SHOULD I BE CONCERNED ABOUT VACCINE SAFETY?

NEW FINDINGS ABOUT COMPANION ANIMAL VACCINE SAFETY

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Abstract:

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Evaluation of benefit and risk of vaccination is a central theme of discussions regarding companion animal vaccination. Although successful vaccination programs have markedly reduced the incidence of infectious diseases, society has also decreased its tolerance for any undesirable outcomes from the practice of modern medicine. Harmful or undesirable health events can be temporally associated with vaccination without being causally related. Nevertheless, vaccine-associated adverse events (VAAE) are of particular concern to practitioners, animal owners, and vaccine manufacturers, because vaccines are generally administered to healthy animals and the medical dictum is to "first do no harm".

Factors known to cause vaccine reactions include the primary vaccine agent or antigen, adjuvants, preservatives, stabilizers, and residues from tissue cultures used in vaccine production. The clinical signs of a reaction caused by a vaccine are not necessarily specific, however, and such signs may also occur in an unvaccinated population. To try to characterize a vaccine-associated adverse event (VAAE) that might occur after administration of a new vaccine, the nature and frequency of adverse events are initially investigated in pre-licensure vaccine safety trials. These trials however are typically too small in patient number (particularly

in selected breeds) and too short in time to demonstrate uncommon events that might be related to repeated exposures.

Large electronic medical databases now allow for research of uncommon or rare events. A study published in JAVMA (2005) involving more than 1 million vaccinated dogs has provided insights into the incidence and risk factors for vaccine-associated adverse events in dogs. In this study, the electronic medical records of Banfield, The Pet Hospital®, were searched for VAAE diagnosed as non-specific vaccine reaction, allergic reaction, urticaria, or anaphylaxis within three days of vaccine administration in pet dogs. The administered vaccines included *Bordetella*, *Borrelia*, coronavirus, *Giardia*, rabies, parvovirus, and/or a multivalent distemper-adenovirus-parainfluenza-parvovirus-leptospirosis (4 serovars) vaccine. In a 2-year period there were 4678 (0.38%) VAAE diagnosed in 1,225,159 vaccination visits. Small (≤10 kg) dogs were at significantly greater risk of adverse events than larger dogs, and the rate of VAAE per 10,000 dogs at-risk significantly decreased as patient weight increased. Dogs weighing >10.0 to 45.0 kg (>22.0 to 99.0 lb) had approximately half the risk of an adverse event compared to dogs weighing <10 kg (22.0 lb).

Breed risk was noted in the 2005 study, as Dachshund, Pug, Boston Terrier, Miniature Pinscher, and Chihuahua breeds experienced the highest rates of VAAE (in the order noted above, i.e. Dachshunds highest). In an update based on >4.5M dogs, just published in JAVMA (doi:10.2460/javma.23.03.0181), the top 5 breeds with highest AE rates were French Bulldogs, Dachshunds, Boston Terriers, Pugs, and Boxers! In fact, in multivariate analysis, breed was the strongest factor in the determination of VAAE risk – indicating genetics is the major

predisposing factor to vaccine reactions. Adverse event risk was also slightly increased in neutered compared to sexually intact dogs. The VAAE rate significantly increased with each additional vaccine administered at the same office visit (a precipitating cause), but the rate increase was greatest in dogs weighing 5 kg or less (2023 study). Another interesting note from the updated 2023 study is, based on evaluation of individual vaccines, greatest AE risk was associated with rabies vaccine, followed by distemper vaccine, and then leptospirosis vaccine.

In summary, both studies found that besides genetically-related breed-specific allergic sensitivities the greatest risk of allergic reactions was in small dogs (<5kg) given multiple vaccinations at one office visit. This risk is roughly equivalent to increased risk of reaction as you increase the total administered volume (mL) of vaccine per kg of body weight. This indicates a dose-response relationship from antigens common to many or all vaccines. Thus antigens within the vaccines were the precipitating cause of vaccine reactions.

A study from Japan (Ohmori et al 2005), examined the IgE concentrations in sera from 10 dogs that developed allergic reactions within 1 hour after vaccination and sera from 50 dogs that did not develop allergic reactions after vaccination. Of the 10 dogs with reactions, 8 had high levels of specific IgE directed to vaccine, whereas the 50 control dogs had low or no levels of specific IgE to the vaccine. Of the 8 dogs that had high serum IgE levels, seven had specific IgE directed to fetal calf serum (a component of cell culture media), and one dog had specific IgE directed to gelatin and casein (stabilizers in vaccines). All dogs with reactions post-vaccination were either of small breeds and/or were young. These dogs included five Miniature Dachshunds, two Pugs, one Miniature Schnauzer, one toy Poodle, and one Welsh Corgi. The investigators also

measured bovine serum albumin concentrations in different vaccines from 4 manufacturers, revealing average concentrations ranging from 4 to 3669 μg/dose [nearly a 1000-fold variation!]. Thus, excipient proteins remaining from vaccine manufacturing may be the primary cause of immediate hypersensitivity following vaccination. The federal regulating agency for veterinary vaccines, USDA Center for Veterinary Biologics, Ames, Iowa, does not require manufacturers however to measure or report quantities of excipient proteins in vaccines.

Researchers at Purdue University recently conducted proteomic analysis on canine distemper, leptospirosis, Lyme, and rabies vaccines from 4 major manufacturers (manuscript in peer review in 2022); and found that rabies vaccines, whether 1-yr or 3-yr DOI, had 10-20x more proteins identified in the vaccines than were identified in canine distemper, lepto, or Lyme vaccines! This is particularly interesting in light of the updated Banfield study noted above. Thus this information with the recently noted higher VAAE rates strongly suggests that if vaccine reactions occur in a dog (or cat) receiving multiple vaccines then it may be wisest to separate the rabies vaccine out in future administrations!

The AKC Canine Health Foundation funded a study at Purdue to try to expand the study from Japan and evaluate canine vaccines in the US. Post-vaccination serum samples were obtained to measure antigen-specific IgE concentrations in dogs experiencing allergic reactions for comparison with concentrations in vaccinated dogs of the same breed that didn't have reactions. Antigen-specific antibody concentrations were measured in 46 affected and 50 non-affected dogs which had received various vaccines. IgE concentrations were increased in both groups of dogs, and there was no significant difference in the concentration between groups. Fortunately, there

were 33 pairs of littermates (1 symptomatic and 1 asymptomatic) that had received the same vaccine(s) before serum sampling. This study provided further evidence that the major cause of post-vaccinal hypersensitivity reactions is genetic (presumably affecting mast cell degranulation).

A genetic basis for adverse events in people after smallpox vaccination has recently been reported. Indeed, this would be an important point to convey in client communication - genetics can be the primary cause of vaccine reactions. Although genetic factors may exist within breeds, these predisposing factors are not readily discernible or removable. Reducing antigens (as precipitating causes) can still reduce the incidence of adverse events following vaccination. The best way to do this is to reduce the total number of vaccines administered at a single office visit. This reduction was endorsed in the AAHA Canine Vaccination Guidelines published since 2011, but must be tempered with evidence that extending the number of office visits may also reduce compliance!

Immune-mediated cytotoxicities, such as ITP and IMHA, may be a concern to some practitioners as these diseases have been diagnosed in the weeks immediately following a vaccination. There are conflicting results from case-control studies, however, and no strong scientific evidence of cause-and-effect has been found to date. If there is a relationship, it may be that the most important information (antigen history before the vaccination) has not been adequately researched. The recent (2019) ACVIM Consensus Statement on the Diagnosis of Immune-Mediated Hemolytic Anemia in Dogs and Cats summarized their critique of the literature as

there was low or negligible evidence of any associated between vaccination and IMHA in either species.

It is a separate/different question to ask whether you should vaccinate an ITP or IMHA dog, even if the disease is in remission. As immune stimulants, vaccines can certainly contain haptogens and trigger a new cytotoxic event. Failure or postponement of vaccination however also leaves the patient susceptible to potentially fatal infectious diseases, and risk-benefit must be discussed with the client/owner on a case-by-case basis.

Painful swelling of the distal radius/ulna, or other long bones, with radiographic changes consistent with hypertrophic osteodystrophy (HOD) have been noted in young dogs within a week or two of vaccination. Irish Setters, Weimaraners, Great Danes, and German Shepherds seem to have increased risk. Associated findings can include fever, leukocytosis and lymphadenopathy. Glucocorticoids have been demonstrated to be superior to NSAIDs in the treatment of these patients. Anti-inflammatory doses, 0.5-1.0 mg/kg/d prednisolone) may be adequate for some cases, but high-dose pulse therapy (an immunosuppressive dose of 2-4 mg/kg/d tapered within a week to physiologic doses) can produce dramatic improvements in moderate to severe cases.

What about cats? In terms of non-sarcomatous reactions, a dose-response relationship to volume has also been found in cats (documented in the 1990s). This finding from a small clinical study was further documented in a 2007 study involving nearly 500,000 cats. This research investigated immediate (type I) hypersensitivity reactions and localized swelling at vaccine-

injection sites. From this we can infer that a reduction in the number of vaccines administered at one time reduces stimulation of the nonspecific innate immunity, reducing vaccine-associated lethargy, anorexia, and localized swellings. An update to the large 2007 study has recently been initiated.

What about injection-site sarcomas in cats? Due to the infrequent occurrence in a large number of cats and long time to occurrence in any cat, most research has used retrospective studies to investigate these dangerous sequelae to injections. Retrospective studies however cannot determine cause and effect. Although the presence of an aluminum crystal identified an association with vaccination (and use of an aluminum-adjuvanted vaccine), injection site sarcomas have been associated with non-adjuvanted vaccines, adjuvanted vaccines, recombinant vaccines, antibiotic injections, even paradoxically the injection of a NSAID. Research has demonstrated that cats with these sarcomas were more likely to have mutations of their p53 tumor suppressor gene compared to disease-free control cats. Cats with the gene mutation also had faster tumor recurrence and decreased survival compared to cats with sarcomas but without the same gene mutation. This gene mutation has also been recently associated with significantly increased cancer risk (soft tissue sarcomas) in people. Until proven otherwise, a cat with an injection-site sarcoma should be assumed to have this gene mutation, and all future injections kept to an absolute minimum.

It is our clinical impression at Purdue that there are fewer reports of vaccine-associated sarcomas in cats, compared to 10-15 years ago. There may be fewer genetically ‘at risk’ cats and/or cats today may be receiving fewer vaccines, e.g. FeLV or rabies, than 10-20 years ago. Nevertheless

a small number of cats may presently be at risk. To not vaccinate a cat greatly reduces the possibility of a sarcoma, but it also greatly increases the possibility of infectious diseases. Currently there are no methods to eliminate all risk. Clinicians have investigated alternative anatomic sites for vaccination, including the tail, in order to minimize the potential impact of amputation.

In conclusion, vaccine 'aversion' or giving fewer vaccines can leave our pets unprotected against important, life-threatening infectious diseases. Continuing research in vaccine duration of immunity may influence our ability to ascertain the best revaccination interval for our pets, thus vaccines may potentially be administered less frequently in the future. In pets genetically predisposed, administering fewer vaccines at one time should reduce the likelihood of a vaccine reaction occurring.

References available on request.