Adverse events diagnosed within three days of vaccine administration in dogs

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Objective—To determine incidence rates and potential risk factors for vaccine-associated adverse events (VAAEs) diagnosed within 3 days of administration in dogs.

Design—Retrospective cohort study.

Animals—1,226,159 dogs vaccinated at 360 veterinary hospitals.

Procedure—Electronic records from January 1, 2002, through December 31, 2003, were searched for possible VAAEs (nonspecific vaccine reaction, allergic reaction, urticaria, or anaphylaxis) diagnosed within 3 days of vaccine administration. Information included age, weight, sex, neuter status, and breed. Specific clinical signs and treatments were reviewed in a random sample of 400 affected dogs. The association between potential risk factors and a VAAE was estimated by use of multivariate logistic regression.

Results—4,678 adverse events (38.2/10,000 dogs vaccinated) were associated with administration of 3,439,576 doses of vaccine to 1,226,159 dogs. The VAAE rate decreased significantly as body weight increased. Risk was 27% to 38% greater for neutered versus sexually intact dogs and 35% to 64% greater for dogs approximately 1 to 3 years old versus 2 to 9 months old. The risk of a VAAE significantly increased as the number of vaccine doses administered per office visit increased; each additional vaccine significantly increased risk of an adverse event by 27% in dogs ≤ 10 kg (22 lb) and 12% in dogs > 10 kg.

Conclusions and Clinical Relevance—Young adult small-breed neutered dogs that received multiple vaccines per office visit were at greatest risk of a VAAE within 72 hours after vaccination. These factors should be considered in risk assessment and risk communication with clients regarding vaccination. (*J Am Vet Med Assoc* 2005;227:1102–1108)

Vaccines are developed to be immunogens and are required to have potency, safety, and efficacy before licensing; however, no vaccine is absolutely reaction free or completely effective. Although manufacturers' premarketing safety trials help ensure that **vaccine-associated adverse events (VAAEs)** occur infrequently, VAAEs have evoked public and professional concern regarding the possible overvaccination of humans and animals.[1-4]

Traditional postmarketing surveillance of veterinary vaccines relies on veterinarians and owners to voluntarily submit reports of suspected reactions to manufacturers or the USDA. Limitations to passive surveillance include variability in report quality, selective reporting, underreporting, and the inability to determine whether a vaccine caused the adverse event described in any report.[5,6] The information submitted in voluntarily generated reports is not necessarily complete and often lacks important details about the animal, observed event, or concurrent medications received by the affected animal. Incidence rates and relative risks for specific VAAEs cannot be calculated because of the lack of information about the overall vaccinated population (denominator data or the population at risk of a VAAE).

Large, population-based medical record databases have been used in recent years to conduct epidemiologic investigations of human vaccine safety.[7,8] Because these databases are usually generated during the routine administration of medical care and do not require the completion of a separate VAAE form, the problem of underreporting of events is reduced. Large populations can be examined for infrequent adverse events, and denominator data on doses given and the availability of appropriate comparison groups make these databases ideal for studying vaccine safety.[9]

Banfield, The Pet Hospital, is a small animal general practice that uses the same computerized medical record system in more than 400 hospital locations throughout the United States. Electronic medical records are stored in a central data warehouse and can be easily retrieved for administrative or medical review and analysis. Proprietary software[a] containing standardized codes for physical examinations, laboratory tests, diagnoses, and treatments is used by all veterinarians in the practice. The codes, when combined with dates, allow determination of temporal relationships between vaccination and potential VAAEs, a factor that is important for assessing causality.[10] Abnormalities noticed within a few days of vaccination may be attributable to an adverse response to the vaccine immunogens, but the risk factors and incidence of these events in companion animals have not been characterized. The purpose of the study reported here was to use the Banfield database to estimate the incidence rate and potential risk factors for VAAEs that occurred within 3 days of vaccine administration in dogs.

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Supported by the CDC National Center for Infectious Diseases (grant No. R01 CI000093).

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Materials and Methods

Electronic medical records of all dogs at 360 Banfield veterinary hospitals from January 1, 2002 through December 31, 2003 were extracted from the Banfield practice database. Records were included in the study if the species code was canine and if treatments included a code for *Bordetella* vaccine,[b] coronavirus vaccine,[c] multivalent distemper-adenovirus-parainfluenza-parvovirus-leptospirosis (serovars canicola, icterohaemorrhagiae, grippotyphosa, and pomona) vaccine,[d] *Giardia* vaccine,[e] *Borrelia* vaccine,[f] parvovirus vaccine,[g] or rabies vaccine.[h] Records for dogs that received both an injectable heartworm preventive and a vaccine during the same office visit were not included in analyses.

The date of birth, breed, sex, neuter status, weight, and date of vaccination were recorded for each dog. Medical records of dogs that received vaccinations were searched for possible VAAEs by use of diagnostic codes (vaccine reaction, allergic reaction, urticaria, anaphylaxis, cardiac arrest, cardiovascular shock, and sudden death). Diagnoses were only included in analyses if the diagnosis date was within 3 days after vaccine administration. Date of death, if recorded, was used to determine if death occurred within 3 days of vaccination. The free-text medical note field was reviewed in a random sample of 400 affected dogs to determine clinical signs and treatments associated with a VAAE.

Statistical analyses—All calculations were performed with statistical software.[i] Sex and neuter status were analyzed as categoric variables. Continuous variables of age and weight were converted to categoric variables because nonlinear trends were detected in the model-fitting process. Dogs were grouped on the basis of age at date of vaccination as follows: 2 to 9 months, > 9 months to 1.5 years, > 1.5 to 2.5 years, > 2.5 to 3.5 years, > 3.5 to 5.5 years, > 5.5 to 8.5 years, and > 8.5 years. Weight was converted from a continuous to a categoric variable of 5-kg (11-lb) weight groups up to 45 kg (99 lb). Incidence rates with 95% confidence limits were calculated via assumption of a binomial distribution for proportions. Tests for trend were performed across ordered groups by use of the Cuzick nonparametric test. All VAAE rates are reported as the number of adverse events/10,000 dogs vaccinated. For categoric variables, rates for affected dogs were compared with rates for nonaffected dogs by use of the χ^2 test for independence.

Potential risk factors for VAAEs were evaluated by use of bivariate and multivariate unconditional logistic regression, and multivariate logistic regression included dog random effects. Estimates of the **odds ratio (OR)** and 95% **confidence intervals (CIs)** for each risk factor were obtained by use of exponentials of the regression coefficients. Interactions between independent variables in the final multivariate model were assessed for an association with an adverse event. Interactions between vaccines were not included in multivariate analysis because of the large number of vaccine combinations (n = 58). Maximum likelihood estimates of the logistic parameters and final model were assessed for significance by use of the Hosmer-Lemeshow χ^2 goodness-of-fit test. A value of $P < 0.05$ was considered significant.

Results

Population—In the 2-year study period, 4,531,837 vaccine doses were administered to 1,537,534 dogs at 360 veterinary hospitals. Excluding from analysis 311,375 dogs that concurrently received injectable heartworm preventive and vaccinations, 3,439,576 vaccine doses were administered to 1,226,159 dogs. Mean number of vaccine doses administered per dog per office visit was 2.8 (range, 1 to 6), and 4,678 dogs had a diagnosis of a VAAE within 3 days of vaccine administration (38.2 VAAEs/10,000 dogs vaccinated; 95% CI, 37.1 to 39.3). The percentage of VAAEs diagnosed on days 0 (same day), 1, 2, and 3 postvaccination was 72.8%, 18.9%, 5.5%, and 2.8%, respectively. Of 4,678 VAAEs, 3,080 (65.8%) were coded as vaccine reactions, 1,481 (31.7%) as allergic reactions, 80 (1.7%) as ana-

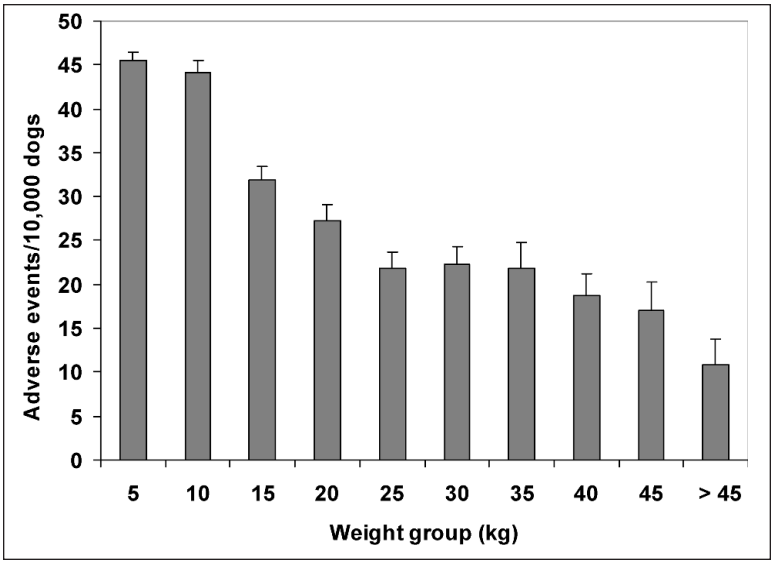

Figure 1—Mean ± SEM vaccine-associated adverse event (VAAE) rates (No. of adverse events/10,000 dogs vaccinated) by 5-kg (11-lb) weight groups in 1,226,159 dogs vaccinated at 360 veterinary hospitals from January 1, 2002, to December 31, 2003. The VAAEs were diagnosed within 3 days of vaccine administration. To convert kilograms to pounds, multiply by 2.2.

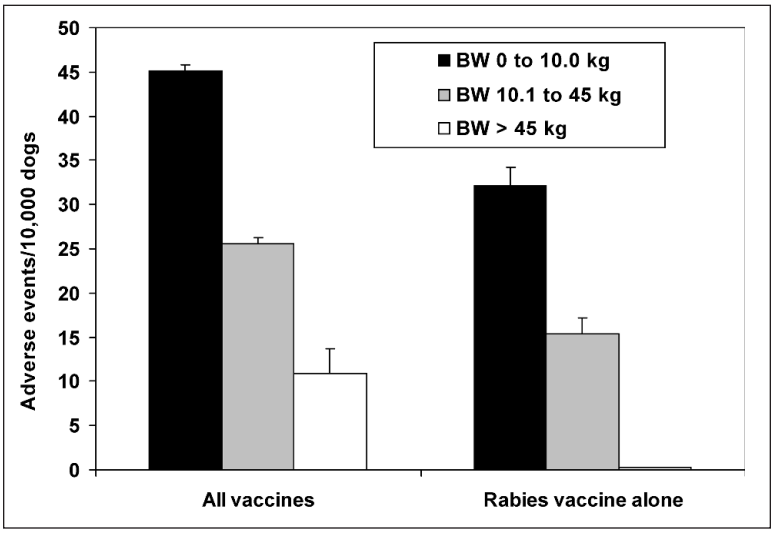

Figure 2—Mean ± SEM VAAE rates for all vaccines (n = 1,226,159) and for rabies vaccine administered alone (118,765) to dogs of various body weights (BWs). *See* Figure 1 for remainder of key.

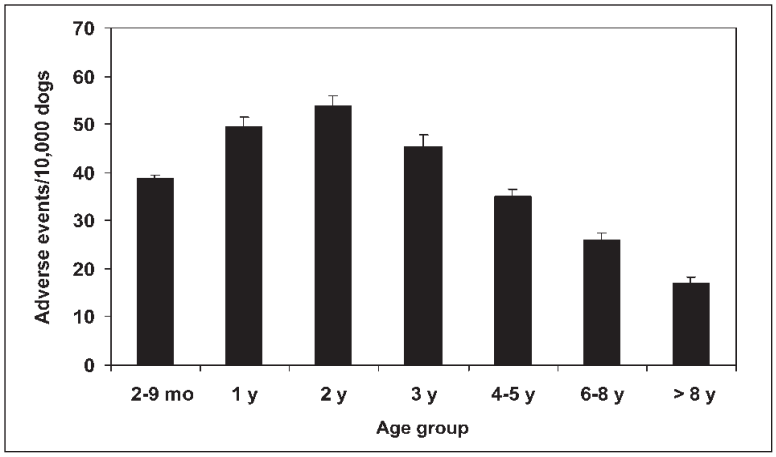

Figure 3—Mean ± SEM VAAE rates by age in dogs administered 1 or more vaccines at 360 veterinary hospitals from January 1, 2002, to December 31, 2003. *See* Figure 1 for remainder of key.

Table 1—Incidence rate per 10,000 dogs and 95% confidence limits (CL) by breed for vaccine-associated adverse events (VAAEs) diagnosed within 3 days of vaccine administration at 360 veterinary hospitals from January 1, 2002, to December 31, 2003. Breeds listed if represented by ≥ 5,000 vaccinated dogs.

Breed	Dogs vaccinated (n)	VAAE (n)	VAAE rate/10,000 dogs	95% CL
Dachshund	41,323	503	121.7	(111.4, 132.8)
Pug	20,214	188	93.0	(80.2, 107.2)
Boston Terrier	9,541	80	83.8	(66.5, 104.3)
Miniature Pinscher	15,310	117	76.4	(63.2, 91.5)
Chihuahua	68,839	524	76.1	(69.8, 82.9)
Maltese	20,663	138	66.8	(56.1, 78.9)
Miniature Schnauzer	15,296	99	64.7	(52.6, 78.7)
Jack Russell Terrier	23,717	129	54.4	(45.4, 64.6)
Toy Poodle	12,311	61	49.5	(37.9, 63.6)
Yorkshire Terrier	33,563	159	47.3	(40.3, 55.3)
Boxer	31,141	142	45.6	(38.4, 53.7)
Pomeranian	27,543	125	45.4	(37.8, 54.0)
Pekingese	9,516	40	42.0	(30.0, 57.2)
Shih Tzu	47,964	199	41.5	(35.9, 47.6)
English Bulldog	5,470	22	40.2	(25.2, 60.8)
Lhasa Apso	15,386	59	38.3	(29.2, 49.4)
Weimaraner	5,393	20	37.1	(22.7, 57.2)
Beagle	34,872	126	36.1	(30.1, 43.0)
Bichon Frise	13,444	46	34.2	(25.1, 45.6)
American Eskimo Dog	5,829	22	33.7	(23.7, 57.1)
American Cocker Spaniel	20,795	70	33.6	(26.3, 42.5)
Shetland Sheepdog	9,891	33	33.4	(23.0, 46.8)
Shar Pei	7,337	24	32.7	(21.0, 48.6)
Miniature Poodle	7,207	23	31.9	(20.2, 47.8)
Golden Retriever	41,779	126	30.2	(25.1, 35.9)
Basset Hound	7,828	23	29.4	(18.6, 44.1)
Welsh Corgi	5,511	16	29.0	(16.6, 47.1)
Siberian Husky	6,362	17	26.7	(15.6, 42.7)
Great Dane	5,211	13	24.9	(13.3, 42.6)
West Highland White Terrier	6,742	16	23.7	(13.6, 38.5)
Labrador Retriever	132,222	312	23.6	(21.1, 26.4)
Doberman Pinscher	6,520	15	23.0	(12.9, 37.9)
American Pit Bull Terrier	6,718	15	22.3	(12.5, 36.8)
Akita	6,161	13	21.1	(11.2, 36.1)
Mixed	44,188	89	20.1	(16.2, 24.8)
Australian Shepherd	16,221	30	18.5	(12.5, 26.4)
Dalmatian	7,234	13	18.0	(9.6, 30.7)
Australian Cattle Dog	5,702	10	17.5	(8.4, 32.2)
Border Collie	13,524	22	16.3	(10.2, 24.6)
Collie	5,708	9	15.8	(7.2, 29.9)
Chow Chow	23,387	32	13.4	(9.4, 19.3)
German Shepherd Dog	60,017	78	13.0	(10.3, 16.2)
Rottweiler	38,538	50	13.0	(9.6, 17.1)

phylaxis, 32 (0.7%) as urticaria, and 5 (0.1%) as cardiac arrest. Death was reported in association with vaccination in 3 dogs (0.024 deaths/10,000 dogs vaccinated [2.4 deaths/1,000,000]; 95% CI, 0.005 to 0.072).

Bivariate analyses—The population included 252,434 (20.6%) sexually intact males, 191,601 (15.6%) sexually intact females, 378,224 (30.8%) neutered males, and 403,900 (32.9%) spayed females. Among those groups, unadjusted VAAE rates/10,000 dogs were 32.9 (95% CI, 30.7 to 35.2), 35.7 (95% CI, 33.1 to 38.5), 39.1 (95% CI, 37.1 to 41.1), and 41.2 (95% CI, 39.8 to 43.8), respectively. Among all dogs, the VAAE rates in 2002 (1,942/515,447 [37.7/10,000]) and 2003 (2,736/710,712 [38.5/10,000]) were not significantly different ($P = 0.47$).

The VAAE rates decreased significantly as body weight increased (P for trend < 0.001; **Figure 1**). For all vaccines or for rabies vaccine alone, the VAAE rate for 10.1- to 45.0-kg (22.2- to 99.0-lb) dogs was approximately half the rate for dogs that weighed 0 to 10.0 kg (0 to 22.0 lb; $P < 0.001$; **Figure 2**). For rabies vaccine administered alone, VAAE rates/10,000 dogs that weighed 0 to 10.0 kg, 10.1 to 45.0 kg, and > 45 kg were 32.1 (222/69,178), 15.3 (69/45,088), and 0.0 (0/1,966), respectively. In 586,817 dogs ≤ 9 months old, the VAAE rate was 38.6/10,000 dogs vaccinated (95% CI, 37.1 to 40.3), and the VAAE rate significantly increased with age until 1.5 to 2.5 years of age (VAAE rate, 53.8; 95% CI, 49.5 to 58.4; **Figure 3**). The VAAE rates decreased progressively thereafter in older age categories. Among breeds with 5,000 or more dogs vaccinated, Dachshund, Pug, Boston Terrier, Miniature Pinscher, and Chihuahua breeds had the highest rates of VAAEs with 121.7, 93.0, 83.8, 76.4, and 76.1 adverse events/10,000 dogs vaccinated, respectively (**Table 1**). The VAAE rate for mixed-breed dogs was in the bottom quintile of all rates.

The risk of a VAAE significantly increased as the number of vaccines administered per office visit increased (P for trend < 0.001). Unadjusted VAAE rates increased from 25.2 for a single vaccine to 56.3/10,000 dogs when 6 vaccines were simultaneously administered (705/279,330 and 397/70,554, respectively). A strong linear dose-response relationship ($r^2 = 0.985$) was detected between adjusted VAAE rates and the number of vaccines administered. In all dogs, each additional vaccine administered per office visit increased the rate of a VAAE by 24.2%; the rate increase was significantly ($P < 0.001$) greater in dogs that weighed 0 to 10.0 kg, compared with dogs that weighed 10.1 to 45.0 kg (27.3% vs 11.5%, respectively; **Figure 4**). The 3 dogs with recorded deaths each had received ≥ 4 vaccines at their last office visit.

The VAAE rates associated with administration of a single dose of different vaccines differed significantly ($P < 0.001$). The lowest rate was observed with parenteral administration of *Bordetella* vaccine (15.4/10,000; 82 VAAEs/53,238 doses), and the highest rate was observed with *Borrelia* (Lyme disease) vaccine (43.7/10,000; 132 VAAEs/30,201 doses). The VAAE rates for *Giardia* vaccine (23.4/10,000; 97 VAAEs/41,447 doses), rabies vaccine (24.7/10,000; 293 VAAEs/118,765 doses), coronavirus vaccine (26.2/10,000; 15 VAAEs/5,735 doses), and distemper-adenovirus-parainfluenza-parvovirus-leptospirosis vaccine (28.8/10,000; 86 VAAEs/29,852 doses) were not significantly different ($P = 0.526$). There were < 100 doses of parvovirus vaccine administered alone, and no adverse events were recorded. There were 8 paired combinations of vaccines administered to at least 5,000 dogs. The VAAE rates for those combinations ranged from 15.5/10,000 for *Bordetella* and *Giardia* vaccines (13 VAAEs/8,405 dogs) to 54.1/10,000 for concurrent administration of *Borrelia* and rabies vaccine (33 VAAEs/6,097 dogs). Concurrent administration of a rabies and multivalent distemper vaccine to 25,171 dogs resulted in 99 VAAEs or a VAAE rate of 39.3/10,000 dogs.

Multivariate analysis—A multivariate logistic regression model including sex, neuter status, age, weight, and number of vaccines received satisfied requirements for goodness of fit ($P = 0.72$). In the final model, the OR of a VAAE increased significantly ($P < 0.001$) as weight decreased and as the number of vaccines increased (**Table 2**). Risk for dogs that weighed ≤ 5 kg was more than 4 times the risk for dogs that weighed > 45 kg (OR, 4.46; 95% CI, 2.67 to 7.46; $P < 0.001$). Compared with the risk of a VAAE associated with a single vaccination, simultaneous administration of 3 vaccines increased the risk approximately 50% (OR, 1.51; 95% CI, 1.37 to 1.67; $P < 0.001$), and with 5 simultaneous vaccinations, risk doubled (OR, 2.06; 95% CI, 1.82 to 2.33; $P < 0.001$). Risk of a VAAE was significantly increased for neutered dogs, compared with sexually intact dogs. The VAAE risk was greatest for dogs approximately 1 to 3 years old and least for dogs ≥ 6 years of age.

Description of VAAEs—In a random sample of 400 dogs with a VAAE diagnosed within 3 days of vac-

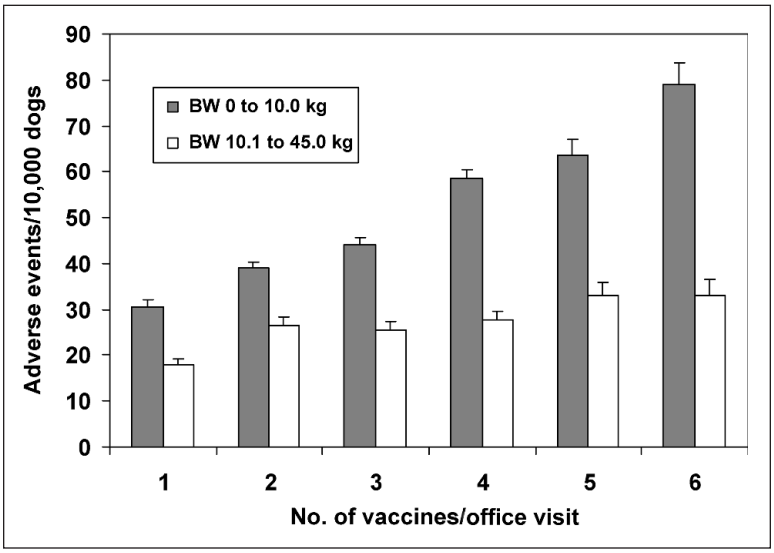

Figure 4—Mean ± SEM VAAE rates by number of vaccines administered per office visit at 360 veterinary hospitals in dogs of various BWs from January 1, 2002 to December 31, 2003. *See* Figure 1 for remainder of key.

Table 2—Adjusted odds ratios and 95% CLs (multivariate logistic regression) for potential risk factors for VAAEs in 1,226,159 dogs.

Risk factor	Odds ratio	95% CL	*P* value
Sex and neuter status			
Male, sexually intact	1.00	NA	NA
Female, sexually intact	1.06	(0.95, 1.18)	0.287
Male, neutered	1.27	(1.16, 1.38)	< 0.001
Female, spayed	1.38	(1.27, 1.51)	< 0.001
No. of vaccines per encounter			
1	1.00	NA	NA
2	1.36	(1.23, 1.51)	< 0.001
3	1.51	(1.37, 1.67)	< 0.001
4	1.91	(1.73, 2.11)	< 0.001
5	2.06	(1.82, 2.33)	< 0.001
6	2.31	(2.03, 2.62)	< 0.001
Weight			
0 to 5 kg	4.46	(2.67, 7.46)	< 0.001
> 5 to 10 kg	4.21	(2.51, 7.05)	< 0.001
> 10 to 15 kg	3.00	(1.77, 5.06)	< 0.001
> 15 to 20 kg	2.52	(1.48, 4.29)	0.001
> 20 to 25 kg	1.93	(1.13, 3.32)	0.017
> 25 to 30 kg	1.93	(1.12, 3.33)	0.018
> 30 to 35 kg	1.91	(1.10, 3.32)	0.022
> 35 to 40 kg	1.68	(0.94, 3.00)	0.081
> 40 to 45 kg	1.54	(0.81, 2.92)	0.183
> 45 kg	1.00	NA	NA
Age			
2 to 9 mo	1.00	NA	NA
1 y	1.51	(1.37, 1.67)	< 0.001
2 y	1.64	(1.49, 1.81)	< 0.001
3 y	1.35	(1.20, 1.52)	< 0.001
4 to 5 y	1.06	(0.95, 1.19)	0.282
6 to 8 y	0.79	(0.70, 0.90)	< 0.001
> 8 y	0.50	(0.43, 0.59)	< 0.001

NA = Not applicable.
To convert kilograms to pounds, multiply by 2.2.

cine administration, the predominant clinical signs were facial or periorbital edema (30.8% [123/400]), wheals or urticaria (20.8% [83/400]), generalized pruritus (15.3% [61/400]), and vomiting (10.3% [41/400]). Localized vaccination-site reactions (eg, swelling, inflammation, or soreness) represented 8.0% (32/400) of VAAEs, and systemic nonspecific signs (eg, fever, lethargy, or anorexia) represented 5.5% (22/400) of VAAEs. Collapse was the only clinical sign recorded in 4 (1.0%) dogs. Most dogs in this sample were treated with an antihistamine and glucocorticoid (34.5% [138/400]), an antihistamine alone (22.5% [90/400]), or glucocorticoid alone (11.5% [46/400]). Less commonly used treatments included fluids, oxygen, diuretics, or nonsteroidal anti-inflammatory drugs; epinephrine was administered to 3.2% (13/400) of dogs. For 69 of 400 (17.0%) dogs, no treatment was prescribed.

Discussion

By use of this large population of dogs that received primary care, it was possible to accurately estimate the incidence rate of practitioner-diagnosed VAAEs that occurred within 3 days of vaccine administration. Although most VAAEs were recorded the same day as vaccination, the 3-day period was selected as a reasonable time for owners to report events or return their dog to a veterinarian for examination. This period increased the likelihood that the observed event was the result of a vaccination but excluded sequelae with a longer latency period. The use of a primary care practice database permitted inclusion of VAAEs that may not have been reported to industry or a federal agency via a separate passive system. Rates for VAAEs were determined by use of the actual number of vaccine doses administered; therefore, a practice database provided more comprehensive event (numerator) data while also providing population (denominator) data. Traditional passive surveillance systems that receive and summarize adverse event reports alone are not useful for determination of incidence rates or potential risk factors and are often characterized by underreporting of events.[6,11]

National vaccine sales data have been used as the denominator in some calculations of VAAE rates, but such calculations result in estimates per dose of vaccine sold rather than per dog, cannot determine the effect of concurrently administered multiple vaccines, and are also influenced by underreporting of adverse events. Such estimates have reported[1,12,13] VAAE rates ranging from 0.13 to 0.40/10,000 vaccine doses, whereas prelicensure clinical studies reported postvaccination reactions in excess of 1% or > 100 reactions/10,000 vaccine doses.[6] In the present study, a VAAE rate of 0.38% (approx 38 adverse events/10,000 vaccinated dogs or 13/10,000 doses administered) was found.

The risk of a VAAE in this study population was inversely related to a dog's weight. This weight-response relationship was previously suggested by results of a study[1] in which dogs of toy breeds had significantly more suspected VAAEs than other dogs, although body weight was not evaluated. The manufacturers' recommended dose for all vaccines administered in our study was 1 mL regardless of body weight, and all vaccines were from single-dose vials. Vaccines, in contrast to virtually all veterinary pharmaceuticals, are prescribed on a 1-dose-fits-all basis, rather than by body weight. Prelicensing clinical trials investigate the safety of vaccines with doses in excess of label directions but only in a limited number of dogs. The results of this study suggest that trials in dogs that weigh > 10 kg underestimate the expected VAAE rate in smaller dogs.

Prelicensing clinical trials also investigate the safety of vaccines in several hundred dogs at multiple hospital locations, but specific breeds may be under- or overrepresented. Mature weights of dogs of different breeds may vary by 5 to 10 times and occasionally by > 50 times. Therefore, a 1-mL vaccine dose results in a ratio of vaccine volume received per kilogram of body weight that can vary widely. When multiple vaccines are simultaneously administered to a dog, the ratio of volume received per kilogram of body weight per patient also varies. The importance of this volume-to-weight ratio in relation to adverse event risk was evident in this study by the increase in VAAE rates as the number of simultaneously administered vaccine doses increased, even when adjusted for weight.

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.[14-17] The overall for-

mulation of various vaccine components (eg, antigen, adjuvants, and diluent) is proprietary information that was unavailable for analysis in our study; thus, the variation in VAAE rates among single-antigen vaccines may not be solely attributable to the primary vaccine antigen. The nearly linear dose-response relationship between number of vaccines simultaneously administered and the VAAE rate suggests that vaccine components other than the primary antigen may contribute to adverse events. In a recent study[18] of 8 dogs that developed immediate-type allergic reactions and had high concentrations of specific serum IgE against the vaccines, 7 had specific IgE against fetal calf serum.

The increased risk of VAAEs in smaller breeds in this study was consistent with the weight-related findings; however, a genetic predisposition of some breeds to VAAEs is also possible. Although Dachshunds have been considered at increased risk for VAAEs,[19] some studies[1,6] have not found a difference in hypersensitivity reactions for this breed, compared with all other breeds. Genetic susceptibility to allergy occurs in humans,[20,21] and both family and breed genetics may play a similar role in dogs with respect to VAAEs. Likewise, because of genetic heterogeneity, the relatively low VAAE rate observed in mixed-breed dogs suggests that laboratory safety trials that use such dogs may underestimate the VAAE rates that would occur in purebred dogs. This is important because purebred dogs comprise at least two thirds of the US dog population.[22]

The risk of allergic reaction has been reported[16] to increase after the third or fourth injection of a vaccine (ie, a booster response). In our study, VAAE risk increased for dogs up to 2 years of age and then declined thereafter. In a controlled study,[23] IgE concentrations were found to be greatest after vaccination at 2 and 3 years of age, corresponding to a dog's third and fourth doses of vaccine, but were not as increased after vaccination at 4 years of age. Because of variations in canine vaccination protocols, the third injection of vaccine may constitute the last puppy vaccination or a booster at 1 year of age. The decline in the VAAE rate observed after 2 years of age in this study may have been attributable to allergen desensitization, initiation of alternative vaccination protocols in predisposed dogs, or owner refusal to revaccinate dogs that previously had a VAAE.

Neutering appeared to increase risk of a VAAE more than sex. Females mount stronger immune responses after vaccination or infection than males because of a dimorphic enhancing effect of estrogens and a protective effect of androgens.[24,25] Neutering reduces serum estrogen and testosterone concentrations and also removes their negative feedback on the pituitary gland, resulting in significant increases in follicle-stimulating hormone and luteinizing hormone concentrations in female and male dogs.[26] These pituitary hormones may independently, or through interaction with primary sex hormones, influence the immune response to vaccination.

In this study, rates for adverse events associated with the administration of single vaccines were not significantly different for multivalent distemper (with 4 *Leptospira* serovars), *Giardia*, rabies, and coronavirus vaccines. Vaccines containing inactivated *Leptospira* bacterins have been considered to be more allergenic than tissue culture lines of virus vaccines, but newer subunit vaccines have been developed to reduce this problem.[19] The multivalent vaccine used by the veterinary hospitals in our study was a purified *Leptospira* product that contained the immunogenic envelope, and increased allergenicity of vaccines containing *Leptospira* was not clearly detected in this large population of dogs. The risk of hypersensitivity reactions after administration of *Borrelia* vaccine has been considered moderate.[27] These reactions can be attributable to an immunologic response to proinflammatory surface antigens,[19] which is a possible cause for the increased VAAE rates associated with administration of the vaccine in this study. Event rates for specific vaccines in this study may or may not be representative of other vaccines, but data pertaining to other products are lacking for comparison.

Clinical signs of VAAEs and the predominance of same-day events in this study were generally indicative of immediate-type hypersensitivity reactions.[28] Signs associated with immediate hypersensitivity vary by species and are related to the location of mast cells that degranulate in the presence of an allergen. Cutaneous or dermatologic events were most commonly reported by veterinarians within 3 days of vaccine administration, consistent with most reports of suspected canine VAAEs submitted to the US Pharmacopeia.[6] Adverse events documented in the patient medical notes reviewed in this study were not generally described as life-threatening, even when the diagnosis code was anaphylaxis.

The size of large practice databases can make full validation of diagnoses or a complete record review of all patient information exorbitantly time-consuming. Validation of a subset of records within large databases has been recommended[29] to overcome this problem, and medical notes were reviewed for a subset of the population in our study. In an assessment of the impact of validating only 1% to 2% of a study population against paper-based medical records, errors of misclassified diagnoses only modestly bias outcome rate ratios toward the null hypothesis.[29] The use of practice databases also presents new but surmountable challenges in processing and analyzing extremely large data sets, sometimes exceeding 500 MB in storage size.

Adverse events in this study, as in all postmarketing surveillance systems, were based on diagnoses made by different practitioners. Although diagnoses consistent with vaccine reactions were selected by practitioners from the available codes in the software, computerized databases are dependent on coded outcomes and some codes may be nonspecific.[8] Standardized case definitions for VAAEs are not available in veterinary medicine and are only currently being addressed in human medicine.[5] Bias may therefore be introduced into a study if adverse events are not captured by the existing database, either because they do not result in an office consultation or because appropriate coding is not chosen. Biases that potentially affect studies with large databases are not unlike those of nonautomated data sources that require case definitions, manual abstrac-

tion, coding, and computerization. In a large practice, reporting biases or misdiagnoses that may potentially be introduced by a few individuals are reduced because of the large number of hospitals contributing data. The random effects variation related to individual veterinarians was not evaluated in the multivariate model, but incorporation of dog random effects into analysis resulted in minimal change in ORs because of the large number of dogs (data not shown).

The population size in large databases produces statistical power such that calculated *P* values are often small and within traditional significance levels. Study results must therefore not be interpreted solely on significance but rather on clinical importance. Although VAAE rates in this study were higher than estimated rates reported from passive surveillance systems, these events are relatively infrequent or uncommon in a hospital population. Dog characteristics that increase VAAE risk should be highlighted in risk communication with clients, but risk aversion of adverse events must be tempered with the risk of sickness and death from infectious diseases.

Research will be required to characterize the primary allergenic components of different licensed veterinary vaccines, and then it will need to be determined whether vaccine allergenicity and volume can be reduced while immunologic protection is maintained, particularly for smaller dogs. Until such time, practitioners may choose to reduce the number of vaccines simultaneously administered to small dogs (but not reduce the volume of an individual vaccine) and alert owners to risk factors for VAAEs.

Although VAAE rates were higher for certain risk factors or some vaccines, compared with other factors or vaccines, the rates for VAAEs were low in the overall population. Evidence of VAAEs does not indicate that vaccines are not safe but rather that there is a small risk of adverse events associated with certain dog factors or vaccines. Premarketing safety studies, when fiscally or logistically limited in size, will remain limited in power to detect rare adverse events that may be more common among animals with particular risk factors.

a. PetWare, Banfield, The Pet Hospital, Portland, Ore.
b. Brochicine, Biocor Animal Health Inc, Omaha, Neb.
c. Duramune Cv-K, Fort Dodge Animal Health, Fort Dodge, Iowa.
d. Duramune Max 5/4L, Fort Dodge Animal Health, Fort Dodge, Iowa.
e. *Giardia* Vax, Fort Dodge Animal Health, Fort Dodge, Iowa.
f. Lymevax, Fort Dodge Animal Health, Fort Dodge, Iowa.
g. Duramune Max Pv, Fort Dodge Animal Health, Fort Dodge, Iowa.
h. Rabvac 3, Fort Dodge Animal Health, Fort Dodge, Iowa.
i. STATA, version 8.2, StataCorp, College Station, Tex.

References

1. Gaskell RM, Gettinby G, Graham SJ, et al. Veterinary Products Committee working group report on feline and canine vaccination. *Vet Rec* 2002;150:126–134.
2. Gobar GM, Kass PH. World Wide Web-based survey of vaccination practices, postvaccinal reactions, and vaccine site-associated sarcomas in cats. *J Am Vet Med Assoc* 2002;220:1477–1482.
3. Rose NR. Immunologic hazards associated with vaccination of humans. *J Autoimmun* 2000;14:11–13.
4. Rundle R. Are annual shots overkill? *The Wall Street Journal* 2002;240:B1.
5. Varricchio F, Iskander J, Destefano F, et al. Understanding vaccine safety information from the Vaccine Adverse Event Reporting System. *Pediatr Infect Dis J* 2004;23:287–294.
6. Meyer EK. Vaccine-associated adverse events. *Vet Clin North Am Small Anim Pract* 2001;31:493–514.
7. 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.
8. Verstraeten T, DeStefano F, Chen RT, et al. Vaccine safety surveillance using large linked databases: opportunities, hazards and proposed guidelines. *Expert Rev Vaccines* 2003;2:21–29.
9. DeStefano F. The Vaccine Safety Datalink project. *Pharmacoepidemiol Drug Saf* 2001;10:403–406.
10. Ellenberg SS, Braun MM. Monitoring the safety of vaccines: assessing the risks. *Drug Saf* 2002;25:145–152.
11. Chen RT, Rastogi SC, Mullen JR, et al. The Vaccine Adverse Event Reporting System (VAERS). *Vaccine* 1994;12:542–550.
12. Brooks R. Adverse reactions to canine and feline vaccines. *Aust Vet J* 1991;68:342–344.
13. Gray AK. Cat and dog vaccination: results from the Suspected Adverse Reaction Surveillance Scheme. *Vet Rec* 1998;143:455.
14. Georgitis JW, Fasano MB. Allergenic components of vaccines and avoidance of vaccination-related adverse events. *Curr Allergy Rep* 2001;1:11–17.
15. Roth JA. Mechanistic bases for adverse vaccine reactions and vaccine failures. *Adv Vet Med* 1999;41:681–700.
16. Martinod S. Adverse effects of vaccination. In: Pastoret P, Blancou J, Vannier P, eds. *Veterinary vaccinology*. Amsterdam: Elsevier Science, 1997;574–580.
17. HogenEsch H, Azcona-Olivera J, Scott-Moncrieff C, et al. Vaccine-induced autoimmunity in the dog. *Adv Vet Med* 1999;41:733–747.
18. Ohmori K, Masuda K, Maeda S, et al. IgE reactivity to vaccine components in dogs that developed immediate-type allergic reactions after vaccination. *Vet Immunol Immunopathol* 2005;104:249–256.
19. Greene CE. Immunoprophylaxis and immunotherapy. In: Greene CE, ed. *Infectious diseases of the dog and cat*. 2nd ed. Philadelphia: WB Saunders Co, 1998;717–750.
20. Huang SK, Mathias RA, Ehrlich E, et al. Evidence for asthma susceptibility genes on chromosome 11 in an African-American population. *Hum Genet* 2003;113:71–75.
21. Ober C. Susceptibility genes in asthma and allergy. *Curr Allergy Asthma Rep* 2001;1:174–179.
22. American Pet Products Manufacturers Association. *2003–2004 APPMA national pet owners survey*. Greenwich, Conn: American Pet Products Manufacturers Association, 2003;7.
23. HogenEsch H, Dunham AD, Scott-Moncrieff C, et al. Effect of vaccination on serum concentrations of total and antigen-specific immunoglobulin E in dogs. *Am J Vet Res* 2002;63:611–616.
24. Beagley KW, Gockel CM. Regulation of innate and adaptive immunity by the female sex hormones oestradiol and progesterone. *FEMS Immunol Med Microbiol* 2003;38:13–22.
25. Verthelyi D. Sex hormones as immunomodulators in health and disease. *Int Immunopharmacol* 2001;1:983–993.
26. Olson PN, Mulnix JA, Nett TM. Concentrations of luteinizing hormone and follicle-stimulating hormone in the serum of sexually intact and neutered dogs. *Am J Vet Res* 1992;53:762–766.
27. Klingborg DJ, Hustead DR, Curry-Galvin EA, et al. AVMA Council on Biologic and Therapeutic Agents' report on cat and dog vaccines. *J Am Vet Med Assoc* 2002;221:1401–1407.
28. Tizard I. Type I hypersensitivity. *Veterinary immunology: an introduction*. 7th ed. Philadelphia: WB Saunders Co, 2004;308–323.
29. Mullooly J, Drew L, DeStefano F, et al. Quality of HMO vaccination databases used to monitor childhood vaccine safety. Vaccine Safety DataLink Team. *Am J Epidemiol* 1999;149:186–194.