

Incidence of and risk factors for adverse events associated with distemper and rabies vaccine administration in ferrets

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Objective—To determine incidence of and risk factors for adverse events associated with distemper and rabies vaccine administration in ferrets.

Design—Retrospective cohort study.

Animals—3,587 ferrets that received a rabies or distemper vaccine between January 1, 2002, and December 31, 2003.

Procedures—Electronic medical records were searched for possible vaccine-associated adverse events. Adverse events were classified by attending veterinarians as nonspecific vaccine reactions, allergic reactions, or anaphylaxis. Patient information that was collected included age, weight, sex, cumulative number of distemper and rabies vaccinations received, clinical signs, and treatment. The association between potential risk factors and occurrence of an adverse event was estimated with logistic regression.

Results—30 adverse events were recorded. The adverse event incidence rates for administration of rabies vaccine alone, distemper vaccine alone, and rabies and distemper vaccines together were 0.51%, 1.00%, and 0.85%, respectively. These rates were not significantly different. All adverse events occurred immediately following vaccine administration and most commonly consisted of vomiting and diarrhea (52%) or vomiting alone (31%). Age, sex, and body weight were not significantly associated with occurrence of adverse events, but adverse event incidence rate increased as the cumulative number of distemper or rabies vaccinations received increased. In multivariate logistic regression analysis, only the cumulative number of distemper vaccinations received was significantly associated with the occurrence of an adverse event.

Conclusions and Clinical Relevance—Results suggest that in ferrets, the risk of vaccine-associated adverse events was primarily associated with an increase in the number of distemper vaccinations. (*J Am Vet Med Assoc* 2005;226:909–912)

Currently available vaccines are highly effective in protecting animals against potentially fatal infectious diseases but may occasionally be associated with adverse reactions. Premarketing safety trials are used to identify potential vaccine-associated adverse events (VAAEs), but the relatively small size of such trials lim-

its their ability to detect uncommon events. Postmarketing surveillance methods in veterinary medicine typically rely on passive reporting of VAAEs by practitioners and pet owners, and as a result, the occurrence of such events is likely underestimated.^{1,2}

Large private corporate veterinary practices that have clinics located in diverse geographic areas and sizable patient populations may provide useful post-marketing surveillance information.³ Information pertaining to VAAEs could be retrieved from computerized medical records, eliminating the dependence on veterinarians and owners to initiate reporting of adverse events. In addition, deriving information from practices employing a large number of veterinarians would reduce the reporting bias associated with determining whether a particular adverse event was associated with vaccine administration.

Adverse event incidence rates associated with distemper and rabies vaccine administration in ferrets have been reported to exceed 5%, but these estimates were based on relatively small sample sizes.^{1,4} Because use of larger populations of patients would be expected to provide more accurate estimates of adverse event incidence rates, the purpose of the study reported here was to collect information from a large patient population to determine incidence of and risk factors for adverse events associated with distemper and rabies vaccine administration in ferrets. Specifically, information was obtained for ferrets examined at Banfield, The Pet Hospital, a private veterinary practice with > 375 primary-care veterinary clinics located in 41 states in the United States. All clinic locations used standardized electronic medical records that were maintained in a central data storage facility.

Materials and Methods

Electronic medical records of all ferrets examined at veterinary clinics owned by Banfield, The Pet Hospital, from January 1, 2002, through December 31, 2003, were transferred to Purdue University. Veterinary clinics that participated in the study used standardized coding for demographic information, clinical observations, diagnoses, procedures, and treatments. Each patient record was identified by a unique encounter number for each office visit. Only records with species coded as ferret and containing a treatment code for distemper vaccine^{ab} or rabies vaccine^c were included in analyses, and the date of vaccination was identified. Eligible records were searched for possible VAAEs by use of numeric diagnosis codes for vaccine reaction, allergic reaction, and anaphylaxis. The number of days between a possible VAAE and the nearest date of vaccination was calculated for each patient. Clinical signs and treatments administered were tabulated for office visits during which a VAAE occurred.

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Cumulative numbers of distemper and rabies vaccinations received, sex, age, and body weight at the time of each patient visit were recorded.

Statistical analyses—All statistical analyses were performed with standard software.^d Sex and year were analyzed as categorical variables, and χ^2 tests were used to test for associations between occurrence of a VAAE (yes vs no) and sex and between occurrence of a VAAE and year. Age and weight were analyzed as continuous variables; the Wilcoxon rank sum test was used to compare age and weight between ferrets that did and did not have a VAAE. Incidence rates (ie, VAAEs/100 vaccine doses) with 95% confidence limits (CLs) were calculated for individual vaccines and vaccine combinations; a binomial distribution for proportions was assumed. The Cuzick test across ordered groups was used to test for trends in regard to the cumulative number of distemper or rabies vaccinations received and risk of a VAAE. Because the specific distemper vaccine used by participating veterinary clinics changed approximately midway through the study period and the vaccine manufacturer was not uniquely coded, the approximate rates of VAAEs associated with the 2 distemper vaccines were evaluated by comparing the rates during 2002 and 2003 by means of a χ^2 test.

Risk factors for VAAE were evaluated by means of multivariate unconditional logistic regression. Estimates of the odds ratio (OR) and 95% CLs for each risk factor were obtained by means of exponentiation of the regression coefficients. Maximum likelihood estimates of the logistic parameters and final model were assessed for significance by use of the Pearson χ^2 goodness-of-fit test. For all analyses, values of $P < 0.05$ were considered significant.

Results

A total of 9,248 office visits involving ferrets were identified during the 2-year study period, of which 3,587 (38.8%) involved administration of distemper or rabies vaccines. During these office visits, a total of 4,995 vaccine doses were administered. These office visits involved 235 veterinary clinics. The percentages of office visits involving ferrets during which both dis-

temper and rabies vaccine were administered, distemper vaccine was administered alone, and rabies vaccine was administered alone were 39.3%, 38.9%, and 21.9%, respectively.

A total of 33 possible VAAEs were recorded. These events were identified as vaccine reactions (23), allergic reactions (7), or anaphylaxis (3). Four of the 7 ferrets with an allergic reaction and all 3 ferrets with anaphylaxis had recently been vaccinated, and these events were thus considered to be VAAEs. The remaining 3 ferrets with allergic reactions did not have any history of recent vaccination, and these 3 events were therefore excluded from further analyses. Thus, a total of 30 VAAEs were considered.

All 30 VAAEs occurred on the same day a vaccination was given, and 24 of the 30 occurred during the same office visit. The 30 VAAEs occurred in 30 ferrets.

Adverse event incidence rates following administration of rabies vaccine alone, distemper vaccine alone, and both rabies and distemper vaccines were 0.51%, 1.00%, and 0.85%, respectively (Table 1). These rates were not significantly ($P = 0.48$) different from each other. Most ferrets received only 1 distemper or rabies vaccine during the study period (64.2% and 66.7%, respectively), but adverse event incidence rates increased significantly ($P = 0.001$ and 0.025 , respectively) as the cumulative number of distemper or rabies vaccinations received increased (Table 2). The adverse event incidence rate associated with distemper vaccine administration during 2002 did not differ significantly ($P = 0.85$) from the rate associated with distemper vaccine administration during 2003 (1.05% and 0.95%, respectively).

Mean \pm SD age of ferrets that had a VAAE ($n = 30$; 1.76 ± 1.53 years) was not significantly ($P = 0.27$) different from mean age of ferrets that did not have a VAAE (3,557; 1.44 ± 1.51 years). Similarly, mean body weight of ferrets that had a VAAE (0.97 ± 0.30 kg [2.13 ± 0.66 lb]) was not significantly ($P = 0.47$) different from mean body

Table 1—Incidence of adverse events associated with administration of distemper and rabies vaccines, alone and in combination, in ferrets examined at veterinary clinics between January 1, 2002, and December 31, 2003.

Vaccine administered	No. of vaccine doses	No. of adverse events	Incidence of adverse events (%)	95% CLs
Distemper	1,395	14	1.00	0.55, 1.69
Rabies	784	4	0.51	0.14, 1.30
Distemper and rabies	1,408	12	0.85	0.44, 1.48

CL = Confidence limit.

Table 2—Incidence of adverse events associated with administration of distemper and rabies vaccines in ferrets as a function of cumulative number of distemper or rabies vaccinations received.

Vaccine	Cumulative No. of previous vaccinations received	No. of vaccine doses	No. of adverse events	Incidence of adverse events (%)	95% CLs	P value for trend
Distemper	0	525	2	0.38	0.05, 1.37	0.006
	1	2,303	14	0.61	0.33, 1.02	
	2	647	13	2.01	1.07, 3.41	
	3	105	1	0.95	0.02, 5.19	
	4	8	0	0	NA	
Rabies	0	1,038	5	0.48	0.16, 1.12	0.025
	1	2,394	21	0.88	0.54, 1.34	
	2	154	4	2.60	0.71, 6.52	
	3	1	0	0	NA	

NA = Not applicable. CL = Confidence limit.

Table 3—Results of multivariate logistic regression analysis of potential risk factors for vaccine-associated adverse events in ferrets.

Risk factor	Odds ratio	95% CLs	P value
Age (y)	1.04	0.81, 1.35	0.741
Sex (male vs female)	1.13	0.52, 2.49	0.753
Body weight (kg)	1.26	0.40, 4.01	0.696
Cumulative No. of rabies vaccinations	1.69	0.81, 3.54	0.163
Cumulative No. of distemper vaccinations	1.80	1.10, 2.93	0.018

CL = Confidence limit.

weight of ferrets that did not (0.93 ± 0.33 kg [2.05 ± 0.73 lb]). Sex distribution of ferrets that had a VAAE (56.7% male) was not significantly ($P = 0.69$) different from sex distribution of ferrets that did not (53.0% male). When a multivariate logistic regression model incorporating variables for age, weight, sex, cumulative number of rabies vaccinations received, and cumulative number of distemper vaccinations received was examined, only the cumulative number of distemper vaccinations received was significantly ($P = 0.018$) associated with occurrence of a VAAE (Table 3). The OR of 1.80 indicated that the risk of a VAAE increased by 80% with each additional distemper vaccination that ferrets had previously received.

Clinical signs were described for 29 of the 30 ferrets with a VAAE. The most common sign was vomiting (24/29 [83%]), which was usually accompanied by diarrhea (15/24 [63%]). Diarrhea, hypersalivation, or collapse was recorded as the only clinical sign in the other 5 ferrets (17%).

Treatments for VAAE involved administration of various combinations of dexamethasone, diphenhydramine, epinephrine, crystalloid fluids, and oxygen. Treatments recorded most frequently were administration of dexamethasone and diphenhydramine (8 ferrets); administration of diphenhydramine alone (5); and administration of dexamethasone, diphenhydramine, and oxygen (4). None of the ferrets with VAAEs died. Four of the 30 ferrets with a VAAE received 1 or more vaccinations at a later date during the study period, and none of the 4 developed subsequent VAAEs. One of these 4 ferrets was pretreated with dexamethasone and diphenhydramine prior to vaccine administration, and 2 were pretreated with diphenhydramine alone. The remaining ferret was not pretreated prior to vaccine administration.

Discussion

In the present study, VAAEs occurred in approximately 0.5% to 1% of ferrets administered rabies or distemper vaccine. It is unlikely such low rates would be detected in vaccine safety trials.⁵ The observed difference between adverse event incidence rates associated with rabies and distemper vaccines in the present study was not statistically significant, even though these rates differed by almost 2-fold and more than 3,500 animals were vaccinated. Detecting a significant difference, with 95% confidence and 80% power, between rates of 0.51% and 1.00% would require a total of 10,598 animals if group sizes were equal. The extremely large sample sizes required to detect uncommon or rare conditions such as VAAEs demonstrate the usefulness

of analyzing medical records from large veterinary practices for postmarketing surveillance.

Multivariate analysis of potential risk factors revealed that an increase in the cumulative number of distemper vaccinations received was significantly associated with an increased risk of VAAE in the present study, with each successive distemper vaccination increasing the risk of a VAAE by 80%. Summaries of adverse events reported to the US Pharmacopeia Veterinary Practitioners' Reporting Program documented that most VAAEs in ferrets involved administration of the distemper vaccine alone, but practitioner-generated reports fail to define the population at risk.¹ Thus, reliance on absolute counts alone can be misleading. Vaccines that by license are recommended to be administered more frequently will be associated with more adverse events than are vaccines that are administered less frequently, even if reaction rates are equal.

Age was not a significant risk factor for VAAE in the present study, although older ferrets have previously been reported to be more likely to experience such events.⁴ Age is expected to be positively correlated with repeated vaccination. Revaccination during a patient's life is designed to booster a waning immunologic response to the primary vaccine antigen, but hypersensitization can also occur with repeated antigenic exposure. Factors responsible for sensitization can include the primary vaccine antigens themselves, product components such as adjuvants and preservatives, and proteins remaining from cell culture and manufacturing processes.⁶ No specific vaccine component has been proven solely responsible for hypersensitivity reactions. Hypersensitization, regardless of cause, is presumed to be long-lived, but the repeatability of these reactions in sensitized patients cannot be presumed. In a study⁷ of children with a history of a nonanaphylactic adverse event following vaccination, most did not exhibit any reaction when revaccinated. These children were not administered antihistamines or glucocorticoids at the time of revaccination, so the lack of clinical reactions could not be attributed to any pretreatment. Although most ferrets that had VAAEs in the present study were not revaccinated during the study period, the 4 that were revaccinated reportedly did not have any recurrence of the adverse event. The true benefit of antihistamine or glucocorticoid administration in 3 of these patients is undetermined.

Although use of automated databases can enhance postmarketing surveillance for VAAEs, validation of diagnoses may be necessary.⁸ Adverse event diagnoses in the present study were confirmed by reviewing history and clinical signs recorded in the medical records. Clinical signs associated with these events (ie, vomiting and diarrhea) were consistent with signs expected with immediate (type I) hypersensitivity reactions. Vaccine-associated adverse events, if not described by the attending veterinarian as a vaccine reaction, were identified and coded diagnostically as allergic reactions or anaphylaxes. Allergic or anaphylactic reactions may be induced by factors other than vaccine administration, but allergic and anaphylactic reactions identified as VAAEs in the present study occurred on the same

day as vaccine administration and without any record of concurrent drug administration. Immediate hypersensitivity reactions mediated by IgE are systemic but are primarily associated with body surfaces, such as lung, skin, and intestine, and clinical signs vary by species.⁹ The predominant hypersensitivity manifestations in this group of ferrets included gastrointestinal tract signs, most commonly vomiting, and this pattern was similar to reactions reported by other investigators.^{1,4}

Because of the close proximity between identification of clinical signs and vaccine administration, an association between these adverse events and vaccination was probably assumed by the attending veterinarians, leading to the predominant diagnosis of vaccine reaction. Other less-immediate types of hypersensitivity reactions would be less clearly associated with vaccination. In the present study, we did not investigate relationships between other conditions, such as immune-mediated disease, and their temporal proximity to vaccination. Vaccine-site fibrosarcomas have been reported in ferrets,^{10,11} but no fibrosarcomas were identified during the study period in any of the vaccinated ferrets.

Traditional surveillance systems that monitor vaccine safety rely on voluntary reporting of adverse events (ie, passive surveillance). Such systems are limited by a lack of information relating to the number of doses of vaccine administered, an element necessary for calculating adverse event rates, and are characterized by underreporting, variable reporting standards, and bias among reporters.¹² In human medicine, automated medical record databases for large, defined populations of health maintenance organization members are currently used for assessing the safety of vaccines.^{13,14} Use of large populations can permit separation of the risks associated with individual vaccines from those associated with vaccine combinations, whether administered as a multivalent product in the same syringe or as different products given simultaneously at different body sites. These databases can also be used for subgroup analysis or to calculate background rates of illness in the absence of vaccination.

The present study demonstrated the feasibility of using a large veterinary practice database to investigate VAAEs in a species seen infrequently in most practices. Analyses of medical records for several thousand fer-

rets examined at many different veterinary clinics suggested that the rate of VAAEs is $\leq 1\%$ with distemper and rabies vaccine administration and that adverse events that are seen were most often hypersensitivity reactions manifested as vomiting and diarrhea. Further use of this database in postmarketing surveillance of vaccine safety in this and other species will enhance our understanding of the incidence rates, manifestations, and possible causes of the adverse events that can occur following vaccination.

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- a. FerVac-D, United Vaccines Inc, Madison, Wis.
 - b. PUREVAX, Merial Inc, Duluth, Ga.
 - c. IMRAB-3, Merial Inc, Duluth, Ga.
 - d. STATA, version 8.2, StataCorp, College Station, Tex.
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References

1. Meyer EK. Vaccine-associated adverse events. *Vet Clin North Am Small Anim Pract* 2001;31:493–514.
2. Jacobson RM. Vaccine safety. *Immunol Allergy Clin North Am* 2003;23:589–603.
3. Glickman LT. Weighing the risks and benefits of vaccination. *Adv Vet Med* 1999;41:701–713.
4. Greenacre CB. Incidence of adverse events in ferrets vaccinated with distemper or rabies vaccine: 143 cases (1995–2001). *J Am Vet Med Assoc* 2003;223:663–665.
5. Wimsatt J, Jay MT, Innes KE, et al. Serologic evaluation, efficacy, and safety of a commercial modified-live canine distemper vaccine in domestic ferrets. *Am J Vet Res* 2001;62:736–740.
6. Martinod S. Adverse effects of vaccination. In: Pastoret PP, Blancou J, Vannier P, et al, eds. *Veterinary vaccinology*. Amsterdam: Elsevier Science, 1997;574–580.
7. Gold M, Goodwin H, Botham S, et al. Re-vaccination of 421 children with a past history of an adverse vaccine reaction in a special immunisation service. *Arch Dis Child* 2000;83:128–131.
8. Hemmelgarn B, Blais L, Collet JP, et al. Automated databases and the need for fieldwork in pharmacoepidemiology. *Pharmacoepidemiol Drug Safety* 1994;3:275–282.
9. Tizard IR. *Veterinary immunology: an introduction*. 6th ed. Philadelphia: WB Saunders Co, 2000;317.
10. Munday JS, Stedman NL, Richey LJ. Histology and immunohistochemistry of seven ferret vaccination-site fibrosarcomas. *Vet Pathol* 2003;40:288–293.
11. Murray J. Vaccine injection-site sarcoma in a ferret (lett). *J Am Vet Med Assoc* 1998;213:955.
12. Chen RT, Rastogi SC, Mullen JR, et al. The Vaccine Adverse Event Reporting System (VAERS). *Vaccine* 1994;12:542–550.
13. Chen RT, DeStefano F, Davis RL, et al. The vaccine safety datalink: immunization research in health maintenance organizations in the USA. *Bull World Health Organ* 2000;78:186–194.
14. Mullooly J, Drew L, DeStefano F, et al. Quality of HMO vaccination databases used to monitor childhood vaccine safety. *Am J Epidemiol* 1999;149:186–194.