred animals, the breed in general can be at increased risk as illustrated in the examples below.

Polyvalent MLV vaccines which multiply in the host elicit a stronger antigenic challenge to the animal and should mount a more effective and sustained immune response. However, this can overwhelm the immunocompromised or even a healthy host that has ongoing exposure to other environmental stimuli as well as a genetic predisposition that promotes adverse response to viral challenge. The recently weaned young puppy or kitten being placed in a new environment may be at particular risk. Furthermore, while the frequency of vaccinations is usually spaced 2-3 weeks apart, some veterinarians have advocated vaccination once a week in stressful situations; a practice makes little sense scientifically or medically.

An augmented immune response to vaccination is seen in dogs with pre-existing inhalant allergies (atopy) to pollens. Furthermore, the increasing current problems with allergic and immunological diseases have been linked to the introduction of MLV vaccines more than 20 years ago. While other environmental factors no doubt have a contributing role, the introduction of these vaccine antigens and their environmental shedding may provide the final insult that exceeds the immunological tolerance threshold of some individuals in the pet population. The accumulated evidence indicates that vaccination protocols should no longer be considered as a "one size fits all" program.

In cats, while adverse vaccine reactions may be less common, aggressive tumors (fibrosarcomas) can occasionally arise at the site of vaccination. A recent study from Italy reported finding similar tumors in dogs at the injection sites of vaccinations (Vascellari et al, 2003). These investigators stated that their "study identified distinct similarities between canine fibrosarcomas from presumed injection sites and feline post-vaccinal fibrosarcomas, suggesting the possibility of the development of post-injection sarcomas not only in cats, but also in dogs".

Additionally, vaccination of pet and research dogs with polyvalent vaccines containing rabies virus or rabies vaccine alone was shown to induce production of antithyroglobulin autoantibodies, a provocative and important finding with implications for the subsequent development of hypothyroidism (Scott-Moncrieff et al, 2002).

For these special cases, appropriate alternatives to current vaccine practices include:

- 1) measuring serum antibody titers;
- 2) avoidance of unnecessary vaccines or over vaccinating;
- 3) caution in vaccinating sick or febrile individuals; and
- 4) tailoring a specific minimal vaccination protocol for dogs of breeds or families known to be at increased risk for adverse reactions.

- 5) considerations include starting the vaccination series later, such as at nine or ten weeks of age when the immune system is more able to handle antigenic challenge;
- 6) alerting the caregiver to pay particular attention to the puppy's behavior and overall health after the second or subsequent boosters; and
- 7) avoiding revaccination of individuals already experiencing a significant adverse event. Littermates of affected puppies should be closely monitored after receiving additional vaccines in a puppy series, as they too are at higher risk.

### **Serologic Vaccine Titer Testing**

Some veterinarians have challenged the validity of using vaccine titer testing to assess the immunologic status of animals against the common, clinically important infectious diseases.

With all due respect, this represents a misunderstanding of what has been called the "fallacy of titer testing", because research has shown that once an animal's titer stabilizes it is likely to remain constant for many years. Properly immunized animals have sterilizing immunity that not only prevents clinical disease but also prevents infection, and only the presence of antibody can prevent infection. As stated by eminent expert Dr. Ronald Schultz in discussing the value of vaccine titer testing, these tests "show that an animal with a positive test has sterilizing immunity and should be protected from infection. If that animal were vaccinated it would not respond with a significant increase in antibody titer, but may develop a hypersensitivity to vaccine components (e.g. fetal bovine serum). Furthermore, the animal doesn't need to be revaccinated and should not be revaccinated since the vaccine could cause an adverse reaction (hypersensitivity disorder). You should avoid vaccinating animals that are already protected. It is often said that the antibody level detected is "only a snapshot in time". That's simply not true; it is more a "motion picture that plays for years".

Furthermore, protection as indicated by a positive titer result is not likely to suddenly drop-off unless an animal develops a medical problem such as cancer or receives high or prolonged doses of immunosuppressive drugs. Viral vaccines prompt an immune response that lasts much longer than that elicited by classic antigen. Lack of distinction between the two kinds of responses may be why practitioners think titers can suddenly disappear.

But, not all vaccines produce sterilizing immunity. Those that do include: distemper virus, adenovirus, and parvovirus in the dog, and panleukopenia virus in the cat. Examples of vaccines that produced non-sterile immunity would be leptospirosis, bordetella, rabies virus, herpesvirus and calicivirus --- the latter two being upper respiratory viruses of cats. While non-sterile immunity may not protect the animal from infection, it should keep the infection from progressing to severe clinical disease.

Therefore, interpreting titers correctly depends upon the disease in question. Some titers must reach a certain level to indicate immunity, but with other agents like those that produce sterile immunity, the presence of any measurable antibody shows protection. The positive titer test result is fairly straightforward, but a negative titer test result is more difficult to interpret, because a negative titer is not the same thing as a zero titer and it doesn't necessarily mean that animal is unprotected. A

negative result usually means the titer has failed to reach the threshold of providing sterile immunity. This is an important distinction, because for the clinically important distemper and parvovirus diseases of dogs, and panleukopenia of cats, a negative or zero antibody titer indicates that the animal is not protected against canine parvovirus and may not be protected against canine distemper virus or feline panleukopenia virus.

Finally, what does more than a decade of experience with vaccine titer testing reveal ? Published studies in refereed journals show that 90-98% of dogs and cats that have been properly vaccinated develop good measurable antibody titers to the infectious agent measured. So, in contrast to the concerns of some practitioners, using vaccine titer testing as a means to assess vaccine-induced protection will likely result in the animal avoiding needless and unwise booster vaccinations.

Our recent study (Twark and Dodds, 2000), evaluated 1441 dogs for CPV antibody titer and 1379 dogs for CDV antibody titer. Of these, 95.1 % were judged to have adequate CPV titers, and nearly all (97.6 %) had adequate CDV titers. Vaccine histories were available for 444 dogs (CPV) and 433 dogs (CDV). Only 43 dogs had been vaccinated within the previous year, with the majority of dogs (268 or 60%) having received a booster vaccination 1-2 years beforehand. On the basis of our data, we concluded that annual revaccination is unnecessary. Similar findings and conclusions have been published recently for dogs in New Zealand (Kyle et al, 2002), and cats (Scott and Geissinger, 1999; Lappin et al, 2002). Comprehensive studies of the duration of serologic response to five viral vaccine antigens in dogs and three viral vaccine antigens in cats were recently published by researchers at Pfizer Animal Health (Mouzin et al, 2004).

When an adequate immune memory has already been established, there is little reason to introduce unnecessary antigen, adjuvant, and preservatives by administering booster vaccines. By titering triennially or more often, if needed, one can assess whether a given animal's humoral immune response has fallen below levels of adequate immune memory. In that event, an appropriate vaccine booster can be administered.

#### **Other Issues with Over Vaccination**

Other issues arise from over vaccination, as the increased cost in time and dollars spent needs to be considered, despite the well-intentioned solicitation of clients to encourage annual booster vaccinations so that pets also can receive a wellness examination. Giving annual boosters when they are not necessary has the client paying for a service which is likely to be of little benefit to the pet's existing level of protection against these infectious diseases. It also increases the risk of adverse reactions from the repeated exposure to foreign substances.

#### **Compliance or Resistance to Current Vaccine Guidelines ?**

For more than a decade, the issues discussed above on overvaccination and vaccine safety for companion animals have been raised by vaccinologists and veterinary clinicians. But, how has this still controversial knowledge impacted the veterinary profession and pet owner today? Have veterinarians really embraced the national policies on vaccination guidelines? Does the public trust veterinarians to be up-to-date on these issues or are they unsure? Do they believe veterinarians have a conflict of

interest if they seek the income from annual booster vaccinations? Given media information regarding autism and measles vaccination, the public is more aware and worried about vaccine safety.

Some veterinarians today still tell their clients there is no scientific evidence linking vaccinations with adverse effects and serious illness. This is ignorance, and confuses an impressionable client. On the other hand, vaccine zealots abound with hysteria and misinformation. None of these polarized views is helpful.

Veterinarians are still routinely vaccinating ill dogs and those with chronic diseases or prior adverse vaccine reactions. This is especially problematic for rabies boosters, as many colleagues believe they have no legal alternative, even though the product label states it's intended for healthy animals. See [www.rabieschallengefund.org](http://www.rabieschallengefund.org)

### **New Breakthroughs**

Failure to standardize the legal mandate for rabies vaccinations nationwide is medically and scientifically unwarranted. The fact that individual states, counties and cities elect to mandate annual rabies boosters despite federally licensed three-year rabies vaccines is misguided.

Now that Arkansas passed a new rabies law authorizing the State Health Department to establish rabies vaccination schedules which adopt a 3-year rabies protocol for dogs and cats (February 2009), Alabama just changed their law to 3 years on August 1, 2009. However, some individual cities and counties still require annual rabies booster vaccination. For Cheyenne, WY and Wichita, KS, pressure from the public and the local veterinary associations effected a recent change to every three years.

Despite these recent changes, the practice of rabies booster vaccination in these states and local areas has been left as optional at the discretion of the client's veterinarian. So this is a Catch-22 situation, because if the veterinarian still believes the rabies booster should be given annually instead of as licensed, they usually can talk their client into doing so.

### **Rabies Vaccines and the USDA/CVB**

Rabies vaccines are the most common group of biological products identified in adverse event reports received by the USDA's Center for Veterinary Biologics (CVB). Currently, 14 rabies vaccines are labeled for use in dogs. These vaccines must meet the standard requirements established in the Title 9 Code of Federal Regulations. This requires that the vaccine provide a protected fraction of  $\geq 83\%$  when comparing vaccinated animals versus control animals. Also, all rabies vaccines are evaluated for safety prior to licensure, which includes performance of a field safety trial. Additionally, each serial of rabies vaccine is tested for potency by use of the National Institutes of Health potency test or another test approved by the CVB, and is tested for safety in the host and laboratory animals.

### Safety Review

Before licensure, a product must be shown to be safe through a combination of safety evaluations. The field safety trial is the most comprehensive evaluation and has the objective of assessing the safety of the product in its target population under the conditions of its intended use. However, safety studies before licensure may not detect all safety concerns for a number of reasons, as follows: insufficient number of animals for low frequency events, insufficient duration of observation, sensitivities of

subpopulations (eg, breed, reproductive status, and unintended species), or interactions with concomitantly administered products.

#### State and Local Authority for Rabies Control Programs

Although the CVB licenses veterinary biological products for use in the prevention of rabies, it is the state and local authorities govern and administer their respective rabies animal control programs. Some of these programs allow exemptions to the vaccination requirements, if medical concerns exist related to potential adverse events, but more commonly, others do not allow exemptions, regardless of the justification.

#### **Reporting Adverse Vaccine Reaction to Manufacturer and the Government**

There is no mandatory reporting of adverse reactions in veterinary medicine. The 2007 World Small Animal Veterinary Association (WSAVA) Vaccine Guidelines states that there is: "gross under-reporting of vaccine-associated adverse events which impedes knowledge of the ongoing safety of these products." WSAVA 2007 Vaccine Guidelines <http://www.wsava.org/SAC.htm>,

Even in humans, where mandatory reporting of adverse vaccine reactions is required, Dr. David Kessler, former head of the Food & Drug Administration, reported that "only about 1% of serious events are reported to the FDA". [JAMA .269:.2785, 1993]. This problem of under-reporting has persisted for many years.

Despite the serious under-reporting of vaccinal adverse reactions, the 2008 Report from the USDA's CVB [JAVMA 232:1000-1002, 2008], states that between April 1, 2004 and March 31, 2007, they "requested manufacturers of rabies vaccines to provide adverse event report summaries for their products. During this period, nearly 10,000 adverse event reports (all animal species) were received by manufacturers of rabies vaccines. Approximately 65% of the manufacturer's reports involved dogs."

The USDA/CVB 2008 Report further states that "Rabies vaccines are the most common group of biological products identified in adverse event reports received by the CVB." During the 3-year period covered in this report, the CVB received 246 adverse event reports for dogs in which a rabies vaccine was identified as one of the products administered. Reports were assessed for causality, and of these,

217 reports were considered possibly related to  $\geq 1$  of the vaccines given, 7 were considered unlikely, and 22 were assessed as unknown. Of reports with age information (n = 206), 21.4% of the dogs were  $\leq 6$  months old, 33.5% were  $> 6$  months old but  $\leq 2$  years old, and 45.1% were  $> 2$  years old. Of reports with sex information (n = 209), 54.5% of the dogs were female.

The following clinical terms were listed "to describe possibly related adverse events in dogs vaccinated against rabies " and reported to the USDA/CVB between April 1, 2004-March 31, 2007. For 217 adverse event reports – the clinical term is followed by the % of dogs affected:

Vomiting-28.1%; facial swelling-26.3%; injection site swelling or lump-19.4%; lethargy-12%; urticaria-10.1%; circulatory shock-8.3%; injection site pain-7.4%; pruritus-7.4%; injection site alopecia or hair loss-6.9%; death-5.5%; lack of consciousness-5.5; diarrhea-4.6%; hypersensitivity (not specified)-4.6%; fever-4.1%;, anaphylaxis-2.8%; ataxia-2.8%; lameness-

2.8%; general signs of pain-2.3%; hyperactivity-2.3%; injection site scab or crust-2.3%;, muscle tremor-2.3%; tachycardia-2.3%; and thrombocytopenia-2.3%.

The overall adverse report rate for rabies vaccines was determined to be 8.3 reports/100,000 doses sold. Adverse events considered possibly related to vaccination included acute hypersensitivity (59%); local reactions (27%); systemic reactions, which refers to short-term lethargy, fever, general pain, anorexia, or behavioral changes, with or without gastrointestinal disturbances starting within 3 days after vaccination (9%); autoimmune disorders (3%); and other (2%). In nearly 72% of the dogs of these reports, other vaccine or medicinal products were administered in conjunction with the rabies vaccine. In those instances, it was generally not possible to determine which product or products might be most closely linked to the adverse event. Additionally, in some instances, dogs had > 1 clinical sign, resulting in the coding of several clinical signs in a single report.

But, IF one applied the only 1% estimated reporting figure of "serious" events from the former head of the FDA to the 10,000 adverse events reported for animal rabies vaccines, 65% of which were in dogs, then the actual number of dogs that had adverse reactions to the vaccine could be as high as 650,000 in that 3 year period with 3,575 (5.5%) of the dogs dying from their adverse reaction.

### **Treatment of Vaccinosis**

The diagnosis of vaccinosis is an exclusionary one -- i.e. nothing will be found upon other testing to explain the symptoms. The animal is given the oral homeopathics, Thuja (for all vaccines other than rabies), and Lyssin to detox the rabies "miasm". IF there are no holistic veterinarians in the area, these homeopathics can be obtained from [www.naturalrearing.com](http://www.naturalrearing.com).

Our therapy typically uses steroids in tapering doses over 4-6 weeks to stop the inflammatory process and clinical symptoms. Therapy begins with an injection of dexamethasone phosphate first, and if the animal improves right away, is continued with prednisone at 0.5 mg per pound twice daily for 5-7 days, then tapered gradually over the next month to every other day. The use of steroids will cause an increase in water intake and urination, but the animal should be able to handle the drug at these tapering doses for a few weeks. IF a holistic veterinarian wants to try an alternative therapy to steroids, this approach can also work. Try it for several days to see if it will work.

We advise that these patients receive no further vaccine boosters, except for rabies, where exemption can be sought on a case-by-case basis but may not be granted in the specific locale.

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### **CANINE VACCINE ADVERSE EVENTS \***

- retrospective cohort study; 1.25 million dogs vaccinated at 360 veterinary hospitals
- 38 adverse events per 10,000 dogs vaccinated
- inversely related to dog weight
- vaccines prescribed on a 1-dose-fits-all basis, rather than by body weight.
- increased for dogs up to 2 yr of age, then declined
- greater for neutered versus sexually intact dogs
- increased as number of vaccines given together increased
- increased after the 3rd or 4th vaccination
- genetic predisposition to adverse events documented

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\* from Moore et al, JAVMA 227:1102–1108, 2005

### **VACCINE CONCLUSIONS FOR CANINES \***

Factors that increase risk of adverse events 3 days after vaccination:

- young adult age
- small-breed size
- neutering
- multiple vaccines given per visit

These risks should be communicated to clients

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\* from Moore et al, JAVMA 227:1102–1108, 2005

## **FELINE VACCINE ADVERSE EVENTS \***

- retrospective cohort study; 0.5 million cats vaccinated at 329 veterinary hospitals
- 51.6 adverse events per 10,000 cats vaccinated
- inversely related to cat weight
- increased for cats about 1 yr of age
- greater for neutered versus sexually intact cats
- increased as number of vaccines given together increased
- Lethargy with or without fever was most common sign

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\* from Moore et al, JAVMA 231:94-100, 2007

## **VACCINE CONCLUSIONS FOR FELINES \***

Factors that increase risk of adverse events 30 days after vaccination:

- young adult age
- neutering
- multiple vaccines given per visit

These risks should be communicated to clients, and the number of vaccines administered concurrently limited

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\* from Moore et al, JAVMA 231:94-100, 2007