

## Vaccination Protocols for Dogs Predisposed to Vaccine Reactions

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There is increasing evidence in veterinary medicine that vaccines can trigger immune-mediated and other chronic disorders (i.e., vaccinosis), especially in certain apparently predisposed breeds.<sup>1-6</sup> Accordingly, clinicians need to be aware of this potential and offer alternative approaches for preventing infectious diseases in these animals. Such alternatives to current vaccine practices include: measuring serum antibody titers; avoidance of unnecessary vaccines or overvaccinating; and using caution in vaccinating ill, geriatric, debilitated, or febrile individuals, and animals from breeds or families known to be at increased risk for immunological reactions.<sup>3,5-8</sup>

Fortunately, the most common effect of vaccine administration is the stimulation of an immune response that conveys protection for that disease. This outcome has resulted in the widespread reduction in morbidity and mortality from the many infectious diseases that have plagued both animals and humans. An excellent example of this benefit is the global eradication of smallpox as the result of a comprehensive immunization program. Despite these intended benefits, however, vaccination does carry with it attendant risks.

### Adverse Effects of Vaccines

As the most commonly recognized adverse effect of vaccination is an immediate hypersensitivity or anaphylactic reaction, practitioners are less familiar with the more rare but equally serious acute or chronic immune-mediated syndromes that can occur. The veterinary profession and vaccine industry have traditionally emphasized the importance of giving a series of vaccinations to young animals to prevent infectious diseases, to the extent that this practice is considered routine and is generally safe for the majority of animals. Few clinicians are prepared, therefore, for encountering an adverse event and may overlook or even deny the possibility.

Beyond the immediate hypersensitivity reactions, other acute events tend to occur 24 to 72 hours afterward, or 7 to 45 days later in a delayed-type immunological response.<sup>1,6,9,10</sup> Even more delayed adverse effects include mortality from high-titered measles vaccine in infants, canine distemper antibodies in joint diseases of dogs, and feline injection-site fibrosarcomas.<sup>3,11</sup> The increasing antigenic load presented to the host individual by modified-live virus (MLV) vaccines is presumed to be responsible for the immunological challenge that can result in a delayed hypersensitivity reaction.<sup>6,9</sup>

The clinical signs associated with nonanaphylactic vaccine reactions typically include fever, stiffness, sore joints and abdominal tenderness, susceptibility to infections, neurological disorders and encephalitis, autoimmune hemolytic anemia (AIHA) resulting in icterus, or immune-mediated thrombocytopenia (ITP) resulting in petechiae and ecchymotic

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hemorrhage.<sup>1-4,9,10,12-15</sup> Hepatic enzymes may be markedly elevated, and liver or kidney failure may occur by itself or accompany bone-marrow suppression.<sup>3</sup> Furthermore, MLV vaccination has been associated with the development of transient seizures in puppies and adult dogs of breeds or crossbreeds susceptible to immune-mediated diseases, especially those involving hematological or endocrine tissues (e.g., AIHA, ITP, autoimmune thyroiditis).<sup>1-3</sup> Postvaccinal polyneuropathy is a recognized entity associated occasionally with the use of distemper, parvovirus, rabies, and possibly other vaccines.<sup>3,6,9</sup> This can result in various clinical signs, including muscular atrophy, inhibition or interruption of neuronal control of tissue and organ function, incoordination, and weakness.<sup>3</sup> Therefore, we have the responsibility to advise companion animal breeders and caregivers of the potential for genetically susceptible littermates and relatives that are at increased risk for similar adverse vaccine reactions.<sup>1-5</sup>

Commercial vaccines, on rare occasion, can also be contaminated with other adventitious viral agents,<sup>6,16</sup> which can produce significant untoward effects such as occurred when a commercial canine parvovirus vaccine was contaminated by blue tongue virus. It produced abortion and death when given to pregnant dogs<sup>16</sup> and was linked causally to the ill-advised but all-too-common practice of vaccinating pregnant animals. The potential for side effects such as promotion of chronic disease states in male and nonpregnant female dogs receiving this lot of vaccine remains in question, although there have been anecdotal reports of reduced stamina and renal dysfunction in performance sled dogs.<sup>3</sup> Recently, a vaccine manufacturer had to recall all biological products containing a distemper component, because they were associated with a higher-than-expected rate of central nervous system postvaccinal reactions 1 to 2 weeks following administration.<sup>3</sup>

If, as a profession, we conclude that we are overvaccinating, other issues come to bare, such as the needless client dollars spent on vaccines, despite the well-intentioned solicitation of clients to encourage annual booster vaccinations so that pets also can receive a wellness examination.<sup>5</sup> 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.

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.<sup>5,6,9</sup> However, this can overwhelm the immunocompromised or even healthy host that has ongoing exposure to other environmental stimuli as well as a genetic predisposition that promotes adverse response to viral challenge.<sup>1-3,9,13</sup> 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 to 3 weeks apart, some veterinarians have advocated vaccination once a week in stressful situations. This practice makes little sense, scientifically or medically.<sup>5</sup>

An augmented immune response to vaccination is seen in dogs with preexisting inhalant allergies (i.e., atopy) to pollens.<sup>3</sup> Furthermore, the increasing current problems with allergic and immunological diseases have been linked to the introduction of MLV vaccines more than 20 years ago.<sup>6</sup> 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.

### Predisposed Breeds

Twenty years ago, this author began studying families of dogs with an apparent increased frequency of immune-mediated hematological disease (i.e., AIHA, ITP, or both).<sup>1,2</sup> Among the more commonly recognized predisposed breeds were the Akita, American cocker spaniel, German shepherd dog, golden retriever, Irish setter, Great Dane, Kerry blue terrier, and all dachshund and poodle varieties; but predisposition was found especially in the standard poodle, long-haired dachshund, Old English sheepdog, Scottish terrier, Shetland sheepdog, shih tzu, vizsla, and Weimaraner, as well as breeds of white or predominantly white coat color or with coat color dilution (e.g., blue and fawn Doberman pinschers, the merle collie, Australian shepherd, Shetland sheepdog, and harlequin Great Dane).<sup>1-3</sup> Recently, other investigators have noted the relatively high frequency of AIHA, ITP, or both in American cocker spaniels<sup>10</sup> and Old English sheepdogs.<sup>13</sup>

A significant proportion of these animals had been vaccinated with monovalent or polyvalent vaccines within the 30- to 45-day period prior to the onset of their autoimmune disease.<sup>1,2,10</sup> Furthermore, the same breeds listed above appear to be more susceptible to other adverse vaccine reactions, particularly postvaccinal seizures, high fevers, and painful episodes of hypertrophic osteodystrophy (HOD).<sup>3</sup> For animals that have experienced an adverse vaccine reaction, the recommendation is often to refrain from vaccinating these animals until at least after puberty, and instead to measure serological antibody titers against the various diseases for which vaccination has been given. This recommendation raises an issue with the legal requirement for rabies vaccination. As rabies vaccines are strongly immunogenic and are known to elicit adverse neurological reactions,<sup>3,5</sup> it would be advisable to postpone rabies vaccination for such cases. A letter from the primary care veterinarian stating the reason for requesting a waiver of rabies vaccination for puppies or adults with documented serious adverse vaccine reactions should suffice.

As further examples, findings from the author's large, accumulated database of three susceptible breeds are summarized below.

### Vaccine-Associated Disease in Old English Sheepdogs

Old English sheepdogs appear to be predisposed to a variety of autoimmune diseases.<sup>1-3,13</sup> Of these, the most commonly seen are AIHA, ITP, thyroiditis, and Addison's disease.<sup>2,17</sup>

Between 1980 and 1990, this author studied 162 cases of immune-mediated hematological diseases in this breed. One-hundred twenty-nine of these cases had AIHA, ITP, or both as a feature of their disease. Vaccination within the previous 30 days was the only identified triggering event in seven cases and was an apparent contributing factor in another 115 cases.<sup>2</sup> Thyroid disease was recognized as either a primary or secondary problem in 71 cases, which is likely an underestimate of the true incidence, as thyroid function tests were not run or were inconclusive in most of the other cases.

Experience with a particular Old English sheepdog family supported a genetic predisposition to autoimmune thyroiditis, Addison's disease, and AIHA or ITP or both—an example of the polyglandular autoimmune syndrome.<sup>2,17</sup> Pedigrees were available from 108 of the 162 Old English sheepdog cases of autoimmune disease; a close relationship was found among all but seven of the affected dogs.<sup>2</sup> Two of three pedigrees available from the studies of Day and Penhale<sup>13</sup> were also related to this large North American study group.

### Vaccine-Associated Disease in Young Akitas

Akitas also are subject to a variety of immune-mediated disorders, including Vogt-Koyanagi-Harada syndrome (VKH), pemphigus, and heritable juvenile-onset immune-mediated polyarthritis (IMPA).<sup>3,14</sup> Juvenile-onset IMPA occurs in Akitas less than 8 months of age. Of 11 closely related puppies in the author's case series, the mean age of onset was 14 weeks.<sup>3</sup> Initial signs appeared 3 to 29 days following vaccination with polyvalent MLV or killed virus or both, with a mean reaction time of 14 days. All had profound joint pain and cyclic febrile illness lasting 24 to 48 hours. Hemograms revealed mild nonregenerative anemia, neutrophilic leukocytosis, and occasional thrombocytopenia. Joint aspiration and radiography indicated nonseptic, nonerosive arthritis. Despite treatment for immune-mediated disease and pyrexia, all eight dogs had relapsing illness and died or were euthanized by 2 years of age from progressive systemic amyloidosis and renal failure. Necropsies were performed on three dogs, two of which had glomerular amyloidosis and widespread evidence of vasculitis. The history, signs, and close association with immunization suggested that juvenile-onset polyarthritis and subsequent amyloidosis in these Akitas may have been an autoimmune response triggered by the viral antigens or other components of vaccines.<sup>3</sup>

The vaccine-related history was reviewed for 129 puppies belonging to the family of Akitas discussed above. Polyvalent MLV vaccine was given to 104 of them, with 10 (9.8%) puppies showing adverse reactions and death. Another six puppies received a polyvalent all-killed vaccine product (no longer commercially available) with no reactors, and 19 puppies received homeopathic nosodes initially followed by killed canine parvovirus (CPV) vaccine, with one reactor that died and one that became ill but survived.<sup>3</sup>

A genetic basis for immune-mediated diseases and immunodeficiencies states is well known.<sup>1,2,12,13,15,17,18</sup> The mechanism for triggering immune-mediated disease is poorly understood, but predisposing factors have been implicated

when genetically susceptible individuals encounter environmental agents that induce nonspecific inflammation, molecular mimicry, or both.<sup>3,17</sup> The combined effects of these genetic and environmental factors override normal self-tolerance and are usually mediated by T-cell imbalance or dysregulation.<sup>17</sup>

Since the modern Akita arose from a relatively small gene pool, understanding the potential environmental triggers of juvenile-onset IMPA has immediate importance. Numerous agents have been implicated, including drugs, vaccines, viruses, bacteria, chemicals, and other toxins.<sup>1-3,10,11</sup> Although the littermates from affected families typically end up in different locales, all undergo relatively standardized immunization procedures at a similar age.

### Vaccine-Associated Disease in Young Weimaraners

The Weimaraner breed appears to be especially prone to both immune deficiency and autoimmune diseases, which have been recognized with increasing frequency in related members of the breed over the past 15 years.<sup>3</sup> Autoimmune thyroiditis leading to clinically expressed hypothyroidism is probably the most common of these disorders, along with vaccine-associated HOD of young Weimaraners.<sup>2,3,17</sup>

During a 2-year period (1986-1988), Couto evaluated 170 related Weimaraners, including affected puppies and their relatives, and the findings were relayed in a breed newsletter as discussed in an earlier reference.<sup>3</sup> Clinical signs of the affected dogs included high fevers, polyarthritis with pain and swelling typical of HOD, coughing and respiratory distress from pneumonia, enlarged lymph nodes, diarrhea, pyoderma, and mouth ulcers. In most cases, clinical signs were first detected shortly after vaccination with a second dose of polyvalent MLV vaccine when the puppies were between 2 and 5 months of age. This author has studied more than 60 Weimaraners with vaccine-associated disease. In 24 cases described in a previous article,<sup>3</sup> the mean age of onset of clinical signs was 13.5 weeks, with a mean reaction time of 10.5 days postvaccination. Males were predominantly affected. All affected puppies showed high-spiking fevers, cyclic episodes of pain, and polyarthritis (HOD)—a group of signs identical to those of the affected young Akitas described previously. Most affected puppies also showed leukocytosis (with neutrophilia or neutropenia), diarrhea, lethargy, anorexia, and enlarged lymph nodes. Some puppies also had levels of immunoglobulin A, immunoglobulin M, or both below those expected for their age, and one puppy had immunoglobulin G (IgG) deficiency as well. Other signs included coughing, pneumonia, depression, seizures or "spaced-out" behavior, refusal to stand or move, and hyperesthesia ("walking on eggshells"). The outcome for half of these cases was good (12 of the 24 are healthy adults), although two died, three were euthanized as puppies, and three remained chronically ill as adults. Another four cases were lost to follow-up.

Management of this clinical syndrome is best accomplished with an initial dose of parenteral corticosteroids followed by a tapering course of corticosteroids over 4 to 6

weeks. Systemic broad-spectrum antibiotic may be given prophylactically, and vitamin C (500 to 1,000 mg daily) can be included to promote immune support. Recurring episodes are treated by increasing the corticosteroid dosage for a few days until the flare-up has subsided. The response to initial corticosteroid treatment is always dramatic, with fever and joint pain usually subsiding within a matter of hours.

Serological titers for canine distemper virus (CDV) and CPV were determined in 19 of the 24 affected Weimaraner puppies, and all were adequate. Upon reaching adulthood, serum antibody titers were reevaluated, and detectable CDV- and CPV-specific IgG persisted. Several of these dogs have subsequently developed hypothyroidism and are receiving thyroid replacement.<sup>3,4,17</sup> Thus, to avoid recurrence of adverse effects, which has been shown to be even more severe if another vaccine booster is given, serological titers for CDV and CPV are measured.<sup>7</sup>

Another approach recommended by Weimaraner breeders and this author is to modify the vaccination protocol, especially for puppies from families known to have experienced adverse vaccine reactions. Examples would be to limit the number of antigens used in the vaccine series to those infectious agents of most clinical concern (i.e., CDV, CPV, and rabies virus), separating these and other antigens by 2- to 3-week intervals, and giving rabies vaccine by itself at 6 months of age. A booster series is administered at 1 year by separating the CDV, CPV, rabies virus, and other vaccine components, where possible, and giving them on separate visits at least 2 weeks apart. Thereafter, serological antibody titers can be measured (except for those vaccines required by law, unless a specific exemption is made on an individual case basis).

## Recommendations

Practitioners should be encouraged during the initial visit with a new puppy owner or breeder to review current information about the breed's known congenital and heritable traits. Several databases, veterinary textbooks, and review articles contain the relevant information to assist here.<sup>2</sup> For those breeds at increased risk, the potential for adverse reactions to routine vaccinations should be discussed as part of this wellness program. Because breeders of at-risk breeds have likely alerted the new puppy buyer to this possibility, we should be mindful and respectful of their viewpoint, which may be more informed than ours about a specific breed or family issue. To ignore or dismiss these issues can jeopardize the client-patient relationship and result in the client going elsewhere for veterinary services or even turning away from seeking professional care for these preventive health measures. As a minimum, if we are unaware of the particular concern expressed, we can research the matter or ask the client for any relevant scientific or medical documentation. The accumulated evidence indicates that vaccination protocols should no longer be considered as a "one size fits all" program.

For these special cases, appropriate alternatives to current vaccine practices include: measuring serum antibody titers; avoidance of unnecessary vaccines or overvaccinating; using

caution in vaccinating sick, very old, debilitated, or febrile individuals; and tailoring a specific minimal vaccination protocol for dogs of breeds or families known to be at increased risk for adverse reactions.<sup>3,5-8</sup> Considerations include starting the vaccination series later, such as at 9 or 10 weeks of age, when the immune system is more able to handle antigenic challenge; alerting the caregiver to pay particular attention to the puppy's behavior and overall health after the second or subsequent boosters; and 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. Altering the puppy vaccination protocol, as suggested previously for the Weimaraner, is also advisable.

Following these recommendations may be a prudent way for our profession to balance the need for individual patient disease prevention with the age-old physician's adage, forwarded by Hippocrates, of "to help, or at least do no harm."

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