The impact of anthropogenic and environmental factors on human rabies cases in China

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Abstract
Human rabies is a public health problem in Asia, especially in less-developed regions where the disease is under-reported because of a lack of epidemiological surveillance. To address this gap, we collected data on human rabies in Yunnan Province, China, between 2005 and 2016. Using statistical mapping techniques, we correlated the occurrence of human rabies to environmental (elevation, precipitation, normalized difference vegetation index [NDVI], temperature and distance to the nearest main rivers) and anthropogenic (human and dog population density, distance to the nearest main roads and gross domestic product [GDP]) factors. We used a performance score, the average area under the receiver operator characteristic curve (0.88), to validate our risk model. Using this model, we found that environmental factors were more strongly associated with human rabies occurrence than anthropogenic factors. Areas with elevation below 2000 metres, GDP per capita between $750 and $4500/year and NDVI below 0.07 were associated with greater risk of human rabies. Rabies control in China should specifically target these areas.

KEYWORDS
China, dog rabies, human rabies, suitability, surveillance, transportation corridors
1 | INTRODUCTION

Rabies is a zoonotic disease that occurs across the world and is caused by rabies virus (RABV). Rabies has a case fatality rate of 100% and causes almost 60,000 human fatalities each year (Fooks et al., 2014), 90% of which are concentrated in Asia and Africa (Meslin & Briggs, 2013). China has a relatively high incidence of rabies compared with other countries in Asia (Zhou et al., 2016). From 1960 to 2014, more than 120,000 cases of human rabies were reported, with large outbreaks occurring in eastern and southern China (Si et al., 2008; Zhou et al., 2016).

Over the past decade, rabies has been gradually spreading to previously low-incidence and non-epidemic areas, from the southern and eastern regions to the northern and western regions of China (Song et al., 2014; Yao et al., 2015). According to phylogeographic analyses, Yunnan Province (21°8′N–29°15′N and 97°31′E–106°11′E, covering an area of 394,000 km²), located in south-western China, is a potential source for rabies spread in South-East Asia (Vietnam, Laos, and Myanmar) and China (Guo et al., 2013; Zhang et al., 2014, 2017). The first human rabies case was reported in Yunnan in 1956, and sporadic cases have been reported from the mid-1990s onwards. A human rabies epidemic had also emerged in Yunnan in 1999 (Tian et al., 2018).

Dogs are the primary reservoir and vector of human rabies in China, causing up to 95% of all human rabies cases (Ameh, Dzikwi, & Umoh, 2014; Gong et al., 2010; Guo et al., 2013; Wang, Tang, & Liang, 2014; Yin et al., 2013). Control of dog rabies is an efficient way to reduce the incidence of human rabies infections (Darlin & Vonville, 2012). Rabies prevention and control efforts are led by the government and are carried out in cooperation with medical, veterinary, and other experts. These measures include comprehensive prevention and control measures such as management, immunization and culling of sick dogs, as well as prevention and treatment of dogs with suspected rabies infections and exposed persons.

During rabies surveillance in Yunnan, brain tissues from rabid dogs and dogs suspected of rabies are collected and a direct immunofluorescence assay is used to detect RABV antigens. The results have indicated that most dogs are infected: 89.19% (66/74) of dogs suspected of having rabies tested positive in Chuxiong from 2011 to 2014 (Guo, Yang, et al., 2018; Hu et al., 2016), and 64.02% (153/239) of dogs tested positive in 12 states and cities in Yunnan from 2011 to 2017 (Zhang et al., 2019). Dogs carrying RABV can also be detected in the canine populations of rabies-endemic villages: in one study, brain tissues from 40 of 1,162 (3.44%) apparently healthy dogs were positive for RABV (Zhang et al., 2015).

Dog rabies was positively associated with human population density in Namibia (Hikufe et al., 2019). Local transmission of dog rabies is also associated with dog population size and their distributions (Brunker et al., 2018; Yin et al., 2012; Zhu & Liang, 2012). Economic development is another anthropogenic factor linked to rabies transmission, with higher prevalence associated with lower economically developed areas (Arias-Orozco et al., 2018; Hampson et al., 2015; Raghavan et al., 2016). Distance from the nearest main roads was also identified as a predictor of RABV transmission, suggesting that transport may facilitate the spread of dog rabies (Brunker et al., 2018).

Human rabies distribution is associated with environmental factors such as temperature (positive correlation) and elevation (negative correlation) (Guo, Yin, et al., 2018). Environmental factors also play a key role in the occurrence of rabies vectored by other mammals, such as raccoons and striped skunks (Brunker et al., 2018; Recuenco, Eidson, Cherry, Kulldorff, & Johnson, 2008; Russell, Real, & Smith, 2006; Smith, Lucey, Waller, Childs, & Real, 2002; Smith, Waller, Russell, Childs, & Real, 2005). Rivers have been suggested to act as natural barriers to RABV dispersal (Brunker et al., 2018; Recuenco et al., 2008; Russell et al., 2006) and can potentially reduce the speed of virus transmission sevenfold (Smith et al., 2002). Wetlands and forest coverage were associated with rabies transmission in raccoons: RABV spread more slowly in townships with high forest coverage (Recuenco et al., 2008; Smith et al., 2005).

In Yunnan Province, human rabies occurrence is spatiotemporally heterogeneous. Most cases occur in the eastern region, and human rabies cases peak between May and October (Zhang et al., 2014). Humans and dog population distribution as well as geography are heterogeneous across Yunnan Province. First, the eastern region of Yunnan Province has a weak economy and high human and dog population density, while the centre is economically developed, and the west has low human and dog density. Second, the terrain of the province is high in the north-west and low in the south-east, with relatively cold weather and low precipitation in the north-west, mild temperatures and moderate precipitation in the eastern and central regions, and hot and humid weather in the south and south-west. Throughout the province, 85% of precipitation falls during the rainy season from May to October.

Here, we aimed to explore the associations between spatial heterogeneity in anthropogenic and environmental factors in Yunnan Province and human rabies cases. More specifically, we aimed to identify the risk factors associated with rabies occurrence in human populations by modelling and generating risk maps for RABV.

2 | MATERIALS AND METHODS

2.1 | Data collection

Data on human rabies for the 2005–2016 period were obtained from the Yunnan Institute of Endemic Disease Control and Prevention. These data included the date of symptom onset, date of diagnosis and residential address for each patient.

We categorized predictor variables into two categories: anthropogenic and environmental variables. Anthropogenic variables included gross domestic product (GDP) per capita, distance to the nearest main roads (DTRoad), dog population density (DogDn) and
human population density (HPD). GDP per capita was obtained from the Yunnan Statistical Yearbook (http://www.stats.yn.gov.cn), and ranged from $630 to $7,000. Dog demographic data were collected by the Yunnan Provincial Center for Animal Disease Control and Prevention at the city level. Human population density was obtained from the WorldPop database (http://www.worldpop.org). Environmental variables included elevation, normalized difference vegetation index (NDVI), distance to the nearest main rivers (DTRiver), temperature and precipitation. Elevation data were extracted from the international scientific data service platform (http://www.scidatasonline.com). The monthly average NDVI was obtained from the MODIS MOD13A2 data set of the Land Processes Distributed Active Archive Center (LP DAAC, https://lpdaac.usgs.gov). Climatic variables, annual mean temperature (TempAnn) and annual precipitation (PreAnn) were obtained from the WorldClim database (http://www.worldclim.org).

## 2.2 Analysis

We used boosted regression trees (BRT) to identify anthropogenic and environmental factors associated with human rabies occurrence and to estimate the probability of human rabies occurrence. BRT is a holistic approach for fitting statistical models that combines the strengths of regression trees and boosting algorithms (Elith, Leathwick, & Hastie, 2008). BRT’s predictive performance is superior to most traditional species distribution modelling methods (Elith et al., 2008; Thanapongtharm et al., 2014; Van Boeckel et al., 2012) and provides approximate effect sizes for each predictor (Buson & Elith, 2011; Shah, De Wolf, Paul, & Madden, 2014) as well as information on interactions between predictors (Lampa, Lind, Lind, & Bornefalk-Hermansson, 2014; Pinkerton et al., 2010). Model fitting was performed using the R package ‘gbm’ (Elith & Leathwick, 2017; Ridgeway, 2007).

To obtain more robust estimates of the model’s predictive capacity, we used spatial subsampling for cross-validation (Adhikari, Chettri, & Barik, 2009; Williams, Fasina, & Peterson, 2008; Xiao et al., 2013). We divided the human rabies occurrence data into four quadrants above and below the median latitude and longitude: East and west of the median longitude (hereafter called the ‘East-West’ test), and north and south of the median latitude (hereafter called the ‘North-South’ test). The first and third quadrants (upper right-hand and lower left-hand quadrants) are off-diagonal, and the second and fourth quadrants (upper left-hand and lower right-hand quadrants) are on-diagonal (hereafter called the ‘diagonals’ test). Finally, human rabies occurrence data for the 2005–2015 period were used to fit the human rabies model. Data for 2016 were used to test the model.

BRT models use data on both presence (occurrence of human rabies infection) and absence of a condition. To take into account potential observational bias in more populated areas, we sampled pseudo-absences as a function of human population density. A pixel level spatial distribution of pseudo-absence was generated using the function 'bgSample' of the 'seegSDM' R package (Phillips et al., 2009; Pigott et al., 2014), with the sampling probability of pseudo-absence directly defined by local log-transformed human population density values. Furthermore, we also prevented sampling of pseudo-absences in areas without human populations. The BRT model of human rabies was run with the following parameters: tree complexity of 8, learning rate of 0.01, bag fraction of 0.5 and 10-fold cross-validation.

We developed an iterative procedure to obtain reliable results for the predictive performance of the model (Martin et al., 2011). The analysis involved a series of steps: (a) randomly selecting 75% of the data from the data set as training data and 25% of the data as test data, (b) building a BRT model using the training data, (c) assessing the relative contribution of each predictor, (d) using the fitted functions from the BRT model to generate predictions based on test data, which in turn were assessed using receiver operating characteristic (ROC) curves, and (e) mapping the predictions produced by the BRT model. Steps (a) to (e) were repeated 50 times. The average area under the ROC curve (AUC) was used to evaluate the predictive accuracy of the model (Fawcett, 2006). The predicted risk of human rabies ranged between 0 and 1, with a higher value indicating greater risk. In addition, 5,000 presence and absence points were randomly generated to describe the characteristics of important predictive factors in the risk map for human rabies.

## 3 Results

### 3.1 Human rabies

In total, 939 human rabies cases were reported from 2005 to 2016 (Figure 1). In recent years, human rabies cases occurred mainly in eastern Yunnan Province, particularly in Honghe, Wenshan, Zhaotong and Qujing. Over the 2005–2016 period, these regions had average annual incidence rates of 42, 29, 22 and 21 cases per 1,000,000 persons, respectively (Figure 1). In recent years, human rabies cases occurred mainly in eastern Yunnan Province, particularly in Honghe, Wenshan, Zhaotong and Qujing. Over the 2005–2016 period, these regions had average annual incidence rates of 42, 29, 22 and 21 cases per 1,000,000 persons, respectively (Figure 1). In recent years, human rabies cases occurred mainly in eastern Yunnan Province, particularly in Honghe, Wenshan, Zhaotong and Qujing. Over the 2005–2016 period, these regions had average annual incidence rates of 42, 29, 22 and 21 cases per 1,000,000 persons, respectively (Figure 1). Notably, the average annual incidence of human rabies in south-west Yunnan Province was also high (for instance, in Pu’er City at 17 cases per 1,000,000 persons). As of 2016, north-western Yunnan remained a low-incidence area for human rabies (Figure 1), with no cases reported in Nujiang from 2005 to 2016, and comparatively low average annual incidences in Diqing (1 cases per 1,000,000 persons), Lijiang (<1 cases per 1,000,000 persons) and Dali (2 cases per 1,000,000 persons). We observed a modest correlation between the number of human rabies cases and dog population density that did not reach the threshold for statistical significance (Figure 1, r = .48, p = .06).

Human rabies cases were few and scattered in Yunnan Province between 2005 and 2006. Since 2007, human rabies cases have been relatively concentrated in the north-east region of Yunnan. By 2010, the entire eastern region had reported cases. Since then, the overall number of human rabies cases has been decreasing. However, the number of regions reporting new rabies cases is increasing in the west of the province and decreasing in the east (Figure 2).
3.2 | Anthropogenic and environmental factors associated with human rabies cases

Environmental factors such as elevation, annual precipitation, NDVI, annual mean temperature and distance to the nearest main rivers contributed relatively more to the BRT models than anthropogenic factors, such as distance to the nearest main roads, GDP per capita and canine population density (Figure 3). The only exception was human population density (HPD), which also contributed significantly to the model.

Predicted risk of human rabies was negatively correlated with elevation, GDP and NDVI, but positively correlated with dog population density (Figure 4). Human rabies risk was overall positively correlated with HPD. Notably, there was an anomaly observed in the response curve for human rabies occurrence and HPD. The risk of human rabies in areas with human population densities of

**FIGURE 1** Rabies epidemic in Yunnan Province, China, 2005–2016. (a) Distribution of human rabies occurrence and (b) rabies-positive brain tissue specimens obtained from dogs from 2005 to 2016. Human and dog population densities were coded from low (light colours) to high (dark colours). DQ, Diqing; NJ, Nujiang; LJ, Lijiang; DL, Dali; BS, Baoshan; DH, Dehong; LC, Lincang; CX, Chuxiong; PE, Puer; XSBN, Xishuangbanna; KM, Kunming; YX, Yuxi; ZT, Zhaotong; QJ, Qujing; HH, Honghe and WS, Wenshan

**FIGURE 2** Distribution of human rabies cases in Yunnan Province, 2005–2016
1200–3000 people per km² was lower than the risk in areas with 500–1000 people per km² (Figure 4).

### 3.3 | Suitability predictions for human rabies occurrence

We developed several pairs of tests to assess the predictive performance of our BRT models based on stratified subsets of rabies occurrence data. The cumulative binomial probabilities of the tests indicated that the BRT model had good suitability ($p < .01$, Table 1). For temporal extrapolations, human rabies occurrences from 2005 to 2015 were used to fit the human rabies model, and human rabies data for 2016 were used to validate the model. Using the 2016 data, the BRT model predicted 30 of 48 cases in high-risk areas, indicating a good level of predictive power (AUC = 0.88, Figure 5). Our results also imply spatial heterogeneity in human rabies occurrence (Table 1). The spatial extrapolation experiments showed good predictive performance for ‘east predicts west’, ‘south predicts north’ and ‘on predicts off diagonal’. We also calculated the average annual incidence of human rabies in each region (‘East’, ‘West’, ‘South’, ‘North’, ‘On’ and ‘Off’) and found that incidence was higher in the ‘East’, ‘South’ and ‘On’ regions (23, 21 and 16 cases per 1,000,000 persons, respectively) and lower in the ‘West’, ‘North’ and ‘Off’ regions (6, 8 and 10 cases per 1,000,000 persons, respectively).

Areas far from main rivers were most suitable for human rabies occurrence. The eastern, southern and central regions of the province were identified as most suitable for human rabies occurrence (Figure 5). Areas with the highest predicted risk were those with elevation below 2000 metres, human population densities of 30–1200 people per km² and GDP per capita (GDP) of $750–$4,500 (Figure 6). Human rabies occurrence was concentrated in areas with relatively high human population densities, and human populations were mostly distributed in low-elevation areas (Figure 6a). Low-elevation and low-income areas were also at high risk for human rabies, consistent with the risk curves for elevation (DEM) and GDP (Figures 4 and 6b). Human rabies mainly occurred in low-income areas with relatively high population densities (Figure 6c). There was a strong correlation between human population density and canine population density, and the occurrence of human rabies was concentrated in areas with high human and dog population densities (Figure 6d).

### 4 | DISCUSSION

Consideration of both anthropogenic and environmental factors, appears essential to understand the spatiotemporal heterogeneity of human rabies. Our analysis revealed significant associations between human rabies and anthropogenic and environmental factors. For example, more human rabies cases were reported during the rainy season than during the dry season; human and dog population densities were positively correlated with human rabies; and the distance to main rivers was positively correlated with rabies transmission, suggesting that river may hinder rabies spread.

A potentially important result of this study compared with previous works was highlighting the complex relationships between dogs and human rabies in an Asian country at a fine scale. The risk curves and the correlation analysis show that human rabies is correlated with high dog population density (Figure 4, $r = .48$, $p = .06$). However, the relative contribution (RC) of dog population density towards human rabies was relatively low (RC = 3.45%). High domestic dog population density may increase the frequency of dog-human interaction, but dog-to-human rabies transmission through bites is also affected by many other factors (Brunette, 2017) such as herd immunity and post-exposure rabies prophylaxis.

In line with previous studies (Arias-Orozco et al., 2018; Guo, Yin, et al., 2018; Hampson et al., 2015; Raghavan et al., 2016), we found that rabies distribution was negatively correlated with economic development and positively correlated with human population density. Human rabies mostly occurred in economically underdeveloped areas (RC = 6.53%). Most high-incidence areas of human rabies in north-eastern and south-eastern Yunnan Province (Zhaotong and Wenshan) are poverty-stricken counties.

This study also identified associations between distance to roads and rivers and human rabies. Main roads and rivers were previously found to directly influence the distribution of domestic dogs (Brunker et al., 2018; Onyango, Sahin, Awiti, Chu, & Mackey, 2016; Patz, Olson, Uejio, & Gibbs, 2008; Zarza, Martínez-Meyer, Suzán, & Ceballos, 2017). In general, the farther a place is from a main road, the more difficult it is to implement public health interventions (Guo, Yin, et al., 2018) and dog vaccination campaigns (Wera, Mourits, & Hogeveen, 2015), and as a consequence, the higher the risk of human rabies following bites by RABV-infected dogs. In contrast, our study showed that closer proximity to main roads, the higher the risk of human rabies cases. In this context, high transportation network between areas may facilitate the spread of dog rabies.
YU et al. (Brunker et al., 2018), and dog rabies outbreaks are often considered to be sources of human rabies (Tricou et al., 2016). In contrast, there are fewer rabies cases near rivers, which may act as natural barriers to the movement of RABV-infected hosts. Elevation and NDVI probably do not directly influence rabies occurrence, but may be indicator variables indirectly associated with the spatial distribution of human and dog populations at a fine scale. Human residences are generally located at low elevations with relatively low vegetation coverage. Vegetation coverage is also affected by temperature and precipitation.

There are several limitations to our study, which could be revisited when detailed data are available. The relationships between human rabies and GDP and dog population density may have been affected by differing degrees of spatial resolution. The data for GDP per capita and dog population density were based on county/city statistics, and thus, differences between human rabies in urban

**TABLE 1** Summary of BRT model predictions and tests applied in this study

<table>
<thead>
<tr>
<th>Model testing</th>
<th>AUC</th>
<th>Training test</th>
<th>No. of successes</th>
<th>Proportion of predicted area (%)</th>
<th>Cumulative binomial probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagonals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On predicts off</td>
<td>0.64</td>
<td>464</td>
<td>427</td>
<td>159</td>
<td>18.94</td>
</tr>
<tr>
<td>Off predicts on</td>
<td>0.68</td>
<td>427</td>
<td>464</td>
<td>123</td>
<td>4.95</td>
</tr>
<tr>
<td>South–North</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South predicts north</td>
<td>0.69</td>
<td>632</td>
<td>259</td>
<td>117</td>
<td>23.29</td>
</tr>
<tr>
<td>North predicts south</td>
<td>0.59</td>
<td>259</td>
<td>632</td>
<td>163</td>
<td>18.95</td>
</tr>
<tr>
<td>East–West</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>East predicts west</td>
<td>0.74</td>
<td>685</td>
<td>206</td>
<td>194</td>
<td>52.45</td>
</tr>
<tr>
<td>West predicts east</td>
<td>0.62</td>
<td>206</td>
<td>685</td>
<td>202</td>
<td>21.03</td>
</tr>
<tr>
<td>Time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005–2015 predicts 2016</td>
<td>0.88</td>
<td>891</td>
<td>48</td>
<td>30</td>
<td>24.93</td>
</tr>
</tbody>
</table>

Abbreviation: AUC, area under the receiver operating characteristic (ROC) curve.
and rural areas may have been underestimated. Data such as DEM, NDVI, temperature, precipitation and human population density were measured at higher spatial resolution. These different spatial resolutions may result in underestimation of the impact of GDP and dog population density on human rabies as well as overestimation of the RC of human population density (HPD). Higher spatial resolution data (e.g. for dog population density and socio-economic conditions) would improve the analysis and our understanding of rabies transmission. Data on vaccine coverage in dogs across regions were not available due to a lack of sustained animal health surveys.

Although vaccination is the most effective strategy for rabies prevention in dogs (Hu, Fooks, Zhang, Liu, & Zhang, 2008; Lembo et al., 2010; Song et al., 2009; Tang et al., 2005; Wu, Hu, Zhang, Dong, & Rupprecht, 2009; Yin et al., 2012; Zhang, Jin, Sun, Zhou, & Ruan, 2011) along with post-exposure prophylaxis (Beyer et al., 2011; Hung & Van Tuan, 2011), low immunization rates of dogs in rural areas have become a significant impediment to rabies control. The average dog rabies vaccination coverage in the province had risen from 7% to 50%, but in most areas, it remains below 40% (Dong, Ma, Zhang, & Yang, 2011). Previously, dog vaccination coverage in urban areas exceeded 70%. However, despite vaccination points located at veterinary stations in every township as well as home visits from veterinarians for vaccination, dog vaccination coverage has remained low and variable (about 20%–70%). This may be in part because of local differences in natural environment and economic development, as well as lack of knowledge about rabies. Our study illustrates the impact of anthropogenic and environmental factors on human rabies and the use of such factors to predict the risk of human rabies. Our results could be used to inform vaccination campaigns.

In conclusion, our results underscore the importance of environmental and anthropogenic factors in rabies transmission. These data may ultimately contribute to better understanding of areas with high potential for rabies occurrence. Our results could also improve our understanding of rabies distribution, and in so doing, facilitate responses and prevention efforts for rabies re-emergence, especially in populated and less-developed areas of South-East Asia.

**FIGURE 5** Predicted risk map for human rabies in Yunnan Province. Human rabies occurrence data from 2005 to 2015 was used as a training data set and overlaid with human rabies data for 2016 as the testing set.

**FIGURE 6** Exploratory visualization of important predicted factors for human rabies in two-dimensional environmental space. The figure was constructed using 5000 randomly generated presence/absence points. Four variables were selected in the human rabies model: human population density (HPD), elevation (DEM), GDP, and domestic dog population density (DogDn). Black and gray points indicate presence and absence data, respectively.
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ETHICS STATEMENT

Experimental procedures were performed according to guidelines established by the China CDC and were approved by the ethics committee of the Yunnan Institute of Endemic Diseases Control and Prevention.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The human rabies cases data are available from the authors with the permission of the Yunnan Institute of Endemic Diseases Control and Prevention.

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