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A space–time cluster of adverse events associated with canine rabies vaccine

George E. Moore^{a,*}, Michael P. Ward^b, Martin Kulldorff^c,
Richard J. Caldanaro^a, Lynn F. Guptill^d, Hugh B. Lewis^e, Lawrence T. Glickman^a

^a Department of Veterinary Pathobiology, School of Veterinary Medicine, Purdue University, 725 Harrison Street, West Lafayette, IN 47907-2027, USA

^b Department of Veterinary Integrative Biosciences, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX 77843-4458, USA

^c Department of Ambulatory Care and Prevention, Harvard Medical School, 113 Brookline Avenue, Boston, MA 02215, USA

^d Department of Veterinary Clinical Sciences, School of Veterinary Medicine, Purdue University, 625 Harrison Street, West Lafayette, IN 47907-2026, USA

^e Banfield, The Pet Hospital, 11815 NE Glenn Widing Drive, Portland, OR 97220, USA

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Abstract

Electronic medical records of a large veterinary practice were used for surveillance of potential space–time clustering of adverse events associated with rabies vaccination in dogs. The study population was 257,564 dogs vaccinated in 169 hospitals in 13 US metropolitan areas during a 24-month period. Using a scan statistic for population rate data, significant space–time clusters were identified involving the Atlanta and Tampa/St. Petersburg areas during a 4-month period. Separate spatial–temporal analyses of these cities using coordinates for individual address coordinates identified one significant patient cluster ($P = 0.002$), associated with a 23.26 km-radius area in Atlanta (20 adverse events in 702 dogs; 2.85%) from November 2002 through February 2003. This percentage of adverse events was significantly increased after adjustment for host-related factors and the number of concurrent vaccinations.

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1. Introduction

Traditional post-marketing surveillance of veterinary vaccines relies on veterinarians or owners to voluntarily report suspected reactions to manufacturers or to the US Department of Agriculture (USDA), the federal regulatory agency for animal vaccines. This type of surveillance provides case (numerator) information only, and it is often characterized by underreporting and variability in report quality [1,2]. Trends in reports of vaccine-associated events (VAE) may be related to the immunogenicity of the vaccine, improper administration of a vaccine, a veterinarian's or owner's perception of an association between the event and vaccination, and/or the

inclination of the veterinarian or owner to initiate a report. Severe or life-threatening VAEs are more likely to be reported voluntarily and may also be more likely to be investigated.

Clustering of adverse events or disease can serve as an indicator of a potential association between an adverse event and vaccine administration [3,4]. Clustering of health events should be considered in the dimensions of both time and space, and clustering can occur in time-and-space without being apparent in either dimension alone. Clusters of VAEs in time may occur with the administration of a newly marketed vaccine or a new batch/lot of routinely used vaccines. Clusters of VAEs in space may occur if the geographic distribution of a new vaccine or lot is not homogenous among veterinary hospitals. Such clustering may also appear with changes in vaccination techniques by hospital personnel or with changes in adverse event reporting policies.

* Corresponding author. Tel.: +1 765 496 3393; fax: +1 765 494 9830.
E-mail address: gemoore@purdue.edu (G.E. Moore).

The “best” situation in which to investigate whether or not a suspected adverse reaction is linked to vaccination has been described as one where there is a clearly defined population with a record of all vaccinations, all instances of the disease event of interest (potential adverse effect), and the possibility of linking these back to individuals [5,6]. Practice consolidations and improved medical informatics have increased the likelihood and availability of such resources in human and veterinary medicine. A large privately-owned veterinary practice, Banfield, the Pet Hospital[®], currently provides primary health care to more than two million dogs and cats each year in more than 400 locations in 42 states, treating approximately 15,000 patients daily. Banfield uses a single fully computerized (paperless) veterinary medical record system at all locations. This proprietary system has standardized codes for >500 different clinical signs, >200 laboratory tests, >1000 diagnoses, and >2000 procedures or treatments. Electronic records from all hospitals are uploaded weekly to a central data facility for quality assurance audits and data warehousing.

The Banfield practice database has been recently used to identify patient characteristics associated with increased risk for adverse events within 3-day post-vaccination in pet dogs [7]. These events were consistent with immediate-type hypersensitivity reactions, and increased risk was associated with body weight less than 10 kg, age approximately one to 3 years of age, and being surgically neutered. Dogs receiving multiple vaccines at one encounter were also at increased risk of VAEs. Because rabies vaccination of dogs is commonly required by local or state authorities, rabies vaccine is often administered alone or concurrently with other vaccines to pet dogs. Patient risk factors and/or practice vaccination protocols may therefore influence the occurrence and potential clustering of reported VAEs. The purpose of this study was to determine if practitioner-diagnosed adverse events occurring within 3 days of canine rabies vaccine administration are clustered in space and time.

2. Materials and methods

2.1. Population

The electronic medical records of Banfield, the Pet Hospital[®], were searched to identify all dogs that received rabies vaccine alone or in combination with bordetella vaccine, coronavirus vaccine, multivalent distemper-adenovirus-parainfluenza-parvovirus-leptospirosis vaccine, giardia vaccine, or borrelia vaccine between 1 January 2002 and 31 December 2003. All vaccines were produced by one manufacturer (Fort Dodge Animal Health, Fort Dodge, IA), except for bordetella vaccine (Biocor Animal Health Inc., Omaha, NE). Records were excluded if the dogs concurrently received vaccine(s) and an injectable heartworm preventive since the latter product may also induce a hypersensitivity reaction. Information extracted from

each patient record included home address, date of birth, breed, sex, neuter status, weight, vaccine received, date of vaccination, and hospital location. VAE were defined as any coded diagnosis of “vaccine reaction”, “allergic reaction”, “urticaria”, “anaphylaxis”, “cardiac arrest”, “cardiovascular shock”, or “sudden death”, if the diagnosis occurred within 3 days of vaccination. Diagnosis validation was performed through a record review for clinical signs and treatments [7].

2.2. Study design and statistical analyses

For this study, Banfield hospitals were grouped into units of 8 or more hospitals located within a 50 miles radius; units were designated as metropolitan-hospital-groups (MHG). Dogs were included in the study only if they were vaccinated at one of these hospitals. Patient addresses (street, city, state, and zip code) were geocoded to determine longitude and latitude coordinates using an address reference dataset and geocoding software (Streetmap USA and ArcGIS v.9, ESRI, Redlands, CA). Addresses that could not be geocoded were assigned the longitude and latitude coordinates of the centroid of their zipcode.

Cases were defined as dogs that experienced a VAE within 3 days following rabies vaccination, and non-cases were vaccinated dogs not diagnosed with a VAE. Data sets of the MHG populations were evaluated separately for spatial, temporal, and spatial–temporal clusters of accumulated VAE. Clusters, a geographically bounded group of events of sufficient size and concentration to be unlikely to have occurred by chance [8], were identified using the space–time scan statistic. This statistic, defined by a cylindrical window composed of a circular geographic base and height corresponding to time [9], imposes overlapping circles of different location and size on the map, each of which is a potential cluster. The scan statistic calculates the expected number of cases within the scanning window based on either a Poisson (rate data) or Bernoulli (case-control data) distribution. For analyses of the large MHG populations, the distribution of VAEs was assumed to be Poisson. Scanning for clusters included spatial and temporal dimensions ranging from 0 up to 25% of the study area and/or study period. The selected time precision for temporal and space–time analyses was 1 month, e.g. calculated VAE rates per month. Data sets were scanned for clusters with only increased rates of VAE occurrence (equivalent to a one-sided statistical test) in time, space, and space-and-time. A likelihood-ratio test statistic was calculated, based on the maximum likelihood function, for each cluster of adverse events identified. Its distribution and corresponding *P*-value were obtained by Monte-Carlo simulation—randomly generating 999 replications of the data set under the null hypothesis of spatial and temporal randomness. The rank of the maximum likelihood from the real data set was compared with the maximum likelihoods from the random data sets. If this rank is *R*, then $P = R/(1 + 999 \text{ simulations})$. The *P*-value was an indicator of the evidence for a real cluster in the 1000 test statistics calculated. In addition to the most likely cluster, any

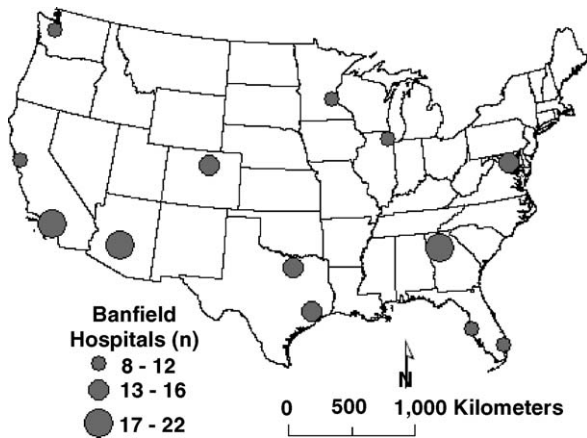


Fig. 1. U.S. cities with ≥ 8 Banfield, The Pet Hospital[®], locations in <50-mile radius during 2002–2003.

other identified cluster was reported if the associated P -value was statistically significant and if it did not overlap with the most likely cluster.

Analyses were adjusted for patient sex (male, female), neuter (intact, neutered) status, age, weight, and number of vaccines received concurrently. Age categories were 2–9 months, >9 months–1.5 years, >1.5–2.5, >2.5–3.5, >3.5–5.5, >5.5–8.5, and >8.5 years. Weight categories were 0–10, >10–20, >20–30, >30–40, and >40 kg.

If MHGs were within a cluster identified by the crude and adjusted Poisson model analyses, the MHG study population was analyzed by a Bernoulli model using the point locations of the geocoded patient addresses of cases and non-cases. Analyses were performed with and without those addresses assigned to zipcode centroids to assess for possible bias introduced by this method. This was useful to compare the sensitivity of the Poisson model assumption for aggregated data to that of the Bernoulli method. If space–time clusters were identified in the Bernoulli model, cases in the cluster were compared to cases located outside the identified cluster in the same city for differences in patient factors (sex, neuter status, age, and weight) and number of concurrent vaccinations. Comparisons of categorical variables were made by chi-square and Fisher's exact test. All space–time analyses were performed using SaTScan software version 5.0 (www.satscan.org); other statistical calculations were performed with STATA statistical software. A type I error of 0.05 was used.

3. Results

3.1. Overall population

Thirteen metropolitan areas were identified with 8 or more hospitals and were designated MHG; a total of 169 Banfield hospitals were located in these groups (Fig. 1). During the 24-month study period, rabies vaccination (alone

or with other concurrent vaccinations) was given to 257,564 dogs; there were 1146 VAEs diagnosed (0.445%; 95% CI: 0.420–0.471%).

3.2. Population-rate-based analyses

In the unadjusted Poisson model for all MHG, the most likely temporal cluster for VAE involved the 6-month period of September 2002 through February 2003, but the identified cluster was not statistically significant. During this time period, there were 289 observed cases and the calculated expected number of cases was 245.9 (ratio = 1.28; $P = 0.075$). In a purely spatial analysis, a single statistically significant cluster that included both Atlanta and Tampa/St. Petersburg was identified, with 219 observed cases and 171.5 expected (ratio = 1.18; $P = 0.003$). In time-and-space, a significant cluster of VAE was also identified; the spatial window was not altered but the cylindrical window was reduced compared to temporal analyses alone (Table 1). The most likely space–time cluster of VAE involved both Atlanta and Tampa/St. Petersburg for a 4-month period of November 2002 through February 2003. The observed/expected case ratio for the space–time cluster was 2.09 ($P = 0.001$).

Analyses of MHG populations with adjustments for patient covariates did not alter the space–time dimensions of the most likely cluster, although the adjustment for the number of concurrently administered vaccines caused the greatest reduction (3.3%) in the ratio of observed-to-expected cases (Table 2).

3.3. Individual-based analyses

Analyses of geocoded address locations for cases and non-cases using a Bernoulli model to further define space–time clustering in Atlanta and Tampa/St. Petersburg was performed separately for each MHG. Significant space–time clustering of VAE was not detected in Tampa/St. Petersburg using the Bernoulli model, but a significant ($P = 0.002$) cluster of VAE was identified in Atlanta (Table 3). This space–time cluster involved 20 VAE in 702 dogs vaccinated in a 4-month time period (VAE percentage = 2.85%; 95% CI: 1.75–4.37%) (Figs. 2 and 3). In comparison, the Atlanta case and study populations for the 20 months outside this time period were 104 and 22,103, respectively (VAE percentage = 0.47%; 95% CI: 0.38–0.57%). In analyses excluding dogs with addresses that could not be geocoded, a significant space–time cluster was not identified in Tampa/St. Petersburg ($P = 0.282$), whereas a significant cluster identified in Atlanta covered the same 4-month period and similar area as detected in the full analysis ($P = 0.018$).

In Atlanta, patients within the identified VAE cluster compared to patients outside the cluster were not significantly different in sex ($P = 0.434$), neuter status ($P = 0.187$), age ($P = 0.250$), or weight ($P = 0.874$); nor were they significantly more likely to be geocoded to a zipcode centroid ($P = 0.185$). Patients within the cluster, however, were significantly more

Table 1

Unadjusted Poisson analyses for space–time clustering of canine rabies vaccine-associated adverse events among 13 Banfield metropolitan hospital groups, January 2002 to December 2003, using different space–time scanning windows

Space–time window (%)	Most likely cluster ^a	Radius (km)	Time year/month (no. of month)	Observed/expected ratio	LLR ^b	P-value
50–50	DFW, HOU, ATL, TAM	1281.27	2002/12–2003/02 (3)	77/39.7 = 1.94	14.32	0.001
25–25	ATL, TAM	745.61	2002/11–2003/02 (4)	53/25.4 = 2.09	11.76	0.001
25–10	ATL, TAM	745.61	2002/12–2003/01 (2)	30/12.6 = 2.39	8.80	0.012

^a DFW: Dallas-Ft. Worth, TX; HOU: Houston, TX; ATL: Atlanta, GA; TAM: Tampa-St. Petersburg, FL.

^b LLR: log likelihood ratio statistic.

Table 2

Poisson analyses, using a scan window of $\leq 25\%$ of the geographic area and $\leq 25\%$ of the study period, for space–time clustering of canine rabies vaccine-associated adverse events among 13 Banfield metropolitan hospital groups, January 2002 to December 2003, unadjusted and adjusted for patient covariates

Covariates adjusted for in model	Most likely cluster ^a	Radius (km)	Time year/month (number of month)	Observed/expected ratio	LLR ^b	P-value
(None)	ATL, TAM	745.61	2002/11–2003/02 (4)	53/25.4 = 2.09	11.76	0.001
Age	ATL, TAM	745.61	2002/11–2003/02 (4)	53/25.9 = 2.04	11.14	0.002
Sex	ATL, TAM	745.61	2002/11–2003/02 (4)	53/25.3 = 2.09	11.82	0.002
Neuter status	ATL, TAM	745.61	2002/11–2003/02 (4)	53/25.3 = 2.10	11.89	0.002
Weight	ATL, TAM	745.61	2002/11–2003/02 (4)	53/25.8 = 2.05	11.26	0.001
Number of vaccines	ATL, TAM	745.61	2002/11–2003/02 (4)	53/26.2 = 2.02	10.84	0.007

^a ATL: Atlanta, GA; TAM: Tampa-St. Petersburg, FL.

^b LLR: log likelihood ratio statistic.

likely to have received 6 vaccinations concurrently, compared to patients outside the cluster (231/702 [32.9%] versus 5445/22,103 [24.6%], respectively; $P < 0.001$). After adjustment for the number of concurrent vaccinations per patient visit, the VAE percentages within the cluster in the Bernoulli model were still significantly increased ($P < 0.001$).

Of the 21 Banfield hospitals in the Atlanta MHG, 7 contributed patients to the identified cluster. Two hospitals contributed 60.0% (12/20) of the cases and 38.9% (265/682)

of the non-case population in the cluster, but this difference was not statistically significant ($P = 0.057$). Supportive evidence for the contribution of cases by these hospitals was indicated when space–time cluster analysis, using a Poisson model with hospital-based populations and VAE rate data adjusted for number of concurrent vaccinations, identified a significant ($P = 0.001$) cluster of VAE involving the same 2 hospitals during a 6-month period of September 2002 through February 2003.

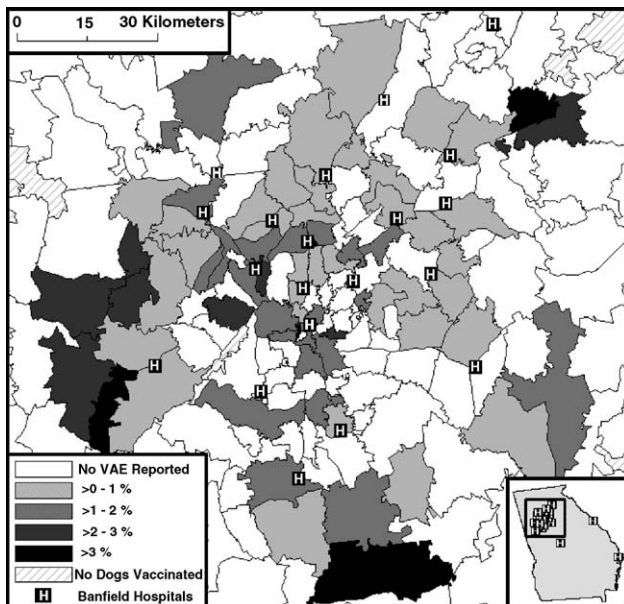


Fig. 2. Zip-code-based rates for canine rabies vaccine-associated adverse events (VAE) during a 24-month period for Atlanta, GA. Inset is state map of Georgia.

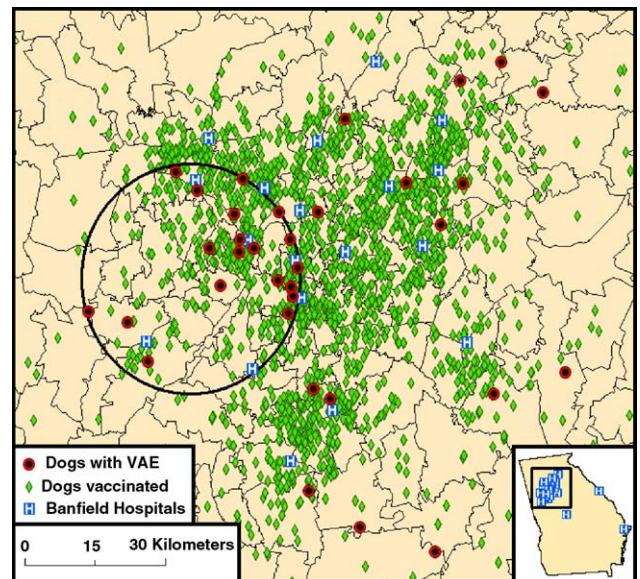


Fig. 3. Most likely cluster location in space (circle) and time (November 2002 to February 2003) in Atlanta, GA, of canine rabies vaccine-associated adverse events (VAE). Inset is state map of Georgia.

Table 3

Results of unadjusted Bernoulli analyses for space–time clustering within Atlanta (ATL) and Tampa/St. Petersburg (TAM) of adverse events associated with canine rabies vaccination during a 24-month period (2002/01–2003/12)

City	Coordinates for most likely cluster ^a	Radius (km) for most likely cluster	Time year/month (number of month) for most likely cluster	Observed/expected ratio	LLR ^b	P-value
ATL	33.833355 N 84.618385 W	23.26	2002/11–2003/02 (4)	20/3.82 = 5.24	18.28	0.002
TAM	27.509394 N 82.718132 W	28.39	2003/09–12 (4)	12/1.93 = 6.23	12.64	0.129

Case and non-case data coordinates were based on geocoded addresses for individual dogs. Scan window was $\leq 25\%$ of the geographic area and $\leq 25\%$ of the study period.

^a There were no other statistically significant clusters identified.

^b LLR: log likelihood ratio statistic.

4. Discussion

This study demonstrated the utility of an electronic medical record database for surveillance of space–time clustering of canine rabies vaccine-associated adverse events. The practice database provided information of post-vaccination events in the exposed population, allowing analysis of group and individual-based data for the study of VAE.

Investigations of increased rates of VAEs in space or time should consider the crude event rate and rate changes after adjustments for important covariates [10]. Separate cluster analyses in this study showed that the greatest change in the ratio of observed-to-expected cases occurred after adjustment for the number of vaccines administered per visit. This covariate did not fully explain the VAE increase in the detected cluster, indicating further investigations are warranted to determine other potential risk factors associated with cluster events.

The veterinary practice database used in this study did not have an entry field for vaccine serial or lot number, an important covariate in VAE inquiries. The national distribution pattern and period of use for different lots of vaccines in the veterinary practice was also unknown. In a recent study of human vaccines, using a convenience sample, 90% of the vaccine doses in each lot were estimated to be used within 5–9 months of distribution [11]. Although a 6-month maximum scan window was used (25% of total study period), the most likely cluster involved only a 4-month period and this time period may have encompassed the use period for a specific lot of vaccine.

The temporal window and primary involvement of two hospitals in the most likely cluster may also indicate changes in vaccination technique or in the personnel preparing or administering the vaccines. Factors related to vaccine administration or aftercare have been demonstrated to impact the risk of VAEs [4]. Hospital protocols for standardization and quality assurance are established in many practices, and Banfield personnel administering vaccinations are instructed on appropriate vaccination techniques.

The scan statistic was selected as a detection tool for clusters because it adjusts for heterogeneous population densities and confounding variables, searches for clusters without pre-

selected bias of their size or location, takes multiple testing into account, and specifies the location of a cluster if the null hypothesis is rejected [9]. Conceptually, the space–time scan statistic provides a cluster detection test that both identifies and evaluates the statistical significance of specific clusters [10]. The test however has low power for clusters with non-circular patterns, such as extending along a long and narrow river or highway.

Analyses in this study used assumptions for two different discrete probability distributions, Bernoulli (binomial) and Poisson. With spatial–temporal information available for each patient (cases and non-cases), the Bernoulli distribution could have been applied in all analyses; however, the Poisson model provided the capability of adjusting for covariates and is much less computationally intensive for larger datasets. In analyses for rare or uncommon events, the Poisson model is a very good approximation to the Bernoulli model and produces slightly conservative *P*-values [9,12].

Spatial analysis with geocoding for point data was facilitated in this study by the use of patient addresses. Aggregated data, e.g. individual hospital populations, identified a most likely spatial–temporal cluster in Atlanta that was similar to the analysis with individual patient addresses. Methods are being developed in geographic information systems for geomasking of patient addresses to protect human subject confidentiality [13]. These techniques can include movement of each address point in a limited but randomized direction and distance before analyses and mapping.

Although diagnoses were selected by practitioners from the available codes in the software, computerized databases are dependent on coded outcomes and some codes may be nonspecific. Standardized case definitions for VAEs are not available in veterinary medicine and are only currently being addressed in human medicine [14]. Due of the large number of hospital locations contributing data, the impact of reporting biases or misdiagnoses that might be potentially introduced by a few individuals is reduced. Nevertheless, validation of automated codes for health outcomes has been advocated [5]. The clinical signs recorded in patient medical notes supported the coded diagnoses when reviewed in a random sample of this study population.

Analyses to detect potential clusters of health events can be considered hypothesis-generating [10]. Cluster detection indicates a concentration of events that are unlikely to have occurred by random chance, but other possible causes must be evaluated through additional investigations. Further epidemiological studies using more intensive methods or more detailed inquiries into patient records may be requested by regulatory agencies, vaccine manufacturers, or hospital administrators. An advantage of the population composing this practice database is its open-cohort structure, contributing cases and controls from the same population for a 'nested' study, e.g. the Bernoulli analysis. Further investigations into potential clustering of VAEs based on diagnostic codes should also address standardization of coding by health care providers.

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