

# Breed, smaller weight, and multiple injections are associated with increased adverse event reports within three days following canine vaccine administration

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## OBJECTIVE

To evaluate patient and vaccine factors associated with adverse events (AEs) recorded within 3 days of vaccine administration in a large cohort of dogs.

## ANIMALS

4,654,187 dogs vaccinated in 16,087,455 office visits in a 5-year period at 1,119 hospitals of a corporate practice.

## METHODS

Electronic medical records of dogs vaccinated between January 1, 2016, and December 31, 2020, were searched for diagnoses of possible AEs recorded within 3 days of administration of vaccines without concurrent injectable heartworm preventative. Patient risk factors (age, sex, breed, and weight) and number and type of vaccine were extracted from records. ORs (and 95% CIs) for risk factors were estimated via multivariable logistic regression mixed models with patient as a random effect.

## RESULTS

AEs were recorded following 31,197 vaccination visits (0.19%, or 19.4/10,000 visits). Reported AE rates increased from 1 to 4 vaccines administered and among individual vaccines were greatest for rabies vaccine. AE rate was generally inversely related to body weight, with largest rates in dogs  $\leq 5$  kg. The largest AE rates were noted in French Bulldogs and Dachshunds (ORs  $> 4$  compared to mixed-breed dogs).

## CLINICAL RELEVANCE

Risk factor information can be used to update vaccination protocols and client communication. Breed differences may indicate genetics as the primary risk factor for adverse vaccine reactions following vaccinations.

Vaccinations are an important component of veterinary preventative medicine, reducing morbidity and mortality associated with infectious diseases. However, vaccines are typically administered to healthy individuals and improvements to immune status are not readily discernible. Adverse events (AEs) or undesired side effects believed to be associated with vaccination are noted by owners, often contributing to reduced acceptance of that vaccine or of vaccines in general.<sup>1</sup> Effective vaccination programs can reduce the incidence of targeted diseases in populations, further causing individuals to question the need or value of vaccination.<sup>2</sup>

AEs related to vaccinations are often due to manifestations of immune stimulation. These responses may be excessive in individuals predisposed immunologically for genetic or acquired reasons.<sup>3</sup> Identification

of genetically at-risk individuals has been advocated to potentially enable personalized rather than mass vaccination,<sup>4</sup> but identification methods are lacking at present. However, predisposed individuals do not manifest adverse reactions unless exposure to an immunological trigger precipitates such a reaction. Owners and veterinarians perceive associations between AEs and possible precipitating risk factors, such as vaccines in general or a specific vaccine in particular. Such perceptions, whether valid or not, often lead to vaccine hesitancy by owners or even veterinarians.<sup>1</sup> These perceptions can have a broad impact across a population.

Vaccine components that have been identified as possible precipitating factors for hypersensitivity reactions include gelatin, egg protein, antibiotics, and latex in people.<sup>5</sup> Some dogs with immediate hypersensitivity

reactions following vaccination have been shown to have increased IgE reactivity to fetal calf serum, a product used as growth media in cell culture.<sup>6</sup> Cell culture media may include albumin and other proteins of bovine origin, which are retained in canine vaccines, as evidenced by recent vaccine proteomic analysis.<sup>6,7</sup> Manufacturing can seek to reduce or even remove such proteins to improve vaccine safety, but specific threshold concentrations that might elevate risk are unknown.

A study<sup>8</sup> using data from 2002 to 2003 investigated potential risk factors for vaccine-associated AEs within 3 days of vaccine administration in approximately 1.25 million dogs. The study evaluated reported AEs from electronic medical records at 360 hospitals in a preventative care-focused practice. Risk of AEs increased with decreasing body weight and with increasing number of vaccines administered per office visit. Breed differences in AE rates were also identified even when controlling for body weight and number of vaccines. This study was cited in subsequent vaccination guidelines nationally and internationally.<sup>9,10</sup> Together with potential changes in canine vaccine-manufacturing methods, in hospital protocols and individual breed popularity in the last 2 decades, risk factors for current canine vaccinations may have altered. The objective of the current study was to use the same veterinary practice to estimate incidence rate and risk factors for AEs recorded within 3 days of vaccine administration in dogs during a recent 5-year period.

## Methods

The study design was purposefully structured to be similar to a large study conducted in the same practice nearly 20 years previously.<sup>8</sup> Banfield Pet Hospital is the largest primary veterinary care network in North America, with over 1,000 hospitals located in 42 states, the District of Columbia, and Puerto Rico. All hospitals share the same proprietary software (PetWare; Mars Inc), and data from all hospital visits are uploaded to a central data warehouse nightly. Electronic medical records of the Banfield patient database were searched for all dogs visiting any of their practice locations from January 1, 2016, through December 31, 2020. Canine patients were identified if administered any of 6 different vaccines (attenuated or inactivated *Bordetella*, inactivated canine influenza virus, attenuated canine distemper virus/canine adenovirus-2/canine parainfluenza virus/canine parvovirus [DA<sub>2</sub>PP], inactivated leptospirosis [serovars Canicola, Grippotyphosa, Icterohemorrhagiae, and Pomona], inactivated or recombinant Lyme [*Borrelia*], or inactivated rabies), as well as whether injectable heartworm preventative was also administered. Records in which both an injectable heartworm preventative and vaccine(s) were administered at the same office visit were not included in statistical analysis for risk factors due to potential confounding or effect modification.<sup>11</sup>

Date of birth, date of vaccination, route of administration, sex, neuter status, breed, and weight were extracted from patient records.

Possible vaccine-associated AEs were identified if, within 3 days of vaccination, a diagnosis or clinical presentation code of vaccine reaction (separate codes for mild, moderate, or severe), allergic reaction, urticaria, anaphylaxis, cardiac arrest, or death was recorded for these patients. Diagnosis or code selection was an independent decision by veterinarians, as there were no standardized definitions in the software. For statistical analyses, AEs were a binary (yes/no) outcome of interest.

Age was calculated as a continuous numerical variable from date of birth to date of vaccination, and then categorized as 2 to 9 months (0.17 to 0.75 years), > 0.75 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 7.5 years, > 7.5 to 9.5 years, > 9.5 to 11.5 years, or > 11.5 years. Weight was also converted into a categorical variable, using 5-kg categories up to 45 kg. Breed was recorded/selected from standardized names from the Banfield database and did not require editing. Rates for breeds in the database were tabulated if > 75,000 vaccination visits were recorded for that breed in the 5-year study period. In multivariable analyses, mixed breed was designated as the referent breed and 14 additional breeds were selected for comparison, due to high or low rates or breed popularity. Any records missing patient demographic information were excluded from analyses. Vaccines, recorded in medical records as any of the aforementioned 6 biologicals, were entered in analyses as administered (yes/no) and the total sum of vaccines administered. Thus, for this study, administration of DA<sub>2</sub>PP and leptospirosis vaccines in the same visit was recorded as 2 in number, even if administered together in the same syringe; components of the DA<sub>2</sub>PP vaccine were not counted separately.

## Statistical analysis

Due to predominantly low incidence rates (< 1%), rates for AEs are expressed per 10,000 vaccination visits. Crude AE rates were compared for selected variables with the  $\chi^2$  test of independence. The Cochran-Armitage test for trend was used to assess trend across ordered groups. Patient and vaccine risk factors were assessed for their association with AE occurrence by multivariable regression logit models with patient as a random effect. Multivariable models included either individual vaccines or vaccine number, but not both, due to collinearity between these variables. Variable coefficients were exponentiated to provide estimates of ORs and associated 95% CIs. A value of  $P < .05$  was considered statistically significant. Commercially available statistical software (Stata SE version 17.0; StataCorp LLC) was used for analyses.

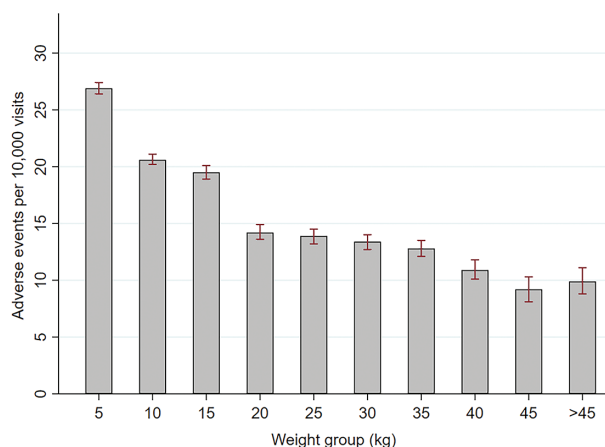
## Results

In the 5-year study period, 4,654,187 dogs received 1 or more vaccinations without concurrent injectable heartworm preventative at 16,087,455 office visits (average of 3.5 visits/dog). Most patients received 1 or 2 vaccines/visit (6,080,503 [37.8%] or

5,132,426 [31.9%] visits, respectively), with decreasing frequencies of additional vaccines. *Bordetella* vaccine alone was the most commonly administered vaccination/combination (16.6% of all visits), followed by *Bordetella* with leptospirosis (8.1%). Most *Bordetella* vaccines were administered mucosally (98.3%), and of these, most were administered intranasally (97.5%) rather than orally.

There were 31,197 AEs entered in patient records within 3 days of vaccination (0.194%, or 19.4/10,000 vaccination visits). AEs were most commonly coded as vaccine reaction mild (14,099 [45.2%]), vaccine reaction moderate (5,924 [19.0%]), allergic reaction (5,814 [18.6%]), or vaccine reaction severe (4,797 [15.4%]).

Dogs vaccinated were predominantly neutered/spayed males (40.7%) or females (39.3%). In unadjusted analysis, AE rates were lowest in intact males (17.2/10,000 visits; 95% CI, 16.9 to 17.5). Dogs of smaller body weight were more common in the study population, and dogs weighing  $\leq 5$  kg had the greatest unadjusted AE rate of any weight group (26.9/10,000 visits; 95% CI, 26.4 to 27.4). The greatest observed differences in AE rates between adjacent groups were noted between the 0- to 5-kg and > 5- to 10-kg groups, and then between the > 10- to 15-kg and > 15- to 20-kg groups (**Figure 1**). AE rates decreased as body weight increased ( $P$  for trend  $< .001$ ).



**Figure 1**—Adverse event rates per vaccination visit in 4,654,187 dogs by 5-kg weight groups presented at Banfield hospitals during a 5-year period. Category number shown is the largest value within the weight group. Error bars represent 95% CIs.

More vaccination visits occurred before 9 months of age than in other age groups, and AE rates were greater in the youngest 2 age groups compared to other groups. AE rates were 24.6/10,000 visits (95% CI, 24.2 to 25.0) and 25.6/10,000 visits (95% CI, 24.8 to 26.4) for dogs 2 to 9 months old and for dogs 9 months to 1.5 years old, respectively. The lowest AE rates were observed in the oldest age groups. Breed differences in AE rates were quite marked (**Table 1**), and 3 breeds had significantly greater AE rates than other breeds ( $P < .001$ ). French Bulldogs had the greatest AE rate (55.9/10,000 visits; 95% CI, 52.4 to 59.5), followed by Dachshunds (49.4/10,000 visits;

95% CI, 47.2 to 51.5) and Boston Terriers (44.9/10,000 visits; 95% CI, 41.5 to 48.4). Mixed-breed dogs had an AE rate of 14.0/10,000 visits (95% CI, 13.1 to 14.8). Breeds with AE rates less than mixed breed included Golden Retrievers (12.6/10,000 visits; 95% CI, 11.6 to 13.6), Labrador Retrievers (11.1/10,000 visits; 95% CI, 10.5 to 11.6), and German Shepherd Dogs (9.2/10,000 visits; 95% CI, 8.5 to 9.9).

Differences in AE rates were observed in visits involving different individual vaccines (**Table 2**). AEs occurred less frequently in any vaccinations involving *Bordetella* or canine influenza virus vaccines (16.0/10,000 visits; 95% CI, 15.7 to 16.2; and 15.1/10,000 visits; 95% CI, 13.8 to 16.4, respectively). *Bordetella* and canine influenza virus vaccines also had the lowest AE rates if administered as the sole vaccination at a visit (10.4/10,000 visits; 95% CI, 10.0 to 10.8; and 12.7/10,000 visits; 95% CI, 11.1 to 14.3, respectively). AE rates were greatest in any vaccinations involving rabies or DA<sub>2</sub>PP vaccines (24.8/10,000 visits; 95% CI, 24.4 to 25.3; and 24.6/10,000 visits; 95% CI, 24.2 to 24.9, respectively). When administered as the sole vaccine in a visit, Lyme and rabies vaccines had the highest AE rates (21.3/10,000 visits; 95% CI, 20.2 to 21.8; and 20.9/10,000 visits; 95% CI, 19.9 to 21.8, respectively).

One, 2, or 3 of the 6 vaccines were typically administered at a visit (37.8%, 31.9%, or 19.6%, respectively). All 6 vaccines were infrequently administered in the same visit ( $< 0.025\%$  of all visits) and AEs infrequently noted (5/31,197). Due to these factors and the very wide CIs related to this AE rate, AE rates for 6 vaccines together are not herein reported. AE rates increased as the number of administered vaccines increased per visit ( $P < .001$ ), and this increase was modified by body weight (**Figure 2**).

In multivariable analyses, adjusting for sex, neuter status, age, weight, breed, and number of vaccines, significant differences were noted between subgroups within each variable (**Supplementary Table S1**). Odds of an AE were greatest in spayed female dogs (OR, 1.26; 95% CI, 1.21 to 1.30) compared to intact male dogs, the referent group. Odds were greater for females than males of the same neuter status and greater for spayed/neutered dogs than sexually intact dogs of the same sex. Adjusted odds of an AE were slightly greater for dogs > 9 months to 1.5 years old (OR, 1.14; 95% CI, 1.09 to 1.19) than for dogs  $\leq 9$  months old (referent group). Odds of an AE were significantly less for dogs > 2.5 years old compared to younger dogs (OR  $\leq 0.76$ ; 95% CI, 0.33 to 0.80). Dogs weighing  $\leq 5$  kg had nearly 2 times the odds of AE occurrence (OR, 1.96; 95% CI, 1.73 to 2.28) compared to dogs weighing > 45 kg. In analysis of 15 selected breeds with mixed breed as the referent group, French Bulldogs and Dachshunds had more than 4-fold increased adjusted odds (OR, 4.14; 95% CI, 3.71 to 4.63; and OR, 4.06; 95% CI, 3.70 to 4.46, respectively). Boston Terriers had more than 3.5-fold increased adjusted odds (OR, 3.69; 95% CI, 3.26 to 4.17). With an increase in the number of vaccines administered per visit from 1 to 4 vaccines, adjusted odds of AE occurrence increased by approximately 25% with each additional vaccine.

**Table 1**—Unadjusted vaccine AE rates with 95% CI in breeds represented by > 75,000 vaccination visits/breed in a 5-year period at Banfield hospitals. Breeds are listed in descending AE rate.

Breed	Total vaccination visits (n)	AE (n)	AE rate/10,000 visits	95% CI
French Bulldog	169,308	947	55.9	(52.4–59.5)
Dachshund	410,313	2,027	49.4	(47.2–51.5)
Boston Terrier	146,436	658	44.9	(41.5–48.4)
Pug	247,330	820	33.2	(30.8–35.4)
American Bulldog	109,612	309	28.2	(25.1–31.2)
Chihuahua	1,258,976	3,545	28.2	(27.2–29.1)
Miniature Pinscher	104,438	287	27.5	(24.2–30.7)
Havanese	86,840	222	25.6	(22.2–28.8)
Boxer	356,914	866	24.3	(22.6–25.8)
English Bulldog	140,227	336	24.0	(21.3–26.5)
Pit Bull	926,674	2,188	23.6	(22.6–24.6)
Maltese	623,599	1,454	23.3	(22.1–24.5)
Miniature Schnauzer	188,717	436	23.1	(20.8–25.2)
American Staffordshire Terrier	75,992	158	20.8	(17.6–24.0)
Yorkshire Terrier	979,922	1,978	20.2	(19.2–21.1)
Schnauzer	90,331	175	19.4	(16.5–22.2)
Pomeranian	322,490	597	18.5	(17.0–20.0)
Shih Tzu	923,077	1,647	17.8	(17.0–18.7)
Jack Russell Terrier	187,651	332	17.7	(15.8–19.6)
Toy Poodle	119,658	209	17.5	(15.1–19.7)
Bichon Frise	171,026	290	17.0	(15.0–18.8)
Miniature Poodle	109,366	184	16.8	(14.3–19.2)
Beagle	323,365	537	16.6	(15.1–18.0)
Great Dane	84,155	136	16.2	(13.3–18.8)
American Cocker Spaniel	135,331	210	15.5	(13.3–17.6)
Welsh Corgi	114,214	176	15.4	(13.1–17.7)
Poodle	426,915	644	15.1	(13.8–16.2)
Cockapoo	88,594	131	14.8	(12.3–17.2)
Siberian Husky	438,524	644	14.7	(13.6–15.8)
Australian Shepherd	303,018	444	14.7	(13.3–16.0)
Mixed	767,062	1,077	14.0	(13.1–14.8)
Cavalier King Charles Spaniel	95,031	132	13.9	(11.5–16.2)
Golden Retriever	464,029	586	12.6	(11.6–13.6)
Australian Cattle Dog	147,819	165	11.2	(9.5–12.8)
Labrador Retriever	1,264,949	1,402	11.1	(10.5–11.6)
Rottweiler	144,934	137	9.5	(7.9–11.0)
German Shepherd Dog	720,061	662	9.2	(8.5–9.9)
Border Collie	152,966	132	8.6	(7.2–10.1)

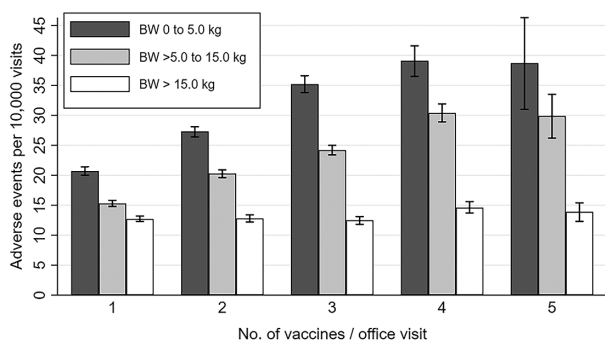
**Table 2**—Rates of recorded adverse events (AEs) following vaccination, alone or in combination with other vaccines, in 4,654,187 dogs during a 5-year period. Unadjusted ORs are for odds of AE occurrence when the specific vaccine was administered, alone or in combination, relative to odds of AE occurrence in vaccinations when specific vaccine was not administered. Adjusted ORs are as above but adjusted for patient age, weight, sex, neuter status, and breed; ORs are expressed relative to other visits not including that specific vaccine.

Vaccine	Doses administered (n)	AEs (n)	AE rate/10,000 doses (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
<i>Bordetella</i>	9,024,865	14,417	16.0 (15.7–16.2)	0.67 (0.66–0.69)	0.75 (0.73–0.77)
CIV	358,607	541	15.1 (13.8–16.4)	0.77 (0.71–0.84)	1.01 (0.92–1.12)
Lyme	3,313,504	6,315	19.1 (18.6–19.5)	0.98 (0.95–1.01)	1.21 (1.17–1.26)
Leptospirosis	8,041,367	17,243	21.4 (21.1–21.8)	1.24 (1.21–1.26)	1.26 (1.23–1.30)
DA <sub>2</sub> PP	7,183,675	17,660	24.6 (24.2–24.9)	1.62 (1.58–1.66)	1.31 (1.27–1.35)
Rabies	5,094,558	12,647	24.8 (24.4–25.3)	1.47 (1.44–1.51)	1.39 (1.35–1.43)

CIV = Canine influenza virus. DA<sub>2</sub>PP = Canine distemper virus/canine adenovirus-2/canine parainfluenza virus/canine parvovirus.

Multivariable analyses evaluating the adjusted odds of an AE when specific vaccines were administered, alone or in combination, determined greatest odds were associated with rabies vaccine administration (adjusted OR, 1.39; 95% CI, 1.35 to 1.43; Table 2). In analysis of the subset of AEs coded as mild vaccine reactions, greatest odds were associated with

leptospirosis vaccine (OR, 1.49; 95% CI, 1.44 to 1.54) or Lyme vaccine administration (OR, 1.38; 95% CI, 1.33 to 1.44). In analysis of the subset of AEs coded as moderate or severe vaccine reactions, however, greatest odds were associated with rabies vaccine (OR, 1.81; 95% CI, 1.71 to 1.92) or DA<sub>2</sub>PP vaccine administration (OR, 1.76; 95% CI, 1.65 to 1.87).



**Figure 2**—Adverse event rates by number of vaccines administered per office visit in 4,654,187 dogs of various body weights at Banfield hospitals during a 5-year period. Error bars represent 95% CIs.

## Discussion

This study investigated AEs recorded within 3 days following vaccination in > 4.5 million dogs during a 5-year period and provided risk estimates of acute AEs in specific breeds and with individual vaccines. It also found increased AE rate associated with decreased body weight, increasing number of administered vaccines, sex and neuter status, and younger age, as previously reported.<sup>8</sup> Although observed AE rates were less than previously observed overall, direct comparisons are inappropriate. The vaccines used during this study period were different than those involved previously, although ideally vaccine safety has improved across all manufacturers in the last 2 decades. Nevertheless, other confounding factors may have affected crude recorded rates.

Breed was the variable with the greatest disparity of AE rates between subgroups, with greatest rates noted for French Bulldogs and Dachshunds. French Bulldogs were not evaluated in the breed list in 2005 due to low numbers, but Dachshunds had been previously noted at high risk.<sup>8</sup> Increasing popularity of French Bulldogs has also led to recognition of increased risk in this breed for some diseases.<sup>12</sup> Breed in this study was an owner- or staff-recorded entry, not necessarily representative of pedigree. Breed represents a concentration of genes to produce a desired phenotype but may mask genes present from cross-breeding. Thus, “breed” may not be absolutely representative of pedigree. Breeding can also lead to concentration of undesired genotypes. Identification of polymorphisms in genes associated with immune responses, particularly undesired responses, will help guide decisions toward reduced risk and personalized vaccinology.<sup>4</sup> The availability of large numbers of registered dogs in selected breeds, experiencing or not experiencing AEs, can provide a critical population for these genetic investigations.

Increasing the number of vaccines administered at a single visit increased AEs with an approximate 25% increase in adjusted odds of an AE with each additional vaccine added, up to 4. Decreasing body weight also was associated with increased AE rates overall. These 2 findings support a possible

relationship between AE occurrence and quantity of vaccine antigens administered relative to body weight, although this relationship appeared minimal in dogs weighing > 15 kg. Awareness of AE risk in smaller dogs may prompt limiting the number of co-administered vaccines,<sup>13</sup> at least in selected breeds. One limitation of such a reduction could be an increase in visits needed to complete hospital vaccination protocols, potentially reducing compliance, as noted in children.<sup>14,15</sup> However, a baseline rate of AE occurrence exists for administering only 1 vaccine. This study was not able to determine a total, or cumulative, risk in patients receiving the same vaccines within abbreviated versus extended time periods. Reducing the vaccine volume administered to smaller dogs (eg, giving half of a manufacturer’s recommended dose) should not be done, as efficacy studies in disease protection have not been conducted nor has this been approved for any canine vaccine by the USDA.

Individual vaccines were assessed in this study for odds of an AE with the administration of specific vaccines, alone or in combination with other vaccines. Lowest AE rates were observed for administration of *Bordetella* vaccine, the only vaccine in the study primarily administered mucosally rather than parenterally. While vaccine safety concerns are often expressed anecdotally about leptospirosis vaccines, crude AE rates in this study were not greater for it than for DA<sub>2</sub>PP or rabies vaccines. Immune reactivity to bovine proteins, including albumin, have been associated with vaccine components.<sup>6</sup> This finding suggests detection and quantification of vaccine proteins may guide investigations into specific protein stimulants of AEs. A proteomic analysis of canine vaccines recently found that rabies vaccines had significantly more proteins than other canine vaccines.<sup>7</sup> This diversity of proteins may influence the immune response, including stimulation of protective immunity following a single vaccination. The adverse effects of these diverse proteins are less clear, whether in nonacute reactions like ischemic dermatopathies or potentially severe, acute reactions.<sup>16,17</sup> Rabies vaccines in this study were more likely to be associated with moderate to severe vaccine reactions than were leptospirosis vaccines, although specific reasons for this remain undetermined.

Female dogs in the study had greater rates of AEs than male dogs, and both sexes had increases in adjusted odds for spayed or neutered animals compared to those sexually intact of the same sex. However, this increase was magnified in females, consistent with the 2005 study from the same practice.<sup>8</sup> The influence of sex hormones, particularly estrogen, on immune responses is recognized,<sup>18,19</sup> even raising the question of whether vaccine formulation or protocols should be altered for women versus men.<sup>4,20</sup> The impact of neutering (ie, removal of primary sex organs) on increased immune responses is less recognized but likely due to loss of hormonal feedback and a subsequent increase in gonadotropins.<sup>21</sup> Age was overall inversely related to AE rates, with significant differences in reduced odds after 2.5 years old

compared to dogs < 9 months old. However, dogs approximately 1 year of age were at increased odds compared to those < 9 months, which may indicate an increased risk with booster vaccinations after the initial vaccination or series. A similar phenomenon was found in the previous Banfield study, although interpretation of the findings between age groups remains difficult due to potential induced bias. While IgE concentrations postvaccination can decline with advancing age,<sup>22</sup> it is unknown whether owners of dogs experiencing vaccination reactions subsequently seek veterinary services at other locations, thereby reducing the at-risk population number.

The study population of > 4 million dogs, with > 15 million visits for vaccinations, yielded a power such that statistical significance could be found on differences too small to be clinically important or discernible. Even large relative differences (eg, in ORs) may be for very small raw numbers. Proper interpretation should therefore consider both absolute and relative values/estimates. Even these values may be distorted due to issues in data quality.<sup>23</sup> Quality in postmarketing vaccine surveillance is dependent upon recognition of an AE by a client (who must then seek veterinary care) and a veterinarian (who must make an accurate and consistent diagnosis). Thus, either underreporting or overreporting of AEs may have occurred. Furthermore, coded outcomes in electronic databases can be somewhat qualitative or nonspecific, necessitating interpretation by individuals. In the current study, there was no universal definition of a mild AE compared to a moderate or severe event. This distinction is left up to the clinician, and thus subjective differences in definitions may lead to differences in data entry. This study collected data retrospectively from a very large cohort, with limitations including inability to validate entries by different veterinarians, as well as differences in how various breeds may be reported and recorded. In the current study, breeds were primarily owner reported and may or may not align with actual genotype.

This study did not include data or analysis on individual vaccine manufacturer. Suppliers of vaccines may have changed over time, due to changes in inventory, recalls, supply chain, or other considerations. This variability was a limitation of the study, precluding the use of any data that could be used to compare vaccine offerings between individual suppliers. It is therefore unknown whether the observed risk factors would have the same magnitude or importance across the same type of vaccine from different manufacturers (eg, inactivated canine rabies vaccines) or between different vaccine types (eg, attenuated vs recombinant canine distemper vaccines). Similarly, there were not enough parenterally administered *Bordetella* vaccines in the study for a meaningful comparison with *Bordetella* vaccines administered mucosally.

The observational study design, a retrospective cohort, was itself a limitation in that there were not predesignated comparison groups. Thus, we could truly assess cumulative risk of an AE in breed-/age-/sex-matched pairs receiving in total the same vaccines in an extended number of visits versus in a reduced

number of visits. Likewise, without lifetime histories, we were not able to determine prior immune stimulation to truly define an “initial” vaccine. Nevertheless, the findings and limitations may help guide the design of both future databases and safety studies.

Postmarketing surveillance of vaccine safety remains critical to identifying potential predisposing or precipitating risk factors of AEs. This is particularly true as vaccine safety improves and, ideally, the incidence of AEs becomes less common. Prudent application of this information to client communication, vaccination protocols, and future research will ideally benefit patients and improve compliance.

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## Supplementary Materials

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