ADVERSE REACTIONS FOLLOWING VACCINATION

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Since the original companion animal vaccines were developed and licensed more than 60 years ago, there has been a continuing effort to make vaccines safer and more efficacious. Vaccination protocols in place today provide animal owners with exceptional value for the cost of the service and the quality of the products available. However, as emerging vaccine-preventable diseases are identified and vaccine technologies are improved, new (and improved) vaccines will continue to be introduced…as soon as this year.

For the most part, our patients derive considerable benefit from immunization. Most respond favorably following vaccine administration with minimal to no adverse consequences. However, inoculating any patient with a biological product (ie, a vaccine) carries some risk. That risk is likely increased with simultaneous administration of several vaccines at the same appointment, especially in small breed dogs.

And…so it is…veterinarians today are faced with a novel balancing act: (1) selecting from among an unprecedented number of licensed vaccines, (2) heightened risk for exposure and infection (dog day-care; dog parks, agility events[a], pet friendly stores and hotels, increasing pet travel), and (3) the desire to maximize protection while minimizing risk of causing a vaccine adverse reaction.

In practice, simply selecting vaccines on the basis of cost (currently at the top of the list of purchasing criteria), is less feasible today than it was just 10 years ago. Vaccines are not commodities. Significant advances in vaccine technology, safety, and efficacy highlight the importance of understanding how individual products, even those indicated for protection against the same agent, differ. The following section addresses vaccine safety, recognition of vaccine-associated injury, and current strategies for treating and preventing adverse events following vaccination.

IMPORTANT: In veterinary medicine, there is no requirement to report adverse events (known or suspected) following vaccination. Although encouraged, formal reports from veterinarians to the US Dept of Agriculture (USDA) or the vaccine manufacturer are seldom filed. Neither the USDA nor the manufacturers are required to divulge information on vaccine adverse event reports. The result: there is *no national database available for the surveillance or documentation of vaccine adverse events in veterinary medicine.*

Definition

According to the USDA, a **vaccine adverse event** is any undesirable side effect or unintended effect (*including lack of desired result*) associated with the administration of a licensed biological product (ie, a vaccine). Adverse events include any reaction that could compromise the health of the dog or cat, including the apparent failure to immunize. NOTE: An adverse event includes any injury, toxicity, or sensitivity reaction associated with the use of a vaccine, <u>whether or not the event can be directly attributed to the vaccine</u>. In other words, it is appropriate to report any known, *or suspected*, reaction associated with vaccination.

<u>HOWEVER</u>…...vaccines are biological products and, as such, can provoke minor reactions lasting from a few hours to as long as a few days. Rarely do these self-limiting side effects escalate into serious adverse

[a] The AKC recently reported that over 1 million dogs participated in agility events in 2013.

events. For this reason, veterinarians are encouraged to inform clientele that their pet, regardless of breed/size, may manifest transient side effects for up to 2, and possibly 3, days following administration of any vaccine or any combination of vaccines. Side-effects commonly observed include: reduced appetite, loss of appetite (lasting for 1 or 2 feedings), pain at the injection side, lethargy (lack of activity), reluctance to walk/run (discomfort?), and mild fever. Treatment is not generally necessary; however, some veterinarians do report administering short-term treatment (e.g., a non-steroidal anti-inflammatory drug) given either before or at the time of vaccination to mitigate expected minor reactions. It is recommended that clientele be advised to contact the practice in the event any physical/behavioral manifestations progressively worsen or continue beyond 2 to 3 days. Clientele should be advised to contact the practice at any time if signs of systemic illness, such as vomiting, diarrhea, seizures, collapse, facial swelling, or difficulty breathing, develop.

Adverse Events Following Vaccination

The actual prevalence of vaccine adverse events in veterinary medicine is unknown. The table that follows is not comprehensive but does represent a summary of known and suspected event categories.

EVENT	Examples	Dog	Cat
Transient injection-site reactions	Visible or palpable lumps caused by abscess, granuloma, or seroma, injection-site pain, pruritus, local swelling.	Yes	Yes
Sustained injection-site reactions	Permanent hair loss (generally associated with ischemic vasculitis), discoloration of skin, focal necrosis of skin. (also called 'rabies vaccine ischemic vasculitis). Granuloma (post vaccination 'lumps').	Yes	No (Yes, for granuloma formation)
Transient non-specific systemic effects	Lethargy, anorexia, fever, regional lymphadenomegaly, non-localizable soreness/discomfort, diarrhea, vomiting, encephalitis, polyneuritis, arthritis, seizures, behavioral changes.	Yes	Yes
Allergic (hypersensitivity) and immune-mediated reactions	**Type 1 (acute anaphylaxis):** Angioedema (acute-onset swelling affecting especially the head and ears), urticaria (hives), anaphylaxis (shock), and death.	Yes	Yes
	Type 2 (cytotoxic): Immune-mediated hemolytic anemia; immune-mediated thrombocytopenia (suspected only; causality has not been confirmed).	??	Not reported
	Type 3 (immune-complex): Cutaneous ischemic vasculopathy (often attributed to rabies vaccine) that can occur at the injection-site or a distant location ("satellite lesions") such as the ear-tips, foot pads, tail, scrotum; undefined immune-mediated diseases (polyarthritis, glomerulonephritis).	Yes	Not reported
	Type 4 (delayed-type hypersensitivity): Less clearly described; associated with cell-mediated immune responses (rather than antibody) and the release of pro-inflammatory cytokines. Likely associated with granuloma formation and possibly feline injection-site sarcoma formation.	??	??
Failure to immunize	Interference from maternally derived antibody (MDA) is considered the most common cause; administration of vaccine at a volume/dose less than that prescribed by		

	the manufacturer; genetically predisposed "non-responder" or “low responder”; inactivation of vaccine antigen (eg, allowing reconstituted CDV vaccine to stand at room temperature for more than 2 hours), mixing of incompatible vaccines in the same syringe.	Yes	Yes
Tumorigenesis	Malignant transformation of mesenchymal cells in susceptible patients, especially Feline Injection-Site Sarcoma. Provocation of tumorigenesis is likely associated with chronic inflammation…	(rare)	Yes
Multi-systemic infectious/inflammatory disorder	Described in young Weimeraner dogs. The syndrome is not well characterized. May be linked to a poorly characterized immune deficiency in the breed.	Yes	No
Transient immune suppression	When combination vaccines containing MLV CDV and CAV-1 or CAV-2, along with other vaccines, are first administered to puppies, transient suppression of cell-mediated immunity may occur as early as 3 days post-vaccination, and can persist for 7 or more days.	Yes	Not reported
Reactions caused by the incorrect or inappropriate administration of vaccine	In addition to serious injection-site abscesses, fatalities have been reported following subcutaneous administration of avirulent-live *Bordetella bronchiseptica* bacterin (intended for intranasal administration); inadvertent or intentional administration of vaccine by the intravenous route.	Yes	Not reported
Reactions associated with residual virulence of attenuated vaccine	Post-vaccinal cough and/or sneezing associated with intranasal administration of attenuated vaccine (eg, *B. bronchiseptica* + parainfluenza virus or feline *B. bronchiseptica*, feline herpesvirus-1 + calicivirus). NOTE: This is **not** vaccine “reversion to virulence”	Yes	Yes
Vaccine-induced interference with diagnostic tests	Examples include: false-positive PCR test results for parvovirus antigen in feces in dogs recently vaccinated with a MLV parvovirus vaccine; false-positive antibody (FIV) test results following FIV vaccination in cats; vaccine-induced leptopspirosis antibody titer may interfere with the diagnostic microscopic agglutination test (MIC).	Yes	Yes
Reversion of vaccine virus to a virulent pathogen	Although frequently discussed in the literature, true reversion to virulence (vaccine-induced clinical infection) is considered rare to non-existent following administration of currently licensed vaccines as long as the vaccines are used in the species for which they were licensed. The potential for reversion to virulence exists when using attenuated (MLV) canine/feline vaccine in a wild, hybrid, or exotic animal.	No	No

Management of Vaccine Reactions-Based on Category (above)

- **Transient Injection-site Reactions** (among the most common reactions reported): Generally, treatment is not required or recommended unless the reaction persists beyond 3 days. Any treatment centers around pain relief. NSAIDs for 5 to 7 days may be indicated. Abscess formation at the injection site following proper administration of vaccine is exceptionally rare. In the event this does occur, the abscess can be treated with local drainage and prophylactic use of a broad-spectrum antibiotic administered parenterally or orally.

- **Sustained Injection-Site Reactions:** Several reports of ischemic vasculitis (described in the presentation) have been reported in dogs (no cases have been confirmed in cats). Reactions typically develop 1 to 3 months (occasionally longer) following administration of a rabies vaccine. Other vaccines (eg, *Crotalus atrox* [Western Diamondback Rattle Snake vaccine]) have been implicated. Hair loss over the injection site, discoloration of skin and hair at the injection site, and even tissue necrosis are reported.[2] Smaller breeds (esp, poodles??) may be at greater risk, although dogs of all sizes and breeds have been affected.[3, 4]

Primary treatment recommendations usually include administration of **pentoxyphylline (Trental)**, 10 to 15 mg/kg, orally, 2 to 3 times daily to promote local circulation. Duration of treatment with pentoxyphylline is not described for this condition although minimum treatment duration of 3 to 4 weeks is recommended. Antibiotics and analgesics may also be indicated. Topical Vitamin E (oil) has been recommended empirically. Systemic corticosteroid use (anti-inflammatory doses) is controversial among dermatologists, but is considered as an optional additional treatment.

Affected dogs may develop new lesions following re-vaccination. When feasible, *do not revaccinate*. However, where rabies exemption authority is **not** allowed by State law, suggest selecting an alternative rabies vaccine brand.

Post-vaccination injection-site granuloma formation is commonly observed in dogs and cats, especially those receiving adjuvant-containing vaccine. These lesions are expected to resolve spontaneously, although some lesions require as long as 6 weeks to resolve. In cats, granuloma formation is especially critical to assess if the 'lump' persists beyond 1 month or continues to grow (see **Tumorigenesis** below).

- **Transient post-vaccinal non-specific systemic effects**: Treatment is only indicated if signs persist for more than 3-days. "Symptomatic" treatment is indicated. Most disorders, if truly related to vaccination, will resolve spontaneously.[4, 5]

- **Allergic (hypersensitivity) and immune-mediated reactions**:

-- Type 1 (acute anaphylaxis): **LOCAL** Anaphylaxis: typically is limited to angioedema (swelling of skin/subq tissues) within minutes to few hours following vaccination.[6] Administration of a single dose of anti-inflammatory dose of corticosteroid (eg, 0.5 mg/kg of prednisone, SQ, IM, or IV) may be indicated. Administering antihistamine once the reaction has developed may not be effective, but is commonly administered prophylactically. Swelling typically resolves within a few hours to as long as 1-2 days. Dogs/cats developing a local reaction seem unlikely to progress to systemic anaphylaxis.

Pre-treatment with **diphenhydramine (Benadryl)**, 2-4 mg/kg, orally or 1 mg/kg parenterally is indicated in patients with a history of developing angioedema following vaccination.

SYSTEMIC Anaphylaxis (SHOCK): Acute-onset (immediate) life-threatening hypotension rarely develops following vaccination. The risk may be greatest among young, small breed dogs (puppies) receiving multiple vaccines at the same appointment.

- Administer **epinephrine**, 0.01 mg/kg (IM route is recommended; slow IV is optional) DO NOT ADMINISTER SQ. Repeat every 15 to 20 minutes as necessary.
- **Intravenous fluids**: (saline, lactated Ringer's, or Normosol-R) at up to 20 mg/kg over 2-3 hours (or 5 to 10 mg/kg as an IV 'push').
- Vasopressor: **dopamine**, 5-10 µg/kg per minute IV infusion.
- CATS: administer a bronchodilator, **terbutaline**, 0.01 mg/kg IM or IV.

Continue fluid therapy as needed after assessing initial response.

Revaccination of patients having a history of SYSTEMIC Anaphylaxis following vaccination. DON'T! (Consider recommending a titer instead for canine distemper, canine parvovirus, feline panleukopenia).

Current guidelines recommend delaying administration of NON-core vaccines to small breed dogs (≤ 10 kg) until completing of the initial CORE vaccine series.[4, 5]

-- Type 2 (cytotoxic): Patients having a history of immune-mediated hemolytic anemia or immune-mediated thrombocytopenia-*regardless of whether or not onset was linked to vaccination*-should not be subjected to re-vaccination…whenever feasible. It is suggested that vaccination may re-activate the condition. Suggest, instead, performing antibody titers. If positive, do not re-vaccinate. If negative, consider re-vaccination of young animals; limit vaccination to core vaccines only. Suggest separating rabies from other core vaccines. (see the 2011 AAHA Canine Vaccination Guidelines)

-- Type 3 (immune-complex): Cutaneous ischemic vasculopathy (often attributed to rabies vaccine in dogs) is the likely result (although not proven) of immune-complex disease subsequent to increasing levels of IgG antibody in circulation.[3] Lesions can occur at the injection-site, but so-called "satellite lesions" (necrosis of skin at sites distant from the injection site), do occur. Problematic is the fact that the lesion develops 1 to 3 months following vaccination, but typically occurs on the ear-tips, around the eyes, over the nose, on foot pads, tail, and scrotum. It is not intuitive that the vaccine caused the lesion. Documentation requires history of the vaccine (type administered and date) plus histopathology of the lesion (skin lesions have a characteristic histologic 'signature'). Medical treatment is outlined above (use of **pentoxyphylline [Trental]**). However, in cases where tissue necrosis occurs, surgical debridement, or skin grafting, may be indicated.

- **Failure to immunize**: a surprisingly common problem in young dogs and cats, but difficult to definitively prove in practice. Most often implicated is interference by maternally derived antibody, a result of discontinuing the initial vaccination series at 12 weeks of age. In both dogs and cats, it is universally recommended to continue the initial series of core vaccines to include a 3rd dose at 14-16 weeks of age. (In cats, it is appropriate to administer core vaccines as late as 16-20 weeks of age where exposure risk is considered high).

In addition, some dogs (and cats?) are genetically predisposed NOT to develop a protective antibody response following vaccination.[2] (Remember parvovirus vaccine failure in Dobermans/Rottweillers?). Genetic NON-responders, and even genetic LOW-responders are recognized in various dog breeds. The failure to immunize, however, is typically limited to one antigen (eg, parvovirus) while the immune response to other antigens administered simultaneously may be protective. NOTE: administering additional doses of vaccine will not 'drive' the patient to respond. Obtaining antibody titers at least 2 weeks following administration of the last vaccine dose in the initial series is the only way to identify non/low-responders.

Improper handling of vaccine can also result in failure to immunize. For example, once reconstituted (hydrated), a modified-live virus (MLV) vaccine should be administered within 1 hour: *use it…or lose it!* This is particularly true of MLV canine distemper virus vaccines.

- **Tumorigenesis**: Emphasis here is on feline injection-site sarcoma, or FISS (aka, vaccine-associated sarcoma). This is the most serious of know vaccine adverse reactions in companion animals. Although not predictable in the individual cat, development of fibrosarcoma at the injection site carries a high risk of mortality among cats that are not afforded (very expensive) treatment. FISS has recently been reviewed.[7,8,9]

Two management factors have emerged:

(1) Avoid administering adjuvant-containing vaccines in cats (**all KILLED feline vaccines contain adjuvant**). For several years, many authors have implicated adjuvant as a (the?) major factor in causing sustained inflammation at the injection site and increasing risk among (genetically) predisposed cats for tumor formation.

A recently published epidemiologic study[1] has provided evidence that adjuvant-containing (killed) vaccine poses 10x greater risk for tumor formation when compared to recombinant vaccine. (**all recombinant and MLV feline vaccines sold in the US and Canada are adjuvant-free**).

(2) Early identification and surgical removal (3-5 cm margins + 2 fascial planes deep) in the event fibrosarcoma is confirmed. Adhere to the Veterinary Cancer Society's "3-2-1" recommendation for early diagnosis (see below). **NOTE:** In addition, performing fine needle aspirates of post-vaccinal lumps in cats may be useful: highly cellular aspirates containing mononuclear inflammatory cells, esp. lymphocytes and macrophages, suggest benign granuloma; hypocellular aspirates suggest mesenchymal cell tumor and warrant biopsy.

The "3-2-1 Rule" for the biopsy diagnosis of suspected injection-site sarcomas

If a mass meets 1 or more of the following criteria, it is recommended to obtain an *incisional* (not excisional) biopsy of a mass lesion…

3 …if the mass is known to persist for 3 months, or longer.
2 …is, or becomes, larger than 2 cm in diameter.
1 …continues to increase in size 1 month following an injection.

- **Multi-systemic infectious/inflammatory disorder of young Weimaraners and Akitas:** Appears to be a rare condition that is not well characterized in the scientific literature and may be linked to immune deficiency in the breed. Affected dogs are from 3 months to 3 years of age and manifest fever, joint swelling, cough (associated with pneumonia), lymphadenomegaly, stomatitis, muscle abscesses (large), surface bleeding, and coat color dilution. Affected dogs are often reported to develop hypertrophic osteodystrophy (HOD) following administration of MLV canine distemper vaccine. Use of the recombinant canine distemper virus (CDV) vaccine is currently recommended over the MLV CDV vaccine to avoid risk of causing this disorder.[2]

- **Transient Immune Suppression:** Administering multivalent, attenuated vaccines, especially CDV + CAV-2, have been shown to induce transient suppression (days) of cell-mediated immunity. The clinical significance of this remains unclear. However, administering a MLV core vaccine in

combination with killed Leptospirosis vaccine has been shown to decrease antibody responses (parvovirus and canine distemper) in dogs compared to MLV vaccines without Leptospirosis.[2,10]

- **Reactions caused by the incorrect or inappropriate administration of vaccine**: Most commonly reported is the unintended subcutaneous administration of a vaccine licensed for intranasal (or oral) use. Fatalities, as well as abscesses at the injection site, have been reported in dogs following subcutaneous administration of a *Bordetella bronchiseptica* bacterin (intended for intranasal administration). The intranasal and oral vaccines for *B. bronchiseptica* contain live (avirulent) bacteria. If parenterally administered, the vaccine bacteria have the potential to replicate and cause serious local or systemic affects, including acute hepatic failure and death.[2] Problematic is the packaging of the oral, and some intranasal, in vials that are similar to those used for injectable vaccines.

Inadvertent or intentional administration of vaccine by the intravenous route may cause acute anaphylaxis and is not recommended under any circumstances.

- **Reactions associated with residual virulence of attenuated vaccine**: post-vaccinal sneezing and/or cough within 24 hours following intranasal administration of vaccine (esp, *B. bronchiseptica* + parainfluenza virus or feline herpesvirus-1 + calicivirus) occur relatively frequently despite appropriate administration technique. Signs are transient but can persist for 2-3 days and may be disturbing to owners. Rarely, treatment with oral antibiotics (eg, doxycycline) for 5 to 7 days is indicated in dogs/cats that develop persistent signs following intranasal administration of *B. bronchiseptica* vaccine.

- **Vaccine-induced interference with diagnostic tests**: Feline Immunodeficiency Virus (FIV) vaccine administration to cats (3 initial doses required) is known to cause false-positive test results by all commercially available testing methods. Today, it is NOT possible to reliably and consistently distinguish an FIV vaccinated cat from an FIV infected cat, even using PCR technology. Furthermore, seropositivity persists for years following initial vaccination. AND…FIV vaccinated queens can pass FIV antibody (maternally derived antibody) to kittens causing false-positive test results in kittens for up to 6 months of age. Current recommendations highlight using a microchip implant (or tattoo) in all cats receiving the FIV vaccine as a means of identifying vaccinates in the event the cat becomes lost and enters a shelter/rescue environment. (See the 2013 AAFP Feline Vaccination Guidelines)

- **Reversion of vaccine virus to a virulent pathogen**: generally considered rare to non-existent among currently licensed vaccines when vaccines are used in the species for which they were licensed. This can become a significant problem when vaccine licensed for use in dogs/cats is used in wild and/or exotic animals.

Reporting an Adverse Event

Vaccine Manufacture: Companies that manufacture vaccines maintain a technical services section that will accept and address adverse event reports from veterinarians who use their product(s). Veterinarians are encouraged to report adverse events to the manufacturer(s) prior to contacting the appropriate regulatory agency. Manufacturers are required to maintain files of any reported vaccine adverse event.

NOTE: manufacturers are under no obligation to compensate the owner or the veterinarian for diagnostic or treatment services related to a known or suspected adverse event.

USDA's Center for Veterinary Biologics (CVB): Subsequent to reporting a known or suspected vaccine adverse event to the manufacturer, veterinarians practicing within the United States may contact the USDA, APHIS CVB in one of the following ways:

Once an adverse event has been reported to the manufacturer, The CVB may be contacted:

- On-line: **Adverse Event Electronic Report Form**.
    - By fax or mail: Download the **pdf form** (17kb) and FAX to (515) 337-6120 or by mail to the CVB.
    - By telephone: Adverse events may also be reported by calling the CVB at (800) 752-6255.

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