Spatiotemporal analysis of rabies in cattle in central Mexico

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Abstract

Spatial epidemiology of bat-transmitted rabies in cattle has been limited to spatial distribution of cases, an approach that does not identify hidden patterns and the spread resulting in outbreaks in endemic and susceptible areas. Therefore, the purpose of this study was to determine the relationship between the three variables average annual maximum, annual minimum temperature and precipitation in the region on the one hand, and the spatial distribution of cases on the other, using geographic information systems and co-Kriging considering that these environmental variables condition the existence of the rabies vector *Desmodus rotundus*. A stationary behaviour between the primary and the secondary variables was verified by basic statistics and moving window statistics. The directions of greater and lesser spatial continuity were determined by experimental cross-semivariograms. It was found that the highest risk for bovine paralytic rabies occurs in areas known as *La Huasteca Potosina* and *La Sierra Gorda* that are characterized by a maximum temperature of 29.5 °C, a minimum temperature of 16.5 °C and precipitation of 1200 mm. A risk estimation map was obtained for the presence of rabies with a determination coefficient greater than 95%, and a correlation coefficient greater than 0.95. Our conclusion is that ordinary co-Kriging provides a better estimation of risk and spatial distribution of rabies than simple Kriging, making this the method recommended for risk estimation and regional distribution of rabies.

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Key words: Rabies; *Desmodus rotundus*; Epidemiology; Cattle; Mexico.

Conflict of interest: the authors declare no potential conflict of interest.

Funding: Researh Support Funding – UAQ, project number FNV201408, and Natural Sciences Faculty.

Received for publication: 25 July 2019.
Revision received: 27 September 2019.
Accepted for publication: 5 October 2019.

Geospatial Health 2019; 14:805
doi:10.4081/gh.2019.805

Introduction

Rabies is a lethal zoonotic disease caused by a neurotropic virus of the genus *Lyssavirus*, which affects all types of warm-blooded animal species around the world. In humans, rabies is responsible for about 60,000 deaths worldwide each year (WHO, 2013; Hampson *et al*., 2015). In cattle and other animal species, it is estimated that the number of cases per year is more than 50,000 (Loza-Rubio *et al*., 2012; PAHO, 2013; Vigilato *et al*., 2013). Currently, in Latin America and the Caribbean, the risk for rabies in humans and cattle is due to the bite of the blood-sucking bat *Desmodus rotundus*. In Mexico, between 2007 and 2015 the number of cases reported was 1,872, in different livestock species in 25 endemic states; the cattle industry loses more than United States dollars 2.6 million a year because of rabies. The number of human cases transmitted by wildlife for the years 2000 to 2006 was 23, 14 of which related to vampire bites (Zarza *et al*., 2017).

The progressive alteration of the bat´s habitat has favoured the spread of rabies over the years, and cases have appeared in areas previously free of the disease. Different studies have reported that *D. rotundus* has increased its range of distribution to areas higher than 1,500 meters above the mean sea level, and that climatic variables such as temperature and precipitation influence the movement of bats within the same geographic area. This phenomenon allows the bats to maintain an exchange of shelters near the food source, which favours infection between bats and transmission of rabies to livestock (Gomes *et al*., 2010; Aguirre *et al*., 2012; de Andrade *et al*., 2016; de Thoisy *et al*., 2016). Due to continuous human invasion of areas occupied by vampire bats, the number of cases in livestock and people is increasing. There is solid evidence that the vampire bat population's distribution has expanded because of climate change, with higher temperatures increasing the risk of disease spread to new regions (Johnson *et al*., 2014).

Geographical Information Systems, remote sensing, spatial statistics and spatially explicit mathematical models are tools useful for the study, prevention and control of rabies (Clements and Pfeiffer, 2009; Mengistu and Haile, 2017). Geostatistics can estimate and predict the distribution of rabies in cattle successfully, even in spatial surveillance data with respect to the potential occurrence in non-sampled environments (Escobar, 2016; Bonwitt *et al.*, 2018), especially when sampling is biased due to attributes of place (Guo *et al.*, 2013; de Andrade *et al.*, 2016). Using these methods in the Amazonian region of Brazil, high-risk areas for rabies in humans and cattle were identified in extensive deforested areas with large herds of cattle and roads (de Andrade *et al.*, 2016). Recently, in Colombia, high-risk areas were determined in various types of ecosystems suggesting that an infectious disease can remain over time even if the ecological variables are not perfectly suited (Cárdenas-Contreras, 2017). Spatial studies have also been useful for supporting practices of rabies control, especially for vaccination of cattle against new outbreaks or modelling various scenarios, including different levels of climate variables, time and the geographical ranges of humans, foxes, bats and dogs (WHO, 2013).

While the number and quality of epidemiological spatial applications of rabies are increasing, the full potential of these methods has not yet been achieved (Rodenbusch *et al.*, 2016). The main critical control point observed in spatial distribution of rabies in cattle is that municipalities that send high numbers of biological material for analysis to the laboratory are those that also present the highest number of cases (Hayes and Piaggio, 2018), *i.e.* the number of cases is not representative of the population of cases in a region.

The proximity to areas with high incidence of rabies with climatic variables that favour the presence of bats is of special interest for an understanding of the presence and spread of the disease in new geographic regions. It has been reported that precipitation and temperature are factors that determine the distribution of the vector and, therefore, the distribution of the disease (Bárcenas-Reyes *et al.*, 2015). Therefore, the objective of this study was to predict the spatial risk and the space distribution of cases of rabies in livestock explained by the climatic variables, such as maximum and minimum average annual temperature and average annual precipitation (AP), in central Mexico with the use of multivariate geostatistical methods.

Materials and Methods

Information of cases was collected between 2001 and 2014 in the States Guanajuato, Queretaro and San Luis Potosi in central Mexico. Presence of the viral N protein in the direct immunofluorescence laboratory test of brain tissue was used as case definition. Coordinates for about 70% of the cases were available, while coordinates for the remaining cases were obtained either from the Mexico's National Institute of Statistics, Geography and Informatics (INEGI)'s database or applying Google Earth for those not recorded in the INEGI's data base using the closest locality as the point of reference. In addition to coordinates, species, month and year of case presentation were also available.

Rapid Extractor of Climatological Information III (ERIC III) (IMTA, 2006) was used to generate a database of the environmental variables maximum annual average temperature (T_{max}), minimum annual average temperature (T_{min}) and the AP for the three states. A bivariate correlation between the number of cases and the climatic variables by municipality was performed with the statistical package SPSS 22.0, released in 2013 (SPSS IBM Corp., Armonk, NY). Statistical significance was set at the P=0.05 level. The following steps were performed for each variable: i) exploratory analysis to obtain a model that better represents the characteristics of variability and the spatial correlation of the phenomenon under study; ii) spatial tendency using series of locations in the simulated study area; and iii) estimation of the variables with validation of the models (Barrios-Gómez *et al.*, 2019).

Assuming spatial continuity, co-Kriging was applied on observed cases of rabies in cattle to obtain values for each location. The number of cases was aggregated by municipality, for a smoothing process and to reduce the random error. To establish the spatial relationship between the values of T_{max}, T_{min} and AP values throughout the estimation domain with the number of cases, we used ordinary Kriging from the geostatistical analyst extension of ArcMap v. 10 (ESRI, Redlands, CA, USA). Kriging and co-Kriging are linear-weighted interpolation methods, whose weights not only depend on distance, but also on the direction and orientation of the neighbouring data to unsampled locations. Co-Kriging is an extension of ordinary Kriging in which observed covariates are used to improve the precision of the interpolation of the variable of interest.

Table 1. The analytics expression of cross-variograms obtained to use in co-Kriging methods.

Semivariogram	Variable combination	Nugget	Sill	Model	Major range	Minor range
γ_{11}	NC_NC	244.82	396.3	Spherical	0.91	0.90
γ_{12}	NC_T_{max}	0.0	4.30	Spherical	0.91	0.90
γ_{13}	NC_T_{min}	0.0	2.67	Spherical	0.91	0.90
γ_{14}	NC_AP	0.0	8544.2	Spherical	0.91	0.90
γ_{22}	T_{max}_T_{max}	0.0	0.82	Spherical	0.91	0.90
γ_{23}	T_{max}_T_{min}	0.0	0.10	Spherical	0.91	0.90
γ_{24}	T_{max}_AP	0.0	6.77	Spherical	0.91	0.90
γ_{33}	T_{min}_T_{min}	0.05	0.94	Spherical	0.91	0.90
γ_{34}	T_{min}_AP	0.0	20.44	Spherical	0.91	0.90
γ_{44}	AP_T_{min}	0.0	221400.0	Spherical	0.91	0.90

A summary of the models made with co-Kriging and the defining parameters. The linear model of coregionalization was verified with the nugget and the sill values (Caro-Benito, 2012; Wackernagel, 1998). NC, number of cases; T_{max}, maximum annual average temperature; Tmin, minimum annual average temperature; AP, average precipitation.

First, the relationship between the climatic variables with the number of cases was analysed considering that those variables condition the existence of cases. The idea was to estimate the number of cases as the primary variable and use climatic variables as the secondary or auxiliary variables. To adjust the parameters, variance and covariance, a linear coregionalization model was used (Caro-Benito, 2012). This model establishes that the individual semivariograms and the crusader are linear combinations of semivariogram models. This approach allows the explanation of a variable based on other auxiliary variables spatially correlated using a cross-semivariogram (Table 1).

The analytic expression of the cross-semivariogram used was (Eq. 1):

$$\gamma(h) = EP + S_I ll_1\ Mod_1\ (\alpha_{x1}\ \alpha_{y2}) + S_I ll_2\ Mod_2\ (\alpha_{x1}\ \alpha_{y2}) + S_I II_3\ Mod_3\ (\alpha_{x1}\ \alpha_{y2}) + S_I II_4\ Mod_4\ (\alpha_{x1}\ \alpha_{y2}) \qquad \text{Eq. 1}$$

where h is the distance that separates a number of data pairs, EP the expression of the sum of the basic spherical models for the four variables, Sill Mod the area of the curve where the values no longer correlate to each model and α the range of scope of the variance, *i.e.* the distance from which the samples begin to be independent of each other.

The relationship between the number of cases with the three climatic variables and combinations of those with cases was calculated to evaluate the effectivity of the methods. Direct and cross validation, which shows the continuity data behaviour of the direction 45°, was also performed. The analytic expression of the spatial variability was (Eq. 2):

$$(G/h) = Co + C_1 + Mod_1\ (\alpha_{x1}\ \alpha_{y1}) + C_2 + Mod_2\ (\alpha_{x2}\ \alpha_{y2}) + C_3 + Mod_3\ (\alpha_{x3}\ \alpha_{y3}) \qquad \text{Eq. 2}$$

where G/h is the number of data pairs that are at a distance, α the range of scope of the variance, Co the nugget effect and C_1, C_2, C_3 the structural components of the variance corresponding to the variability explained by the model (Mod). The linear model of coregionalization was verified with the nugget value, which measures the nugget effect, and the sill value, which measures the plateau, both values unique for each model (Wackernagel, 1998).

Results

Table 2 shows the number of cases per year, the number of municipalities affected, the annual average maximum, the minimum temperature and the average AP for the years 2001 to 2013. It can be observed that the number of municipalities affected increases with the maximum temperature varied between 29.0 °C and 29.5 °C, the minimum temperature between 16.0 °C and 16.5 °C, and the precipitation between 1,190 and 1,200 mm (Tables 3 and 4).

Figure 1 shows the risk estimation map for the presence of cases based on the three climatic variables and the number of cases. It can be observed that the region known as *La Huasteca Potosina*, is the region with the highest number of cases and the area with the highest risk for more cases. Figure 2 shows the estimated risk obtained with co-Kriging for the presence of cases based on the three climatic variables and the number of cases reported. It can be observed that the region with the highest risk for the presence of cases in cattle is *La Huasteca Potosina*, in the

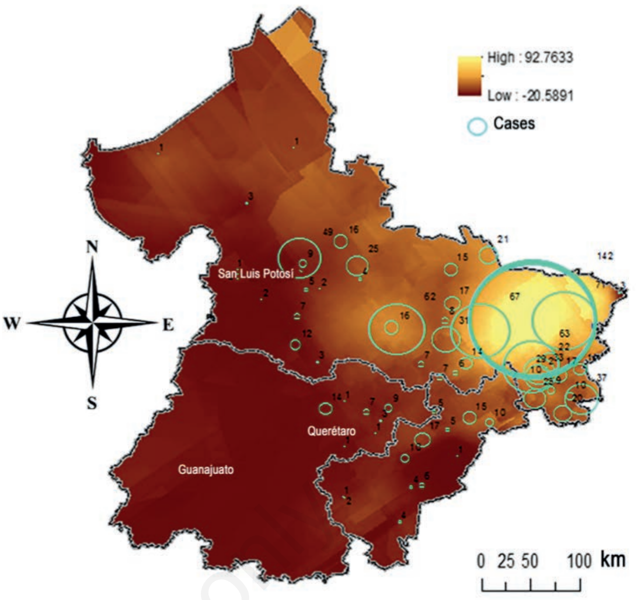

Figure 1. Spatial distribution of risk for the presence of cases of rabies in the study area. Light colour shades indicate a higher number of cases. The radii of the green circles represent the number of cases reported in the different municipalities (larger circles - more cases). Numbers in black are the real number of cases by municipality for the study period. The figure is based on T_{max}, T_{min} and annual precipitation by co-Kriging. Higher quadratic mean error means higher risk for cases. Green circles indicate number of cases by municipality.

Figure 2. Risk distribution of cases of rabies in the study area. The figure is based on T_{max}, T_{min} and annual precipitation by co-Kriging.

Northeast of the State of San Luis Potosí, and the region known as *La Sierra Gorda* in the Northeast of the State of Queretaro. There are regions of low risk in other parts of the study area, where, based on the climatic variables considered, the presence of cases is only probable. In fact, a low number of cases has recently been reported.

In the variogram, the presence of anisotropy was identified, which was also checked with the calculation of the omnidirectional and the directional semivariograms, where 45° was the direction of higher and lower spatial continuity. To validate the estimation between the prediction using a multivariate analysis and the univariate analysis explaining the area of risk, individual cross validations were built. The middle quadratic error measures the amount of error existing between two datasets, usually observed and predicted datasets. This value was obtained by multivariate analysis comparing the robustness of the Kriging and co-Kriging methods; 0.98 for Kriging and 1.4 for co-Kriging, respectively (data not shown).

Table 2. Number of cases of rabies in cattle by year, municipality and climatic variables in central Mexico, 2001-2013.

Year	Number of cases	Affected municipalities	Average T_{max} (°C)	Average T_{min} (°C)	Average AP (mm)
2001	10	6	30.82	17.97	1,470.8
2002	98	16	29.28	16.34	1,196.0
2003	121	13	29.33	16.53	1,222.1
2004	93	11	29.31	16.53	1,228.8
2005	88	18	29.32	16.40	1,213.3
2006	52	12	29.29	16.46	1,216.7
2007	56	17	29.50	16.27	1,216.8
2008	78	22	29.32	16.39	1,212.4
2009	87	22	29.33	16.43	1,217.2
2010	90	22	29.34	16.50	1,225.7
2011	136	25	29.31	16.39	1,210.1
2012	68	26	29.32	16.41	1,213.5
2013	60	25	29.31	16.37	1,197.8

T_{max}, maximum annual average temperature; T_{min}, minimum annual average temperature; AP, annual precipitation.

Table 3. Spatial characteristics and areas with presence of cases of rabies in central Mexico over the period 2001-2007.

Year	Pattern	Places with cases of rabies
2001	Small number of cases reported from the SLP State in regions with average temperature of 24.4 °C and average precipitation of 1,470.8 mm.	Aquismón, Lagunilla, Sta. Catarina. Tamasopo, Tancanhuitz, Tampamolón, and San Martín in the State of SLP.
2002	Rabies spreads to free areas and the number of cases increases. Cases presented at average temperature of 22.8°C and average precipitation of 1,195.97 mm.	Aquismón, Axtla, Ciudad Valles, Coxcatlan, Ebano, Rayón, San Vicente, Sta. Catarina, Tampacán, Tamazunchale, Tancanhuitz, Tampamolón, Tanlajás, Tanquian and San Martín in the State of SLP.
2003	Rabies spreads to most of SLP State and arises in new places.	Alaquines, Aquismón, Armadillo, Axtla, Ciudad Valles, Rio verde, San Vicente, Tampacán, Tamazunchale, Tancanhuitz, Tampamolónn, Tanlajás, and Venado in the State of SLP.
2004	The number of cases reported decreases at average temperature of 22.9 °C and precipitation of 1,228.7 mm.	Aquismón, Axtla, Ciudad Valles, Coxcatlán, Ebano, El Naranjo. Huehuetla, San Vicente, Sta. Catarina, Tamuín, Tanlajás, and Xilitla in the State of SLP.
2005	The number of cases reported decreases; however, the disease spreads to more places in SLP, for the first time also reported in QRO State.	Alaquines, Aquismón, Armadillo, Axtla, Ciudad Valles, Coxcatlán, Lagunilla, Rayón, San Luis, Río verde, Sta. Catarina, San Martín, Tamuín, Tamasopo, Xilitla belonging to the state of SLP and towns of Jalpan, and Landa de Matamoros in the State of QRO.
2006	Cases are reported in places with average temperature of 22.8 °C and average precipitation of 1,216.7 mm.	Ciudad del Maíz, Ciudad Valles, Coxcatlán, Lagunilla, Río Verde, Sta. Catarina, Sto. Domingo, Tamasopo, Tamuín, Tancanhuitz, Tierra Nueva in the state of SLP, and Landa de Matamoros in the State of QRO.
2007	Places with high prevalence in SLP State include Ciudad Valles, Río Verde and Tamasopo.	Alaquines, Aquismón, Cárdenas, Ciudad del Maíz, Ciudad Valles, El naranjo, Lagunilla, Rayón, Río Verde, Tamasopo, Tamazunchale, Tancanhuitz, Tanlajás, Tierra Nueva, in the State of SLP, and Arroyo Seco y Jalpan in state of QRO.

SLP, San Luis Potosi; QRO, Queretaro.

Discussion

This is the first geostatistical study on the distribution of rabies in cattle with a focus on the role of *D. rotundus* and the climatic variables that favour the presence of this bat species as vector of this disease in the central region of Mexico. Our results show correlation between the risk for the presence of cases and the range of maximum and minimum temperatures and rain fall. Our results agree with those reported by Patten (2004), who mentions that the vampire bat does not tolerate temperatures higher than 39 °C or lower than 10 °C, oscillating on average between 20 °C and 27 °C. That is why it is distributed mainly in tropical and subtropical environments where there is also a high density of cattle per km^2 (Lee *et al*., 2012; Zarza *et al*., 2017).

According to Patten (2004), AP, temperature and topography are better predictors for species richness in Chiroptera than vegetative cover and latitude. It has been reported that the common vampire bat can inhabit areas with a temperature difference of less than 4 °C between the cold and the warm months, *i.e.* a very low variation in annual temperature (McNab *et al*., 1973; Zarza *et al*., 2017). In contrast, our study found a more than three times higher average (12.9 °C) suggesting good adaptation of the vampire bat to the climatic conditions in the study region. It is known that *D. rotundus* does not hibernate, but lives long periods in caves, in tree holes, under bridges and in old buildings during the day where the microclimate differs from that of the general environment (Torquetti *et al*., 2017). In fact, it has been reported that the factors that most contribute to the spatial distribution of rabies in livestock are temperature and precipitation as these variables offer a microclimate inside bat refuges that favour the distribution of possible infected vampire bats with the rabies virus (Bárcenas-Reyes, 2013; Bárcenas-Reyes *et al*., 2015; de Thoisy *et al.*, 2016; Hayes and Piaggio, 2018). It was found that the highest risk, and the highest number of cases, occur in La Huasteca Potosina in the State of San Luis Potosí, and in La Sierra Gorda in the State of Querétaro. The reason could be that these areas offer climatic conditions appropriate for the survival of *D. rotundus*, including high livestock density. This is consistent with Hayes and Piaggio (2018), who report that the presence of vampire bats is common in various habitats of central Mexico, and that vampire bats look for areas with moderate winter temperatures that allow continuous activity throughout the year and the availability of food. The areas with medium and low risk have low livestock density, a risk factor that influences the distribution of the disease in cattle but is less important than the potential areas with climatic conditions that influence the distribution of *D. rotundus* (Galicia-Castillo, 2015).

One of the main risk factors for the persistence and distribution of rabies in a specific region is the presence of livestock, the main source of food for the vector *D. rotundus*. It has been previously reported that areas with a high probability of suitable conditions for this bat species in Mexico are the states of San Luis Potosi and Veracruz (Zarza *et al*., 2017), which are also two of the Mexican states with the highest density of cattle because of the availability of pasture. Therefore, the presence of cases of rabies correlates with the population density of cattle (Suzán, 2005; Bárcenas-Reyes *et al*., 2015), and it must be admitted that it would have been useful if this variable would have been included in our study.

Escobar (2016) mentions the need to evaluate prediction models using different algorithms to select the best prediction that can

Table 4. Spatial characteristics and areas with presence of cases of rabies in central Mexico over the period 2008-2013.

Year	Pattern	Places with cases of rabies
22008	Cases are reported in GTO State.	Ahualulco, Alquines, Aquismón, Axtla, Cárdenas, Ciudad del Maíz, Ciudad Valles, El naranjo, Guadalcazar, Rayón, Río Verde, San Ciro de Acosta, San Martín, Tamazunchale, Tampamolón y Tanlajás in the State of SLP; Arroyo Seco, Cadereyta, Jalpan, Peña Miller, and Pinal de Amoles in the State of QRO.
2009	The number of cases reported increases in the three states. Average temperature of 22.9°C, and average precipitation of 1,217 mm.	Alaquines, Aquismón, Ciudad del Maíz, Ciudad Valles, Ciudad Fernandez, El naranjo, Huehuetla, Rayón, Río Verde, San Ciro de Acosta, San Martín, San Vicente, Tamasopo, Tampamolón, Tamuín, Tancanhuitzy Tanquean in the State of SLP; Cadereyta, Jalpan and Landa de Matamoros in the State of QRO; Xichu and Atarjea in GTO.
2010	Similar number of cases in 2010 and 2011. No new places affected.	Aquismón, Ciudad del Maíz, Ciudad Valles, Ciudad Fernández, El Naranjo, Guadalcazar, Río Verde, San Luis, San Vicente, Santa Maria, Tamasopo, Tamuín, Tancanhuitz, Tierra Nueva, Victoria, and Villa Juárez in the State of SLP; Ezequiel Montes y Pinal de Amoles in the State of QRO; Atarjea, Sta. Catarina and Xichu in GTO.
2011	Similar number of cases in 2010 and 2011 but new cases and new affected places reported.	Aquismón, Ciudad Valles, Cerritos, Ciudad Fernández, Guadalcazar, Huehuetla, Río Verde, San Antonio, San Juan, San Luis, San Martín, Santa Maria, Tamasopo, Tamuín, Xilitla, and Villa Hidalgo in SLP. Cadereyta, Landa de Matamoros, Peñamiller, Pinal de Amoles, and Toliman in QRO; Sta. Catarina in GTO.
2012	The number of cases reported decrease by 50%.	Alaquines, Aquismón, Armadillo, Cárdenas, Ciudad Fernadez, Ciudad Valles Cocaxtlan, El naranjo, Guadalcazar, Rayón, Río Verde, San Ciro, San Juan, San Luis, San Nicolas, Tamasopo, Tamazunchale, and Tamuín in SLP; Arroyo Seco, Cadereyta, Ezequiel Montes, Jalpan and Toliman in QRO; Sta. Catarina in GTO.
2013	The number of cases and the size of infected areas decrease.	Alaquines, Aquismón, Armadillo, Axtla, Cárdenas, Ciudad Valles, El naranjo, San Luis, San Martín, San Vicente, Tamasopo, Tampacán y Tamuín, Tancanhuitz, Tanquian and Zaragoza in SLP; Cadereyta, El Marques, Jalpan, and Landa de Matamoros in QRO; San Jose in GTO.

GTO, Guanajuato; QRO, Queretaro; SLP, San Luis Potosi.

differentiate between those of biological and those of statistical importance. The advantage of co-Kriging is that it offers results with less statistical bias because it uses secondary information correlated with the attribute under study. Multivariate co-Kriging in our study allows the study of the association between the presence of cases in cattle with different variables that include the distribution of the vector by providing unbiased global estimates in the structure of spatial variability; *i.e*. the variogram.

The report of cases in areas previously free of the disease in the states under study has been constant lately (Galicia-Castillo, 2015). It is not clear, however, if those cases occur because of vampire bat's bites cattle in the location where the case is reported, or the cases occur in animals brought in from endemic areas; in our data set the precise origin of the infected animals was not always available. There are reports of the presence of *D. rotundus* in these areas but only a few with infection have been found.

Conclusions

The presence of the risk for rabies in cattle has been estimated with advanced multivariate geostatistical methods based on three environmental variables: minimum and maximum temperature together with average precipitation. The outcome shows that the risk for cases in the central region of Mexico is higher in La Huasteca Potosina in the State of San Luis Potosí, and in La Sierra Gorda in the State of Querétaro. It seems that these endemic regions are acting as the source of infection for other regions in the area.

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