EBVM
Evidence-Based Veterinary Medicine

Critically appraised topic (CAT): vaccines

Risk of vaccine reactions is related to both the number of vaccine injections per visit and the antigen dose rate.

By Patrick Shearer, BVMS, PhD
Contributing Author

In this issue of the Banfield Journal*, we launch a new feature, the "critically appraised topic," or CAT. CATs are summaries of research evidence driven by a clinical question. In the future, we hope to enlist veterinarians from across the country in preparing CATs for publication. If you are interested in providing a CAT, please contact the Banfield Applied Research and Knowledge team (formerly DataSavant) at: BARK@banfield.net. The topic for review in this CAT was inspired by an e-mailed question regarding vaccinations.*

Dr. Zimmerman:
We are having a debate regarding the combination vaccines. We received an e-mail a while ago stating that we shouldn't give more than four vaccines to a Pet at a time, and fewer than four for really small Pets. Some of us thought this was to decrease the number of antigens given at one time to decrease vaccine reactions, and some of us believe it was so a Pet isn't repeatedly injected.

Which is it? If you take the lepto/corona/lyme combination vaccine, for instance, do you count that as three vaccines, because you're injecting three antigens? If so, should a Pet only get one more vaccine on that visit? Or, do you count it as one vaccine injection, so you could, for example, give lepto/corona/lyme, rabies, distemper/adenovirus/parvovirus (DAP), and bordetella, at that visit?

– Karianne Trotsky, DVM

Dr. Trotsky:
That is a very good question. If you go back and look at the vaccine reaction data that was published in *JAVMA* from our hospitals, it showed that *reactions increased as the number of injections increased.* It did not prove that the combination vaccine (more antigens) had any higher reaction rate, however, than single antigen/injection vaccines.

So the "new" thought is to limit the number of injections (not necessarily the number of antigens). The rationale behind this is that each vaccine vial (whether one or four antigens) will have the same amount of adjuvant (which is the suspected cause

for some reactions). Thus, if you limit the number of injections, you limit the amount of adjuvant the Pet is exposed to at any given time. We have tried to get more of our vaccines in combination now than before (lepto and corona, lyme and lepto, etc.), so it would be easier for you to achieve this concept of fewer injections.

– Nancy Zimmerman, DVM, DABVP

CRITICALLY APPRAISED TOPIC

Clinical question

- Is the rate of Type I hypersensitivity vaccine reactions related to the number of individual vaccinations per visit, or the antigen dose?

Clinical bottom line

- In dogs and cats, the risk of Type I hypersensitivity reactions is related to the number of vaccine injections administered and the dose rate of antigen. The dose rate is determined by the number of antigens per dose and patient body weight.
  - *For a given body weight, the risk of reaction is less when administering single multivalent vaccines than multiple monovalent vaccines.*
- It is not clear how the individual components of vaccines contribute to these reactions or how the reaction rate varies between products from different manufacturers.

Evidence summary

Search string

- Google Scholar: Vaccine reaction canine feline; vaccine reaction adjuvant canine feline; vaccine reaction adjuvant
- Veterinary Information Network (journal articles): vaccine reaction

For a given body weight, the risk of reaction is less when administering single multivalent vaccines than multiple monovalent vaccines.

- Article databases: PubMed, Wiley InterScience, AVMA journals, ScienceDirect, JSTOR.

Main results

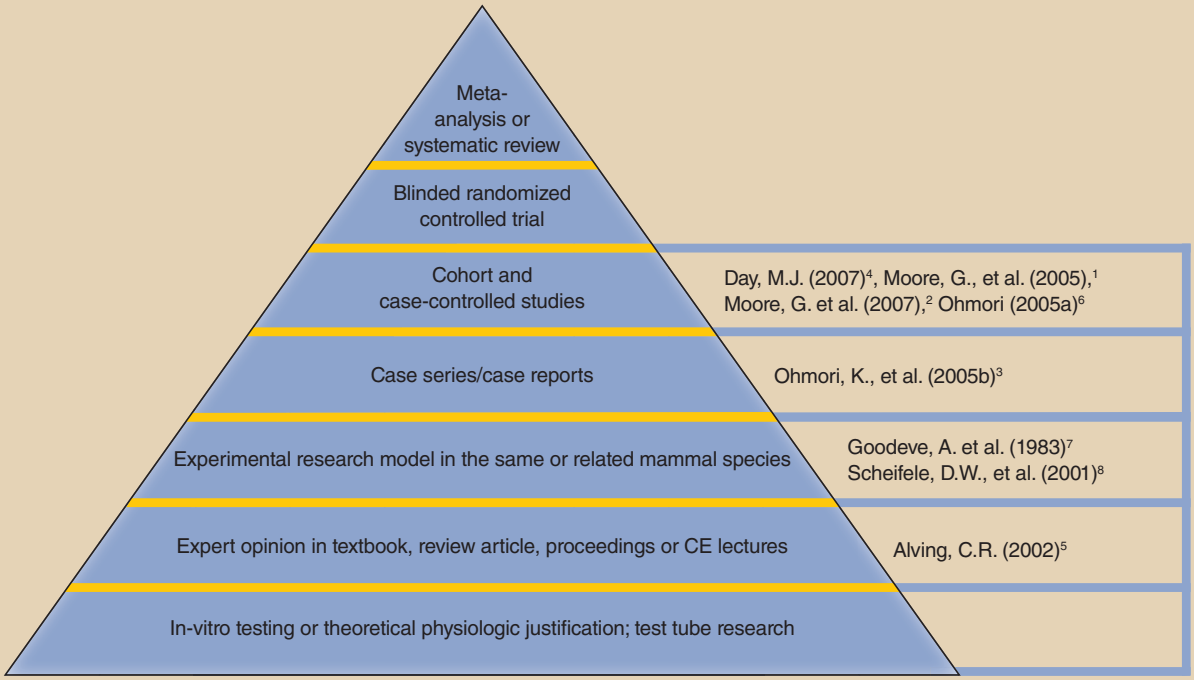
- In dogs, there is good evidence that the risk of a reaction is directly related to the antigen dose rate in µg/kg (*i.e.*, *inversely* proportional to the patient's weight).[1]
- In dogs and cats, there is fair to good evidence that the risk of a reaction increases with the number of vaccination events (*i.e.,* the number of visits that include a vaccination) until the fourth or fifth event.[1,2]
- In dogs and cats, there is fair evidence that, for a given body weight, the risk of a reaction is greater with the injection of multiple monovalent vaccines than a single injection of a multivalent vaccine.[1,2]
- There is limited evidence for both dogs and cats that adjuvants and other nonantigen components are also responsible for vaccine reactions.[3-5]
- There is limited evidence that the nature and severity of reactions varies between species.[5]
- There is equivocal evidence that, for a single vaccine injection, the risk of a reaction is increased with multivalent vaccines compared to monovalent vaccines.[1,2]

Strength of Evidence (*Figure 1,* page 16)

Comments

- This CAT focuses only on Type I hyper-

Figure 1: Strength of Evidence



Note: See corresponding Evidence Summary, ***Table 1***, page 17

sensitivity reactions and has not included literature on other types of reactions (such as autoimmune hemolytic anemia and vaccine-associated sarcomas). It should also be noted that the signs of Type I hypersensitivity reactions vary in their nature and timing.

- There is little research, human or veterinary, on the risks associated with vaccine reactions or the components of vaccines responsible for reactions.
- Balancing the risks of vaccine reactions in a clinical setting can be challenging. For example, a medium-sized dog injected with four separate vaccines may have a similar risk of reaction as a small dog injected with one vaccine containing four antigens.
- Adverse event reporting is irregular; criteria used are inconsistent. This will affect any investigation into vaccine-associated adverse events. Accurate estimation of reaction rates is, therefore, difficult, and comparison between publications even more so.
- Many factors contribute to Type I hypersensitivity reactions: antigen type, antigen dose, number of antigens, number of vaccines received in a patient's lifetime, vaccine components (accidentally included viruses), adjuvant and patient attributes (age, weight, species, breed, gender).
- For a given antigen, reaction rates may vary between products from different manufacturers; however, such investigations have not been conducted. Accounting for differences in reaction rates between manufacturers may affect the outcomes of the referenced studies.
- Vaccine formulations are proprietary, and, therefore, investigation into which

Table 1: Evidence Summary

Study	Methods	Key Findings
Day, M.J. (2007)[4]	One of the test vaccine combinations (adjuvanted or nonadjuvanted) was administered to two dorsal subcutaneous sites in groups of 14- to16-week-old kittens, and two control injections of saline were made to adjacent cutaneous sites. Injection sites were sampled 7, 21 and 62 days post-vaccination, and histopathological assessment was made of five levels of each injection site by four independent pathologists. Scoring system was developed to ascribe overall severity; the nature of the cellular inflammatory and tissue repair phases were then examined at each time-point.	Adjuvanted vaccines induced a more severe and extensive tissue inflammatory reaction at all three time-points of the study. Although there had been almost total repair of these inflammatory sites by day 62, there was clear evidence of persistence of significant quantities of either alum or lipid adjuvant (largely within the cytoplasm of macrophages in granulomatous foci).
Moore, G, et al. (2005)[1]	Banfield records of canine patients were searched for specific diagnostic codes indicating reactions within three days of vaccine administration. Free-text medical records were reviewed for a subset of 400 records. Univariate and multivariate statistical analyses were conducted, examining the effects of age, weight, gender, vaccine type and number of vaccine injections per visit.	Risk of reaction was inversely proportional to body weight, and greater for neutered vs. intact dogs; greater for 1- to 3-year-olds than 2- to 9-month-olds or >3 years; increased with more vaccine injections per visit. Small dogs that received multiple vaccine injections per visit were at the greatest risk.
Moore, G, et al. (2007)[2]	Banfield records of feline patients were searched for specific diagnostic codes indicating reactions within 30 days of vaccine administration. Free-text medical records were reviewed for relevant records. Univariate and multivariate statistical analyses were conducted, examining the effects of age, weight, gender, vaccine type and number of vaccine injections per visit.	Risk of reaction was greater for neutered vs. intact cats, and greater for approximately 1-year-olds than 2- to 9-month-olds or >2 years; increased with more vaccine injections per visit. Young adult neutered cats were at greatest risk of reaction.
Ohmori, K, et al. (2005a)[3]	Serum samples from 10 dogs with a history of Type I hypersensitivity reactions were tested for IgE reactivity to whole vaccines and specific components of the vaccines (such as fetal calf serum, gelatin, etc.).	Eight dogs had high levels of vaccine-specific IgE. Of these, seven had high levels of IgE to fetal calf serum.
Goodeve, A, et al. (1983)[7]	Human participants were vaccinated with varying doses of influenza vaccine. The response to vaccination was compared between groups.	Groups receiving higher doses of antigen had slightly more severe reactions.
Scheifele, D.W, et al. (2001)[8]	Human participants were monitored for vaccine reactions after a fifth dose of pertussis vaccine.	Local reactions to a fifth dose of pertussis vaccine were frequent.
Alving, C.R. (2002)[5]	Types and mechanisms of action of vaccine adjuvants were reviewed.	Comparative potency of a selected adjuvant varied, not only according to antigen tested, but also to the animal species it was injected into. Meaningful comparisons between different adjuvants derived from ***in vitro*** studies, or from studies using adjuvants in rodents or other animals, are often not predictive for safety, adjuvant effects or vaccine efficacy in humans.
Ohmori, K, et al. (2005b)[6]	Records of 85 dogs with suspected Type I hypersensitivity vaccine reactions were reviewed. Breed distribution was described. Reactions were classified as cardiovascular signs, dermatological signs and both cardiovascular and dermatological signs. The distribution of reactions among vaccine types and total number of vaccines received were described.	Cardiovascular signs of reactions appeared earlier than dermatological signs. More dogs with reactions had received multivalent vaccines than monovalent vaccines. Most dogs with reactions had received two or more vaccines; however, nearly 20 percent had never received a vaccine.

specific components are responsible for reactions is unlikely at this time.

CAT appraiser: Patrick Shearer, BVMS, PhD

Date CAT was "born"/expiration date: 08/06/2009.

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Patrick Shearer, BVMS, PhD, graduated from Murdoch University School of Veterinary and Biomedical Sciences in Perth, Western Australia. Dr. Shearer joined Banfield's Applied Research and Knowledge team (BARK) as an associate medical advisor in 2009. He and his wife, Danielle, have two dogs and two cats.

IRIDIO COLOR SERVICE
5050 First Ave. S.
Seattle, WA 98134
t 206.587.0800
f 206.587.0356 888.587.0911