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Spatial and temporal dynamic analysis of rabies: A review of current methodologies

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Abstract

Rabies continues to be one of the deadliest, high risk diseases worldwide, posing a severe threat to public health. The lack of human-to-human transmission means that the spread of rabies is not significantly affected by the distribution of humans or migration. Thus, the spatiotemporal dynamic of cases in both wild and domestic animals is an important issue that can result in human cases. This paper gives an overview of the methodologies for the spatial and temporal dynamic analysis of this disease. It introduces the most representative research progress of spatial aggregation, dynamic transmission, spatiotemporal distribution, epidemiological analysis and application of modelling in the study of rabies transmission in recent years. This overview should be useful for investigating the spatial and temporal dynamics of rabies, as it could help understanding the spread of cases as well as contribute to the development of better prevention and control strategies in ecology and epidemiology.

Introduction

Rabies is caused by neurotropic viruses of the genus *Lyssavirus*. The untreated disease, presenting as progressive encephalomyelitis, has an almost 100% case fatality rate (Fooks *et al.*, 2014; Hemachudha *et al.*, 2002). Africa and Asia, with thousands of deaths recorded annually, account for more than 99% of all human rabies infections (Fooks *et al.*, 2014; Knobel *et al.*, 2005). Although infected cases are uncommon in wealthy nations, the potential dissemination of the common rabies virus (genotype 1) in different animal species continues to be one of the most significant and feared risks to public health in the 21st century (Yu *et al.*, 2012). Dogs constitute the main reservoir and almost all human cases of infection are caused by infected canine bites. However, rabies has formed chronic transmission networks in various other terrestrial carnivores, including foxes, coyotes, raccoons, skunks and several bat species. Although animal bites are the principal route of rabies transmission, alternative ways, including aerosol, ingestion and transplantation have also been reported (Beran, 1994; Kaplan *et al.*, 1986).

During the past century, numerous countries have carried out successful, extensive vaccination campaigns to eradicate canine rabies, dramatically lowering the frequency of human infections (Müller *et al.*, 2015). In Western Europe, Latin America, USA, Canada, Japan and Malaysia, dog-mediated human cases were eliminated. These initiatives have helped to decrease enzootic dog rabies in many metropolitan areas, but they have mostly failed to control the spread of the disease from wildlife to livestock species and humans in most of these nations (Mitmoonpitak *et al.*, 1998; Touihri *et al.*, 2011). However, there are still high-risk countries with a tendency towards spatial expansion of the disease. Examples in Asia include China (Zhang *et al.*, 2011; Zhou *et al.*, 2016), Republic of Kazakhstan (Abdrakhmanov *et al.*, 2016), India (Brookes *et al.*, 2018), Thailand (Thanapongtharm *et al.*, 2021), Indonesia (Ward, 2014); in the Americas Mexico (Bárcenas-Reyes *et al.*, 2019; Ortega-Sánchez *et al.*, 2022), Chile (Escobar *et al.*, 2015), Brazil (Oviedo-Pastrana *et al.*, 2015); in Europe Germany (Eckardt *et al.*, 2015) and Ukraine (Polupan *et al.*, 2017); and Africa Tunisia (Kalthoum *et al.*, 2021). The World Health Organization (WHO) mapped the rabies risk in 2013 with Asia and Africa being at the highest level (Figure 1; source: World Health Organization, modified).

In the temporal domain, a distinct seasonal pattern has been observed. Furthermore, the spread of rabies cases is not particularly significant to the distribution and migration of humans since there is no human-to-human transmission (Heeney, 2006). For these reasons, the spatial and temporal dynamics of rabies are crucial for understanding the rabies distribution, both in humans and in the animal reservoirs. We outline the methods for analysing the dynamics, which may contribute to finding the best ways to lessen the risk of new outbreaks by increasing the understanding of how these epidemics start. Risk-based techniques can improve veterinary surveillance by determining the requirements and priorities for monitoring (Thanapongtharm *et al.*, 2021), which would lead to effective prevention and management of both animal and human rabies.

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Spatial analysis and mapping

In the field of spatial epidemiology, disease mapping refers to the process of visualizing disease data using geographic information systems (GIS) tools, which may most naturally show the spatial distribution of diseases. The British physician John Snow first drew a famous case map of the London cholera outbreak in 1854, revealing the connection between cholera and wells for drinking water (Elliot *et al.*, 2000). Rabies case data can be visualized in a similar way (Seetahal *et al.*, 2019). In addition, maps can be combined with histogram or line chart to be more effective in describing the temporal and spatial trend of rabies (Mondul *et al.*, 2003).

When all the animal rabies cases in Sri Lanka from 1999 to 2010 were projected on a map, it was evident that the western provinces had the majority of instances (Karunanayake *et al.*, 2014). The geographical distribution of animal rabies cases in Tunisia from 2012 to 2018 showed that the disease was mainly restricted to the North and the Centre of the country (Kalthoum *et al.*, 2021). The maps of human rabies cases in China between 2005 and 2012/2013 present a decreasing incidence trend in high-risk areas but an increasing one in low-risk areas (Song *et al.*, 2014). In addition, Guo *et al.* (2018a) showed that cases are more common in the East and South in China, with a widening geographical pattern indicating that the extent of infection was still growing. Despite a drop in the overall number of rabies cases in people in Brazil, recent, three high-risk clusters of equine rabies have very recently been reported (Oliveira *et al.*, 2022).

Spatial aggregation analysis

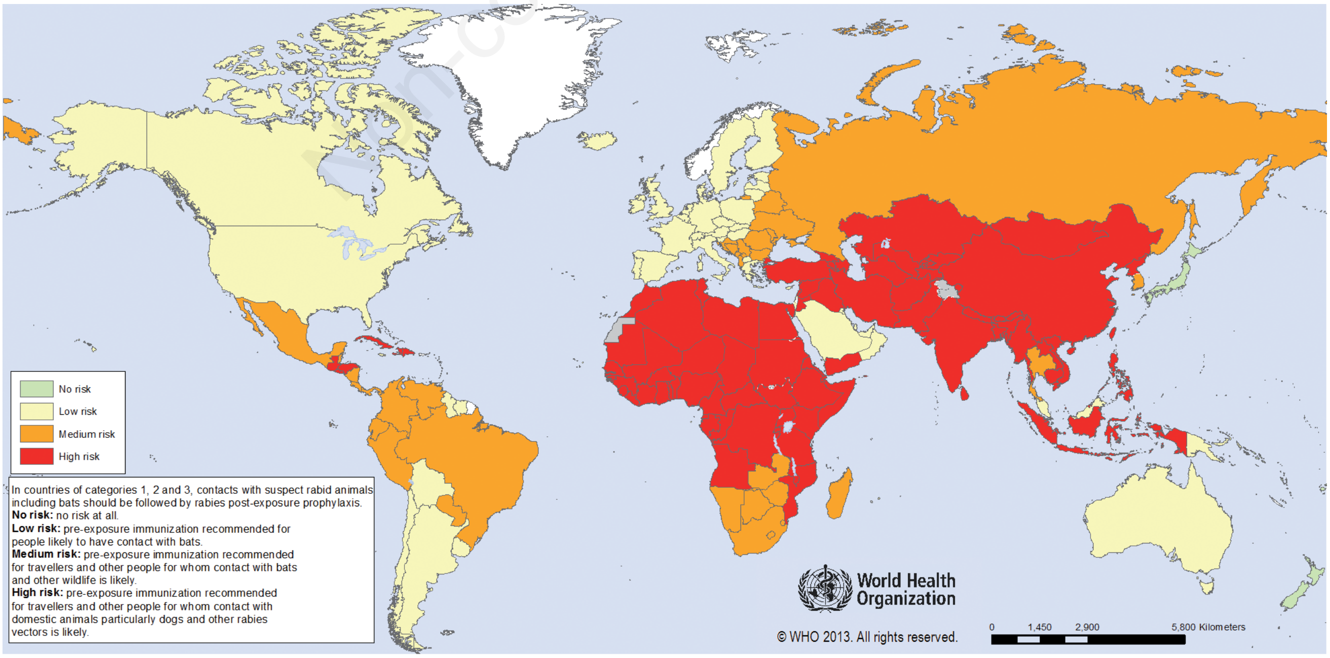
Waldo Tobler stated in his First Law of Geography in 1970 that everything is connected and the closer the distance, the more related things are (Tobler, 1970). Spatial autocorrelation refers to the notion that the locations of objects or phenomena are interconnected, *i.e.* they show some degree of spatial aggregation. Analysis of this comes in two types: global and local, where the former is used to determine whether attributes supplied throughout the whole study range show autocorrelation but without revealing where they are clustered, while the latter can tell whether or not specified attributes in a local area are autocorrelated.

The three most commonly used global spatial autocorrelation methods are Moran's *I* (Moran, 1950), Geary's *C* (Geary, 1954) and Getis-Ord's *G* (Getis and Ord, 2010; Ord and Getis, 1995). Moran's *I* varies between 1 and -1, where >0 indicates a positive spatial correlation between research objects, <0 a negative spatial correlation or dispersion, and = 0 a spatial random distribution. Geary's *C* compares the difference of attributes of adjacent items with values ranging between 0 and 2, with those close to 0 indicating a higher spatial positive correlation; those close to 2 a stronger negative correlation; and those closer to 1 a more randomly distributed set of data. Getis-Ord's *G* estimates the degree of correlation between the value at one location and that at other locations within a distance. It can tell whether there is a spatial clustering area and further determine whether it is strong or weak. All these methods can be tested by Monte Carlo simulation (Binder *et al.*, 1993).

Moran's *I* is the most commonly used method and it can be calculated according to Lee and Wong (2001) as follows:

$$I = \frac{\sum_{i=1}^{n}\sum_{j=1}^{n} w_{ij}(x_i - \bar{x})(x_j - \bar{x})}{s^2 \sum_{i=1}^{n}\sum_{j=1}^{n} w_{ij}} \quad (1)$$

$$s^2 = \frac{\sum_{i=1}^{n}(x_i - \bar{x})^2}{n} \quad (2)$$



In countries of categories 1, 2 and 3, contacts with suspect rabid animals including bats should be followed by rabies post-exposure prophylaxis.
No risk: no risk at all.
Low risk: pre-exposure immunization recommended for people likely to have contact with bats.
Medium risk: pre-exposure immunization recommended for travellers and other people for whom contact with bats and other wildlife is likely.
High risk: pre-exposure immunization recommended for travellers and other people for whom contact with domestic animals particularly dogs and other rabies vectors is likely.

Figure 1. World Health Organization (WHO) rabies risk map (Source: World Health Organization, modified).

where (Eq. 2) is the sample variance; n the number of spatial units indexed by i and j; x the variable of interest; $\overline{x}$ the mean of x; and w_{ij} a matrix of spatial weights with zeroes on the diagonal.

The global Moran's I reflects the spatial correlation of the whole research region. Local spatial autocorrelation analysis can be done to determine whether there are any minor and possibly undetected aggregations between sub-regions when no aggregation occurs in the global autocorrelation analysis. The local index of spatial association (LISA) by Anselin (1995), on the other hand, is a widely used technique for local autocorrelation analysis, which generates the cluster diagram and scatter diagram, with four spatial patterns: high-high (HH) specifying high-density units surrounded by high-density units, low-low (LL) specifying low-density units surrounded by low-density units; in addition there are two so called outliers, i.e. low-high (LH) specifying low-density units surrounded by high-density units and high-low (HL) specifying high-density units surrounded by low-density units.

The nearest neighbour distance method, proposed by Skellam (1952) and further developed by Clark and Evans (1954), is frequently used to determine whether a cluster is present. The anticipated average distance is derived using a fictional random distribution of the same number of instances in the same area. The average nearest neighbour ratio is calculated through dividing the observed average distance by the predicted average distance; if the ratio is <1, the case pattern is clustered. The Z-score is another factor indicating the level of clustering, where a high absolute Z-score denotes a high level of clustering (Guo *et al.*, 2013). In addition, the epizootic direction of spread can be detected by calculating the standard deviational ellipse, showing the dispersion in two dimensions of the mean centres; if two species are involved, the Watson-Williams test (Zar, 1999) can be applied to determine whether the mean centres of each species rotate at different angles. A

Z-test may be assessed to check whether the epizootic direction of the spread is different between the species. The cumulative mean direction and circular variance of the mean centres can also be calculated (Guerra *et al.*, 2003).

A spatial autocorrelation study on rabies case data can determine whether, and to what extent, the occurrence of rabies is spatially correlated. The findings indicate that the geographical aggregation studies should be considered a priority for rabies prevention and management. Attention should also be concentrated on regions with a high prevalence of rabies. In the Sultanate of Oman, Moran's I was applied from 2006 to 2010 to calculate the spatial distribution of each species, with a Z-test used to determine the statistical significance. There was no discernible clustering of confirmed rabies cases across all species with Moran's I at 0.0359 and p=0.1189 and also no discernible clustering across different species with I<0.0345 and p>0.1362 (Hussain *et al.*, 2013). In several districts of the Indonesian archipelago, human cases were found to be highly clustered with Moran's I at 0.47 and p=0.005 (Ward, 2014). A LISA test for bat-borne rabies cases, conducted between 2003 and 2013 in two regions of Chile, Metropolitana and Valparaiso, resulted in Moran's I of 0.0857 and 0.0977, respectively (Alegria-Moran *et al.*, 2017). Although this demonstrated a significant positive geographical association, none of the findings were statistically significant. Ellipsoids for bat rabies spatial density in Chile demonstrated a particularly strong relationship with metropolitan regions (Escobar *et al.*, 2015). The geographic heterogeneity of rabies cases in the state of Ceará, Brazil are shown in Figure 2, which illustrates the four spatial patterns HH, LL, HL and LH (Cavalcante *et al.*, 2019).

Spatial regression analysis

Spatial regression analysis is the primary method for the study and exploration of the geographical connection between estimated values; standard regression techniques are inappropriate for spatial analysis due to the spatial dependence and spatial variety of objects (Kanankege *et al.*, 2022). These methods include simultaneous autoregressive, conditional autoregressive and spatial moving-average models. Through the lens of geography or ecology, these analytical approaches primarily allow the study of the relationship between the spatial distribution of incidence or death from disease on the one hand, and various environmental/socioeconomic factors on the other (Raghavan *et al.*, 2016).

Temporal analysis

Temporal aggregation analysis

Temporal aggregation analysis includes two foci: the degree of circular distribution and that of the concentration. The former is generally used to analyse data with periodic changes testing whether or not they show a tendency of cyclical, centralized distribution. Each original piece of information is regarded as that of a position on the circumference through angle conversion. The circular distribution method is suitable for diseases with unimodal or slightly bimodal distribution and is often used in the study of infectious diseases with seasonal trends (Polupan *et al.*, 2019). However, this approach cannot give reasonable results for diseases with multiple peaks, which are similar in an observation period; in this case, some studies propose splitting multiple peaks and analyzing them separately to obtain more accurate results. Theoretically, the 95% reference value range calculated as mean angle ± 1.96 standard deviation (SD) is more appropriate to represent the peak onset date. The concentration degree approach, on the other hand, deals with the degree of aggregation of a disease in one year using m as an indicator of the seasonal intensity at the onset time. This indicator can be calculated from the ratio of the monthly incidence to the annual incidence and takes a value between 0 and 1. The higher the m, the stronger the seasonality of the onset time, and the lower the m, the more distributed the onset time. The disadvantage of the concentration degree method is that it only shows the degree of the seasonality of the onset time of the disease in question, while the specific aggregation time cannot be estimated as this requires a combinatorial approach (Arias-Orozco *et al.*, 2018; Mogano *et al.*, 2022).

Time series analysis

A time series is constituted by trend, seasonality and error components and can be statistically characterized as follows:

$$Z_t = T_t + S_t + E_t \tag{3}$$

where Z_t is the observed data in period t; T_t the trend component; S_t the seasonal component; and E_t the part that the model did not account for, also known as the error or random residual.

The time series decomposition of bat-borne rabies in Chile from 2003 to 2013 revealed that the highest and lowest risk is in March and in July, respectively, which suggests that the cases tended to occur more frequently during the hot season (from October to March) and less frequently during the cold season (from April to September) (Alegria-Moran *et al.*, 2017). Regression analysis of monthly dog cases in India revealed seasonal volatility, with high numbers of cases in March and August (Brookes *et al.*, 2018). A spatial and temporal analysis of dog rabies cases reported between 2015 and 2019 was conducted in a region in the Northeast of Tunisia, where the infection displayed seasonal trends with a robust spring peak followed by weaker summer and winter peaks (Hassine *et al.*, 2021). To evaluate the cyclical trend in the data, a centred moving-average was used for seasonal numbers of the cases, with variance and the *F*-test employed to determine the seasonality of rabies incidence (Hassine *et al.*, 2021). A veterinary study in the State of Tocantins, Brazil, conducted from 2006 to 2019, broke down the cattle cases seasonal, and residual components (Figure 3) and found that the average number of cases was lower from April to June (Dos Santos *et al.*, 2022); however statistical significance was not reached (p>0.05).

The autoregressive integrated moving-average (ARIMA) statistical models (Brockwell and Davis, 2002) are used to examine and predict time series data. They offer a simple yet efficient method for creating precise time series forecasts since they directly handle a variety of typical time series data. It is common to use the notation ARIMA (p, d, q), where p represents the lag order, d the degree of difference and q the order of moving average. The parameters are replaced by integer values to readily identify the particular ARIMA model being employed. A parameter can have a value of 0, which denotes that the model should not use that specific component. This means that ARIMA models might be configured to serve the same function as an autoregressive moving-average (ARMA) model or even a straightforward autoregressive (AR), integrated (I) or moving average (MA) model. The long short-term memory (LSTM) model has been tested for rabies outbreak prediction (Saleh *et al.*, 2019), whose results indicate that the LSTM model achieved a great result with higher accuracy and lower root mean squared error (RMSE), compared with the standard ARIMA model.

To assess the temporal distribution properties of infectious disease cases and forecast their short-term trend, researchers may utilize the ARIMA models, but the stationarity of the original sequence must be assessed. If it is not stationary, the data should first be checked for transformation and differentiation; second, apply the autocorrelation diagram and partial autocorrelation diagram to identify and select the model; third, carry out parameter estimation and model diagnosis on the selected model; fourth, chose the best model; and finally use the established time series model to forecast the development trend of the infectious disease

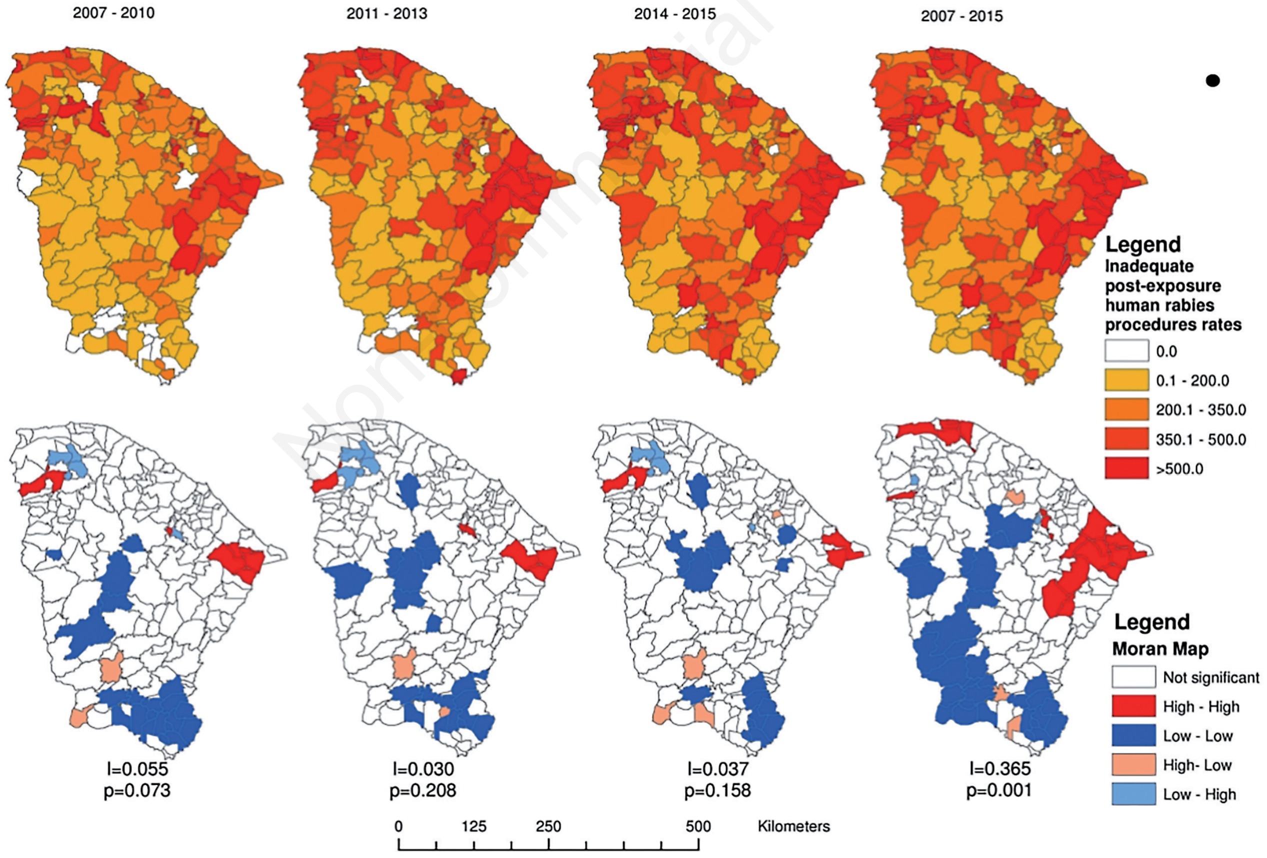


Figure 2. Spatial distribution and Moran map of rabies cases coefficients (per 100000 population of inadequate conducts of post-exposure human anti-rabies services in Ceará, Brazil, (a) 2007-2010, (b) 2011-2013, (c) 2014-2015 and (d) 2007-2015 (adapted with permission from Cavalcante *et al.*, 2019).

cases. For the rabies cases in the Sultanate of Oman from 2006 to 2010, a fitting of 16,384 candidate models was required to find the optimal ARIMA model (identification). The best fitting model was acquired and the statistics showed that each model coefficient was significant at $p < 0.001$ (Hussain *et al.*, 2013). For the Tocantins State study in Brazil, the ARIMA could forecast the rabies cattle cases in 2022. All monthly records for this disease stayed within the anticipated 95% confidence interval (CI) in 2020 and 2021 (Dos Santos *et al.*, 2022).

Mathematical dynamics model

The susceptible-infected-recovered (SIR) model (Kermack and Mckendrick, 1927) is the most widely used method for analyzing the dynamic transmission features of infectious diseases. The model simulates the movement of individuals between susceptibility, infection and recovery based on ordinary differential equations, such as:

$$\frac{dS}{dt} = -\beta\frac{SI}{N} \tag{4}$$

$$\frac{dI}{dt} = -\beta\frac{SI}{N} - \gamma I \tag{5}$$

$$\frac{dR}{dt} = \gamma I \tag{6}$$

$$N = S + I + R \tag{7}$$

where N defaults to a constant value; the natural parameter β indicates the likelihood of being susceptible (S) compared to being infected (I) and the parameter γ reflects the probability of being infected (I) compared to recovered (R). These integers represent the number of people in the relevant population. Zhang *et al.* (2011) expanded the basic model by including the condition "exposed (E)" creating the susceptible-exposed-infected-recovered (SEIR) model.

Based on the seasonal and geographic variability of rabies incidence in China, Zhang *et al.* (2011, 2012a, 2012b) investigated the dynamics of rabies transmission and how rabies spreads between dogs and from dogs to humans. They first constructed a database of dogs with variables such as birth rate, immunization loss rate, time of infection of an infected person, exposed individuals (infected or susceptible), natural mortality, vaccination rates and disease-related mortality using the human SEIR model (Zhang *et al.*, 2011). Then, a human-dog contact diffusion model was developed to analyze the effect of canine migration on the geographical spread of rabies (Zhang *et al.*, 2012b). Finally, a susceptible-exposed-infected-recovered-susceptible (SEIRS) model with periodic transmission rates was employed to examine seasonal rabies outbreaks (Zhang *et al.*, 2012a).

Methods combining genomic and epidemiological data

Whole-genome sequencing of viruses is a valuable method for analysing viral evolution and tracking outbreaks (Brunker *et al.*, 2018b; Nahata *et al.*, 2021). A systematic analysis of epidemiological and pathogen genetic sequence data can describe the temporal dynamics of canine rabies and reveal its spatial transmission mechanism (Biek *et al.*, 2007; Bourhy *et al.*, 2016; Real *et al.*, 2005; Yu *et al.*, 2012). Gene sequencing was performed on rabies-positive specimens and several strains were plotted using disease mapping to analyze the transmission (Zhang *et al.*, 2014). In addition, analysis and epidemiological modelling based on phylogenetic methods can define and anticipate the spatial spread of rabies, evaluate possible influencing factors and assess the impact of rabies management (Talbi *et al.*, 2010).

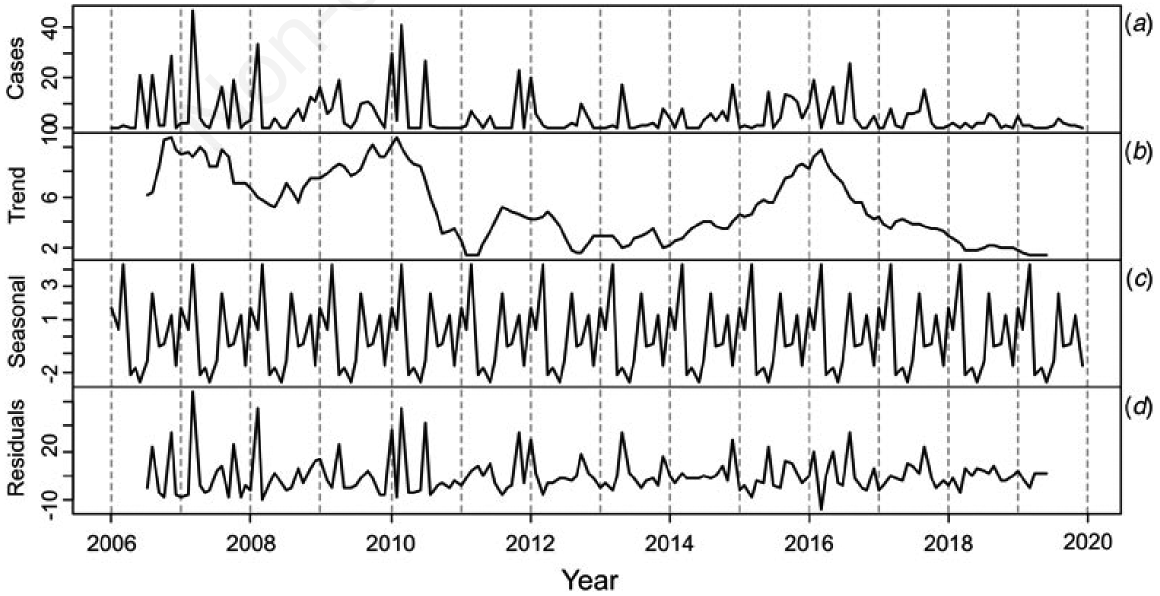


Figure 3. Decomposition of the time series of cattle rabies cases in Tocantins state, Brazil, 2006–2019. (a) Original series, (b) trend component, (c) seasonal component, and (d) residual component (adapted with permission from Dos Santos *et al.* 2022).

Spatiotemporal analysis

Knox spatiotemporal interaction model

Spatiotemporal models deal with data collected across both time and space generating dynamics that result in large-scale spatiotemporal patterns including modes and transitions between the modes. The Knox method (Knox and Bartlett, 1964) is a global spatiotemporal aggregation detection method. It artificially sets spatial thresholds and time threshold that bridge all event points in pairs calculating the spatial distance between point i and point j and a corresponding temporal distance t_{ij} between two points. When, s_{ij}? s, the event points are considered to be adjacent in space and when t_{ij}? t, the event points are considered to be adjacent in time. The logarithm of events of different categories is then counted giving the logarithm of the adjacent events in space and time giving the Knox index, which tells whether the events are adjacent in time and space.

The setting of the spatiotemporal threshold plays a key role in the results of the Knox test, which determines at which spatiotemporal scale the null hypothesis (Pearson's chi-squared (χ^2) test) will be rejected or accepted. Spatial thresholds are usually determined empirically or draw on research results from other fields, such as incubation periods and transmission characteristics. There are also other relevant threshold determination methods, such as the average nearest neighbour and the average critical value of Ripley's K-function. The greatest disadvantage of the Knox index is that its results are affected by changes in the exposed population; however this is not efficient for infectious diseases with long incubation periods and high incidences.

Statistical analysis of spatiotemporal scanning

Through disease mapping, it is intuitively possible to determine whether a disease is spatially grouped, while further clustering analysis is necessary to determine the precise clustering. The commonly used analysis method for spatiotemporal aggregation is the spatiotemporal rearrangement scan statistic using SaTScan software (Kulldorff, 1997), which can pinpoint places and times of spatiotemporal aggregation. It is assumed that case distributions follow the Poisson distribution and that the defined scan window is cylindrical (the approach relies on a cylinder with the bottom corresponding to geographic space and the height to time). For each scanning window, the expected number of cases is determined using the population and the actual number of cases. The predicted and the actual number of cases arrive at the log likelihood ratio and the relative risk. A disease can be scanned and tailed through the movement and the modification of the scanning window to detect the time and geographical location of all cases (Kulldorff *et al.*, 2006). SaTScan can monitor diseases geographically and detect whether or not they are randomly dispersed in time, space or spatiotemporally. This method can thus indicate if the phenomena under study are clustered and assess the statistical significance of risk. Other advantages include repeated time-periodic disease monitoring and the ability to signal outbreaks at an early stage.

The statistical approach of spatiotemporal scanning applies to the study of almost all types of disease. In this way, Hikufe *et al.* (2019) found a cluster of animal rabies epidemics centred in northwestern Namibia, while Olugasa *et al.* (2009) detected rabies-infected cases due to dog bites in Ilorin, Nigeria within a 3-km radius of the city's central slaughterhouse and its nearby open-air beef market. In addition, it is possible to observe the spatial and temporal variations of rabies risk by comparing spatial scan statistics results for two distinct periods at the same location. This was the way it was found that the risk area of animal rabies in Minas Gerais, Brazil was at a growing phase after the millennium shift (Olugasa *et al.*, 2009). In addition, county level clusters in the raccoon rabies enzootic zone in the United States was shown to have a higher cross-species transmission rate when studied from 2007 to 2011 using a spatial-temporal scan statistics (Wallace *et al.*, 2014).

Cluster detection based on spatiotemporal density

Spatiotemporal scan statistics need to presuppose the probability distribution model of the data, and the results are greatly affected by the scan window, which cannot describe the location and shape information of the spatiotemporal clusters in detail. To overcome these problems, additional methods for spatiotemporal density-based clustering have been proposed. Density is used as a measure of similarity between entities, and spatiotemporal clusters are regarded as a series of high-density connected regions divided by low-density (noise) regions. A commonly used method is density-based spatial clustering of applications with noise (DBSCAN), which also can become spatiotemporal DBSCAN (ST-DBSCAN) by adding the time dimension. It assumes that i and j are two core points that are directly density-reachable and if the average distance of the non-spatial attributes of two neighbourhoods of these core points is less than a threshold, clustering is revealed. ST-DBSCAN does not require a priori assumption about the distribution model of the data and can detect clusters of arbitrary shapes. Detecting 480 clusters, Guo *et al.* (2013) were the first to use ST-DBSCAN to analyze the distribution of rabies cases in China from 2005 to 2011. The DBSCAN methodology is very sensitive to user-defined parameters, whose selection thus is critical. The disadvantage is that this approach needs to set space, time, non-spatial distance thresholds and density thresholds. At present, DBSCAN is mostly used in the field of road traffic, and its application in disease aggregation is still in its infancy.

Factors influencing the dynamics of rabies

It is believed that both environmental and anthropogenic factors contribute to rabies (Yu *et al.*, 2020). Environmental factors include elevation, temperature, land cover, etc (Guo *et al.*, 2018a), while anthropogenic factors include population density, economic development level and so on (Wilson *et al.*, 1997). The generalized additive models may be used to forecast the geographic risk regions for the spread of rabies to quantify the relationship between monthly occurrences of rabies and explicable factors. Estimating the temporal and spatial trends can help to predict the future risk trend of rabies and implement efficient epidemic prevention and control measures.

Environmental variables

The main steps for comparing the data of viral phylogenies and environmental landscape are i) extracting spatiotemporal information from phylogenies; ii) estimating dispersion and epidemiological statistics; iii) computing environmental weights; iv) correlation analysis; and v) significance testing based on randomization (Dellicour *et al.*, 2016). The temporal and spatial distribution of human rabies has been found to be positively correlated with temperature (Guo *et al.*, 2018a) and negatively correlated with altitude (Yao *et al.*, 2015). Outbreaks starting during the dry season are generally more severe than during the rainy season (Gabriele-Rivet *et al.*, 2021). The influence of landscape elements on disease dynamics lessens as population immunity rises (Rees *et al.*, 2013).

Mountains and rivers function as barriers to the development of rabies pandemics as such features can limit the transmission rate of the virus by as much as seven times (Wheeler and Waller, 2008). The transmission of raccoon rabies has been linked to wetlands and forest cover, with rabies spreading more slowly in certain places (Dhand and Ward, 2012; Smith *et al.*, 2005). Plateaus and rough rocky terrain have been identified as deterrents for animals, such as stray dogs. Even in plain areas, rabies scarcely spread through stray dogs if the distance between communities is greater than their normal range. This implies that prevention and management strategies in mountains, plateaus and plains are different. Controlling stray dog migration and their reproduction is crucial for mountainous areas, especially in those with rocky and wooded terrain. While, on the plains, the goal is to manage the link between the rabies-infected communities and those that are unaffected (Guo *et al.*, 2018a). Environmental factors can be integrated with genetic data into phylogeographic frameworks to quantify how different attributes influence the transmission processes (Nahata *et al.*, 2021).

Socioeconomic variables

The socioeconomic characteristics include the human population density, annual gross domestic product, ratio of illiteracy, etc. (Guo *et al.*, 2018a). Economic growth is thought to be another anthropogenic element that contributes to the spread of rabies (Yao *et al.*, 2015), which is more common in less developed areas (Arias-Orozco *et al.*, 2018; Hampson *et al.*, 2015). Canine rabies has been found to have a positive correlation with the human population density (Hikufe *et al.*, 2019) but its local transmission is also related to the canine population size and distribution (Brunker *et al.*, 2018a; Yin *et al.*, 2012; Zhu and Liang, 2012). Rabies introduction in areas close to communities results in larger epidemics (Gabriele-Rivet *et al.*, 2021). The effectiveness of vaccination campaigns, status of vaccine supply and poor rabies awareness should also be included in the list of socioeconomic variables (Mulatti *et al.*, 2011; Polupan *et al.*, 2019).

Transportation variables

Traffic may contribute to canine rabies transmission (Brunker *et al.*, 2018a). Distance to the nearest road has been linked to the spread of the virus (De Andrade *et al.*, 2016). The collection of variables has expanded to include accessibility and transportation parameters, such as the Euclidean distances from a hamlet to the road network, the closest city centre and the closest hospital or clinic. Public health initiatives, such as various programmes for disease prevention and control, are in reality constrained by traffic patterns and accessibility. In Tunisia, dogs who test positive for the rabies virus have been observed to be spatially connected to roads and irrigated areas (Hassine *et al.*, 2021). Since residential rubbish in Tunisia is commonly dumped along primary and minor roads, it serves as the main source of food for stray dogs, as do also formal waste disposal sites. Attraction of pack of canines to such places supports the spread of the canine rabies virus. Conversely, high road traffic volumes act as functional barriers to dog migration (Hassine *et al.*, 2021; Laager *et al.*, 2018).

Epidemiologic variables

The epidemiologic characteristics include the least geographical distance to another case, the least temporal distance to the most recent case, and the least spatiotemporal distance to the nearest case. Correlations between infected areas may be discovered using epidemiological variables. Furthermore, the separation from the closest or most recent case reveals the amount of potential risk that has been disclosed by previous cases. Two independent but related approaches for recreating the dynamics of epidemics utilizing geographical, temporal and genetic data have been developed for spatial epidemiological models of transmission and for basic genetic drift models (Mollentze *et al.*, 2014). The first approach uses coalescent models, which include a diffusion model for the pathogen's spatial evolution and a population dynamic model to connect the pathogen's demography to its development, while the second reconstructs the transmission tree directly reflecting "who-infected-whom". It also recognizes the epidemiological processes that control the interaction of host and disease and the host population structure (Mollentze *et al.*, 2014).

Data sources

Information on human rabies cases in China can be collected from the yearly reports of the Chinese Center for Disease Control and Prevention (China CDC) as done by Yu *et al.* (2012) or the China National Notifiable Disease Reporting System (http://www.stats.gov.cn/). In Chile, there is an electronic database with rabies records from the Instituto de SaludPública de Chile (Escobar *et al.*, 2015). Rabies cases in the Democratic the Republic of the Congo can only be collected from the veterinary clinic of Ngaliema, the Office for Rabies Vaccination and Control (OVCR) at the veterinary clinic of Gombe, the Institut National de Recherche Biomédicale (INRB) and the Veterinary Laboratory of Kinshasa (LaboVetKin)(Twabela *et al.*, 2016).

In Tunisia, the National Laboratory of Rabies Diagnostic at Institut Pasteur in Tunis (IPT) (http://www.pasteur.tn/) and the Directorate-General of Veterinary Services (DGSV) publish annual reports detailing animal rabies cases and dogs having been vaccinated. The Basic Health and Care Management division of the Ministry of Public Health [Direction des Soins et de Santé de Base (DSSB)] in Tunisia supplied statistics on Post Exposure Prophylaxis (PEP) instances. Some influencing factors can be acquired from the DIVA-GIS website (https://www.diva-gis.org/) and the Tunisia Agriculture map (Kalthoum *et al.*, 2021).

Dog population data in Thailand can be obtained from local administration organizations (LAOs) at http://www.thairabies.net/trn/, while the Land Development Department (LDD) provides geographic information, including administrative divisions and highways (http://www.lddservice.org/lddapp/client/#/map) (Thanapongtharm *et al.*, 2021). The Worldpop project (https://www.worldpop.org/) is also helpful as it provides raster maps of human population density with a 100-m resolution (Thanapongtharm *et al.*, 2021). Other factors and data sources are listed in Table 1 (modified from Guo *et al.*, 2018a), with China as an example.

Descriptive statistics of the distribution of rabies cases can be performed by SPSS software (Twabela *et al.*, 2016) and SaTScan software (Kulldorff *et al.*, 2005) provides the discrete Poisson spatial model for spatial analysis. It uses the space-time permutation model to identify regions and times where there is a substantial concentration of dog rabies cases (Bouslama *et al.*, 2020). The R software's package "spdep" can be used for geographical analysis (Kalthoum *et al.*, 2021) and the average nearest neighbour approach for determination of separations between canine rabies cases. Using the spatial point pattern analysis (spatstat) tool in the R and the open source geographic information systems (QGIS) software systems, it is possible to determine the typical shortest Euclidian distance between the location of rabid dogs and the nearest feature (Hassine *et al.*, 2021). The R "secr" package has been used to calculate the dingo density in Australia using the maximum pseudo-likelihood spatially explicit mark-resight analysis (Gabriele-Rivet *et al.*, 2020). Furthermore, R software is useful for mapping the geographic distribution of canine and human rabies cases, while the Kruskal-Wallis (Breslow, 1970) and Chi-square tests (Mchugh, 2013) can be employed for descriptive comparisons between their frequencies; p values < 0.05 are regarded statistically significant at the 95% confidence level. Associations between the various factors can be evaluated using the correlation test and the Joint point software for trend analysis (Kalthoum *et al.*, 2021).

The geographical distribution of cases of rabies with laboratory confirmation may be described using a semivariogram. A variety of spatial lag lengths have been used to generate directed semivariograms with the Variowin software (Hussain *et al.*, 2013). The geostatistical analyst tool from the ArcGIS software (ESRI, Redlands, CA, USA) can be used to construct and display interpolated surfaces of anticipated case occurrences (Hussain *et al.*, 2013). The Bayesian Markov chain Monte Carlo (MCMC) approach, which is included in the BEAST software package (Drummond and Rambaut, 2007; Bouckaert *et al.*, 2019) that supports to estimate population evolutionary rates and population growth models (Drummond and Rambaut, 2007; Yu *et al.*, 2012; Feng *et al.*, 2020). An open spatial computing and data resource (OSCAR) platform has been developed to offer a framework for integrating spatial computing capability and data aggregation for emergency public health management (Guo *et al.*, 2018b).

Typical cases

Three representative case study areas, *i.e.* Tunisia in Africa, China in Asia and Brazil in South Africa, were chosen to show the application of the spatial, temporal and spatiotemporal analysis of rabies.

Cases in Africa: Tunisia as example

The progression of canine rabies cases from 2012 to 2018 in Tunisia is depicted in Figure 4 (Bouslama *et al.*, 2020; Kalthoum *et al.*, 2021). Here, the North and the Centre-east of the nation have produced the majority, with four statistically significant clusters found using spatial analysis. There was a noticeable shift in the spatial patterns from year to year. When the north-eastern governorates, which were rabies-free in 2011, became endemic even though all of the spatiotemporal clusters found were in the North and the Centre-east (Bouslama *et al.*, 2020). A possible return of rabies in some governorates or a viral transmission from nearby

Table 1. List of variables influencing rabies distribution.

Category	Dataset	Data sources
Environmental variables	Average temperature (and other natural variables, such as digital elevation, digital slope, etc.)	United States Geological Survey (USGS) The Moderate Resolution Imaging Spectroradiometer (MODIS) onboard the Terra/Aqua satellites The NASA/USGS Landsat Program
Socioeconomic variables	Human population density Ratio of illiteracy Annual Gross Domestic Product (GDP)	National Statistics Bureau
Transportation variables	Distance to the road network Distance to the city centre Distance to the nearest hospital	National Administration of Surveying, Mapping, and Geoinformation
Epidemiologic variables	Minimum spatial and temporal distance to nearest cases	Rabies Surveillance data from the Chinese Center for Disease Control and Prevention (China CDC)

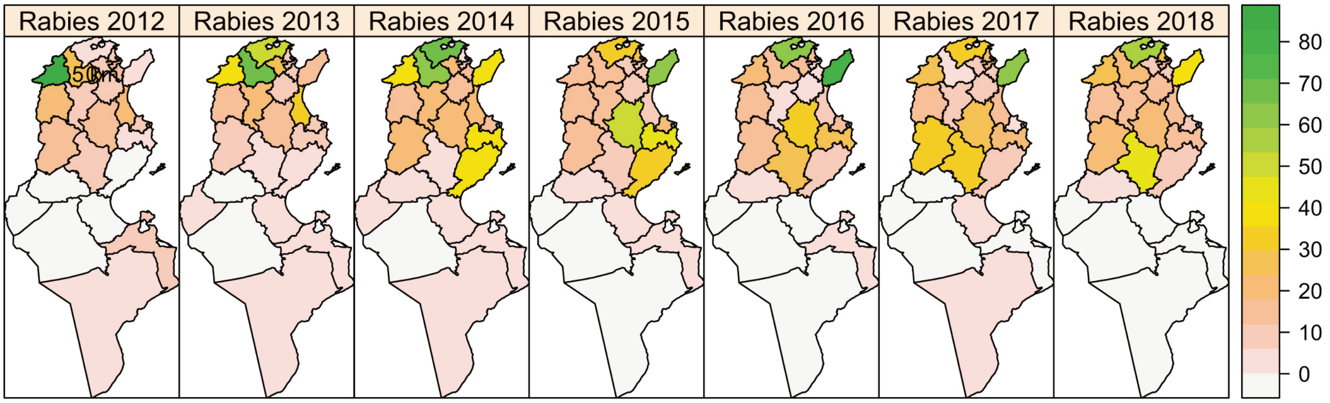


Figure 4. Spatial distribution of animal rabies cases in Tunisia from 2012 to 2018 (adapted with permission from Kalthoum *et al.*, 2021).

governorates might explain the spread of disease. Two geographically distinct phylogenetic forms of the canine rabies virus have been identified in Tunisia, one in the north-western part of the country and the other in the North-east, Centre and South. As a result, non-overlapping clusters may represent either distinct phylogenetic variations or a modification of the geographic distribution of previously discovered phylogenetic variants. This idea might be confirmed by a phylogeographical analysis of canine rabies isolates from 2011–2016, especially in the North and Centre-east (Bouslama *et al.*, 2020).

Cases in Asia: China as example

In China, 30 of the 31 provinces (excluding Tibet) have reported human rabies cases between 2004 and 2013 (Guo *et al.*, 2018a; Yao *et al.*, 2015). The high-incidence provinces were primarily in the southern, eastern, and eastern parts of central China (Figure 5). Overall, the annual incidence decreased in the provinces with high incidence but increased over the 10 years in the provinces with low incidence (Guo *et al.*, 2018a; Yao *et al.*, 2015). During the temporal analysis, the monthly incidence revealed a distinct seasonal pattern with peaks in the summer and fall, particularly in the months of August through October every year. The annual incidence curve demonstrate that human rabies had been increasing fast between 2004 and 2007 but dropped precipitously in 2008 and then been steadily dropping (Yao *et al.*, 2015).

Cases in South America: Brazil as example

Examination of the equine population's distribution by state in Brazil found greater relative frequencies in the Southeast (43.6%) and the Midwest (26.7%), while the Northeast with 8.3% of cases and the North with 9.4% of cases had the lowest relative frequencies. The notification of rabies cases in horses in Brazil showed a progressive increase between 2010 and 2013, with a dramatic spike in 2012 and 2013. There was an apparent linear drop in the following years, with decreasing values of notified instances up to 2015. The corresponding levels saw another rise between 2016 and 2017. The Midwest exhibited a tendency of declining instances of rabies in horses in the examination of the temporal patterns of Brazilian areas, whereas the North-east showed a trend of increasing cases. Only two states indicated a decline in the trend of rabies in horses and only one revealed a rise in instances; the others showed stable patterns (Oliveira *et al.*, 2022).

Discussion

Spatiotemporal aggregation analysis of diseases has become a very popular field and the corresponding statistical methods are constantly being improved. Most of those discussed in this paper are widely used to explore the spatial and temporal distribution patterns of infectious and chronic non-communicable diseases. For example, Mshelbwala *et al.* (2020) produced a meta-analysis of the methodological characteristics of geographical, epidemiological studies of rabies in animals and humans reviewing a total of 81 publications from 27 nations. They noted that passive surveillance data were employed in most investigations and just six publications analysed time series data to identify seasonal rabies incidence or trends. To identify geographical clustering and hotspots, only 21% of research employed spatial analytical methods, with only 9% of the research papers producing predictive maps of the global distribution of human and animal rabies, although 35% of the studies modelled spatial correlations between rabies and various risk variables. Importantly, none of the spatial modelling studies adjusted their findings using all clustering criteria (Mshelbwala *et al.*, 2020)

Descriptive analysis of rabies geographical distribution is widely highlighted (Bouslama *et al.*, 2020; Gabriele-Rivet *et al.*, 2020; Guerra *et al.*, 2003;). On the other hand, with reference to raccoon rabies epidemics, Smith *et al.* (2002) introduced a novel method integrating huge datasets, GIS and stochastic simulations to develop predictive, probabilistic models for geographical dynamics and forecast of temporal evolution of the disease. To stop

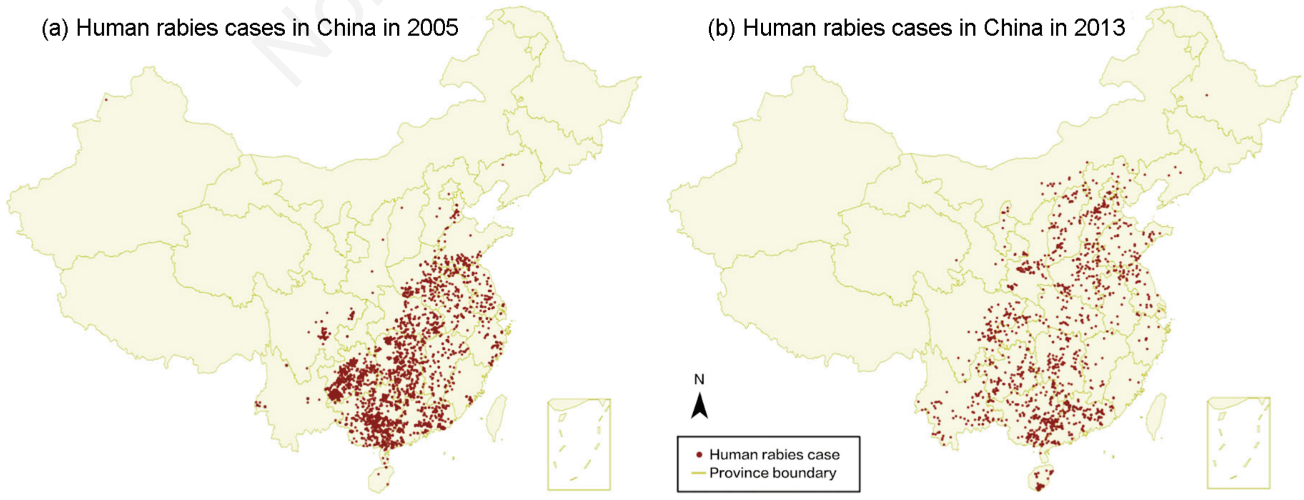


Figure 5. Spatiotemporal distribution of human rabies cases in China in (a) 2005 and (b) 2013 (adapted with permission from Guo *et al.*, 2018a, modified).

the spread of rabies, monitoring effectiveness is just as crucial as vaccine coverage (Bouslama *et al.*, 2020). According to research by Escobar *et al.* (2015), all reported instances of rabies in dogs and cats are caused by bat-borne rabies, at least in Chile. Regrettably, recent research from other countries in South America reveals has not borne out these results as efforts to reduce bat populations have not halted the spread of rabies. In this connection, it should be borne in mind that bat eradication might result in ecological imbalance, which could be detrimental to agriculture and public health.

Competing species, host population redistribution due to habitat change, host immunization and host population decrease due to various control activities all impact transmission. Initiatives should therefore place priority on education to control rabies through limiting exposure and boosting immunization rates. The spatial and temporal dynamics of isolates are also important for studying the dynamics of case distribution, which could be implemented by Bayesian analysis to estimate the origin and expansion of isolates and to determine whether or not some isolates have derived from a common ancestor (Gong *et al.*, 2010). Indeed, the Bayesian phylogeographic inference framework can incorporate the spatial and temporal dynamics of gene flow.

Several issues should be noted when selecting and applying spatiotemporal or spatial statistical methods. First, the methods introduced in this paper are all applicable to the analysis of point data, *i.e.* specific case data with locations (for example the data shown in Figure 5); in practice, it is often easy to obtain surface data after regional cases are summarized (for example the data shown in Figure 4). Spatial autocorrelation methods and the spatiotemporal scanning statistics are also suitable for cluster analysis of surface data. Provided that the surface data need to be processed by points, the centroid of the area can be used for calculation. However, when the spatial resolution of the surface data is lower than the point data, the ability of spatiotemporal aggregation detection weakens. Second, the statistical methods discussed in this paper are still under development. When conducting an exploratory analysis of disease clustering, it is recommended to use a combination of methods to improve the accuracy of identification as much as possible to avoid missed and false positives in clustered areas.

Conclusions

With the continuous accumulation of spatiotemporal data, improvement of spatiotemporal statistical methods and upgrading of statistical software, the application of spatiotemporal aggregation analysis of disease distributions has continued to develop. In the future, efforts should be continued to strengthen the acquisition of data from the spatiotemporal disease dimensions, continuously improve the refinement of data collection and conduct in-depth research in this area, so that it can play a greater role in public health monitoring and decision-making.

The ultimate purpose of the analysis for rabies cases is to determine the spatial heterogeneity characteristics of epidemics to be able to generate early warnings for future high-risk locations. Dynamical models and phylogenetic analysis can be employed as key tools to explore the transmission mechanisms and how various variables affect rabies. Geographical analysis is of key importance, including mapping and analysis by aggregation and regression techniques. The factors that may influence the dynamics of rabies are both environmental and socioeconomic, with transportation and epidemiological variables playing key roles. The spatial and temporal distribution, spatial aggregation, spatial autocorrelation and mathematical models can simulate the dynamic transmission of rabies, support the formulation of public health measures and strategies and protect health and safety of exposed populations.

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