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Environmental suitability of *Yersinia pestis* and the spatial dynamics of plague in the Qinghai Lake region, China

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Abstract: Plague, a highly infectious disease caused by *Yersinia pestis*, has killed millions of people in history and is still active in the natural foci of the world nowadays. Understanding the spatiotemporal patterns of plague outbreaks in history is critically important, as it may help facilitate the prevention and control for potential future outbreaks. This study's objective was to estimate the effect of the topography, vegetation, climate, and other environmental factors on the *Y. pestis* ecological niche. A maximum entropy algorithm spatially modelled plague occurrence data from 2004–2018 and the environmental variables to evaluate the contribution of the variables to the distribution of *Y. pestis*. Our results found that the average minimum temperature in September (–8 °C to +5 °C) and the sheep population density (250 sheep per km^2) were influential in characterising the niche. The rim of Qinghai Lake showed more favourable conditions for *Y. pestis* presence than other areas within the study area. Identifying various factors will assist any future modelling efforts. Our suitability map identifies hotspots and will help public health officials in resource allocation in their quest to abate future plague outbreaks.

Keywords: infectious diseases; MaxEnt; niche modelling; zoonosis

List of abbreviations

AUC = area under the curve; **GIS** = geographic information system; **MaxEnt** = maximum entropy; **PC** = principal component; **PCA** = principal component analysis; **ROC** = receiver operating characteristics; **SPSS** = Statistical Package for Social Sciences; **TSS** = true skill statistics

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Plague, caused by the gram-negative bacterium *Yersinia pestis*, is a highly infectious zoonotic disease (WHO 2004). This plague is classified as class A "infectious disease" according to the infectious diseases prevention and control law of the People's Republic of China, due to its serious nature (Xinhua 2004). Due to its high infectivity and fatality rate, plague has played an important role in human history. Three large-scale pandemics have occurred since the 6th century causing millions of deaths, in addition to numerous smaller epidemics and sporadic cases (Zietz and Dunkelberg 2004; Stenseth et al. 2008). The plague epidemic in China reached its peak between 1900 and 1949, affecting more than 500 counties in 20 provinces and causing 1.15 million human cases and 1.02 million deaths (Ji 1988). In July 2009, a large-scale epidemic was avoided in Xinghai county in Qinghai province due to the immediate government intervention (CNR 2009).

The highest diversity and most significant area of plague foci is in China, which is hosted by different groups of rodents, including marmots, ground squirrels, gerbils, voles, and rats (Wong et al. 2009). Therefore, it is important to improve our understanding of the plague in an effort to effectively manage and prevent the disease. A total of 468 human plague cases with 240 deaths were reported in Qinghai province between 1958 and 2014 (Wang et al. 2016). Based on the history of plague in Qinghai, 162 cases originated from marmots (34.62%), 39 cases originated from Tibetan sheep, goats and a gazelle (*Procapra picticaudata*) together (rate: 8.33%), 16 cases originated from carnivorous animals (3.42%), and 216 cases of plague were caused by person-to-person transmission (46.15%) (Wang et al. 2016). Notably, hunting, mainly the processing and skinning of marmot and sheep, is a major risk factor for plague in Qinghai. Also, eating undercooked meat is another cause of plague infection (Wang 1999). In the natural foci of plague, such as Qinghai-Tibet, fleas are its main vectors. Besides fleas, other species of blood-sucking arthropods (Argasidae, Gamasidae, Ixodidae, Anopluran, Heteropteran etc.) also harbour the bacterium; still, they do not play a significant role in plague epizootics and epidemics (Dubyanskiy and Yeszhanov 2016).

The enzootic cycle of plague is maintained among rodent hosts and their fleas; however, transmission to humans and other mammals can occur (often during epizootic conditions) through flea bites or direct contact and, in some cases, results in severe morbidity and death (Gage and Kosoy 2005). Recently, the number human cases have declined following the official prohibition of marmot hunting (Xu et al. 2018). However, there has been a paradigm shift in the disease patterns that challenged the initial understanding of plague transmission. For instance, an outbreak of primary human pneumonic plague in 2009 in Xinghai county was introduced by an infected dog (Wang et al. 2011), although, dogs, cats, and other carnivores are referred to as incidental hosts.

Many previous studies have employed the use of spatial epidemiology to predict the potential natural plague foci in the Qinghai – Tibetan plateau (Qian et al. 2014; Lu et al. 2016), most significantly, the application of a geographical information system (GIS), remote sensing (RS), and global positioning system (GPS) technology which have delivered promising outputs (Li et al. 2016). GIS models, such as the ecological niche model (ENM), neural network model, and Bayesian model, have been widely applied in the prediction of infectious diseases (Werner et al. 1984). Also, spatial modelling methods, such as the maximum entropy (MaxEnt), and the genetic algorithm for rule-set production (GARP) require only disease presence/occurrence data (Peterson et al. 2007), and have been used extensively in the field of ecology and conservation to model species distribution and habitat suitability (Hueffer et al. 2020).

Presently, plague is a remerging disease in northwest China, although outbreaks have been rare. An index case in 2014 was a herdsman in Jiuquan city of Subei county who grazed his sheep in a pasture where a widespread plague had been reported among the marmot in recent years (Xinhua 2019a). Also, in Yumen city, western Gansu province, China, a 38-year-old resident died of plague following an outbreak on November 12th, 2019 where two patients from inner Mongolia were diagnosed with pneumonic plague, which was followed by a case of bubonic plague (November 17, 2019) after a farmer hunted wild rabbit in Xilingol League, inner Mongolia (Xinhua 2019b). Therefore, concerns have been heightened to abate future outbreaks in other part of Northwest China.

In this study, we tested the hypothesis that the topography, vegetation, climate, and other environmental factors are thought to influence the spatial distribution and temporal dynamics of plague

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in the Qinghai Lake region (QLR), which is located in the natural focus of the Himalayan marmot. We added the sheep population density to our analyses to represent an additional risk factor in the transmission process. Among the species distribution models, MaxEnt has been shown to provide better identification of suitable versus unsuitable areas when compared to other presence-only modelling methods (Elith et al. 2006; Phillips et al. 2006). Therefore, we used MaxEnt, presence-only niche modelling, to describe the potential distribution of plague foci in QLR.

MATERIAL AND METHODS

Study area

The study was carried out in the QLR in China (36°15'–38°20'N, 97°50'–101°20'E). The region covers an area of ca 55 700 km^2 which includes four counties within three prefectures: Gangcha and Haiyan counties in Haibei prefecture, Tianjun county in Haixi prefecture, and Gonghe county in Hainan prefecture. The elevation ranges from 2 543 m to 5 607 m above the sea level (a.s.l.) (Figure 1) and Qinghai Lake nature reserve lies within our study area with an area of ca 5 000 km^2 for the protection of biodiversity in the area. Our study area's climatic conditions are composed of dry, cold, and long winters, intense solar radiation, and a short frost-free period. Its mean the annual temperature is 0.5 °C and has an extreme low temperature of –31 °C. The mean annual air temperature is 1.7 °C; the highest temperature is recorded in July

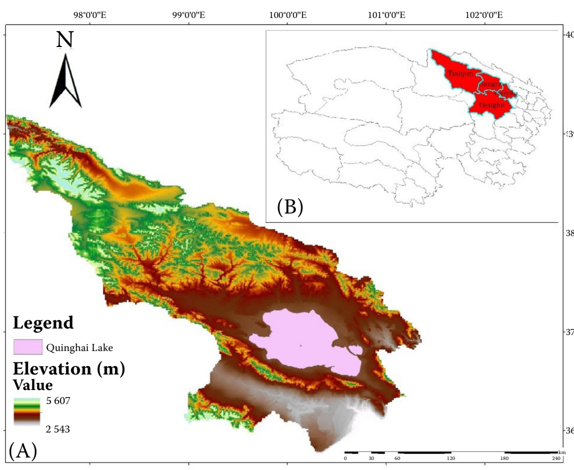

Figure 1. Study area indicating (A) Qinghai Lake region (B) Qinghai province (study area in red)

while the lowest is recorded in January. The average annual precipitation is 580 mm, with 80% of the precipitation occurring in the growing season from May to September (Li et al. 2015). The mainstay of the rural economy in Qinghai is livestock farming which has a history of more than 4 500 years (Miller 2002). Also, a vast area of grassland is the major land cover type accounting for about 63% of the area (Gong et al. 2017). This study area falls within the Qinghai-Tibet plateau natural plague foci of the Himalayan marmot.

Collection of occurrence data and environmental variables

All the occurrence data used in this study were collected from historical records provided by the World Organization for Animal Health at www.woah.org, the World Health Organization (n = 2) and published literature (n = 50) (Qian et al. 2014; Li et al. 2015; Xu et al. 2018). We constructed a database with a total of 52 points, a summary of the data collected between 2004–2018 from *M. himalayan* (n = 32), human (n = 3), *Procapra picticaudata* (n = 6), and *Ovis aries* (n = 11). The data were stored in a Microsoft Excel spreadsheet and then edited and screened to remove records with geocoordinate errors. After removing any duplicate records in the same pixel, we had a total of 45 spatially unique points which were then used in MaxEnt modelling.

The environmental variables used in this study were categorised into: climatic variables, vegetation, host, and geomorphology (Table 1, Figure 2). Climatic variables were extracted from WorldClim v1.4 (2018) obtained from weather stations around the world from 1950–2000 at 30 arc-second resolutions (www.worldclim.org). The extracted climate variables were the monthly precipitation (n = 12), monthly mean, minimum and maximum temperature (n = 36), and derived bioclimatic variables (n = 19). The geomorphology variables, were the elevation, slope, and aspect. The slope and aspect were derived from the elevation raster downloaded from WorldClim (www.worldclim.org) and processed with the spatial analyst toolset in ArcGIS. Each pixel in these rasters represents the value of the measurement for that approximately 1 km^2 area on the Earth's surface. The vegetation variables were the land cover which revealed the proportion

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Table 1. Ecological variables (class, data type and measurement unit) used to predict the plague distribution in the Qinghai Lake region

Classification	Ecogeographical variable	Data type	Unit
	annual mean temperature	continuous	°C
	average minimum temperature in September	continuous	°C
	mean temperature of coldest quarter	continuous	°C
Bioclimatic[a]	annual precipitation	continuous	mm
	precipitation of wettest month	continuous	mm
	precipitation of driest month	continuous	mm
	precipitation of coldest quarter	continuous	mm
	elevation	continuous	M
Geomorphology[b]	aspect	continuous	9 categories
	slope	continuous	%
Host[c]	sheep population density	continuous	sheep/km^2
Habitat[d]	normalized difference of vegetation index	continuous	–
	land cover and use	categorical	22 categories

[a]Source: www.worldclim.org; [b]Source: www.worldclim.org; [c]Source: www.fao.org/livestock-systems; [d]Source: www.gscloud.cn/search

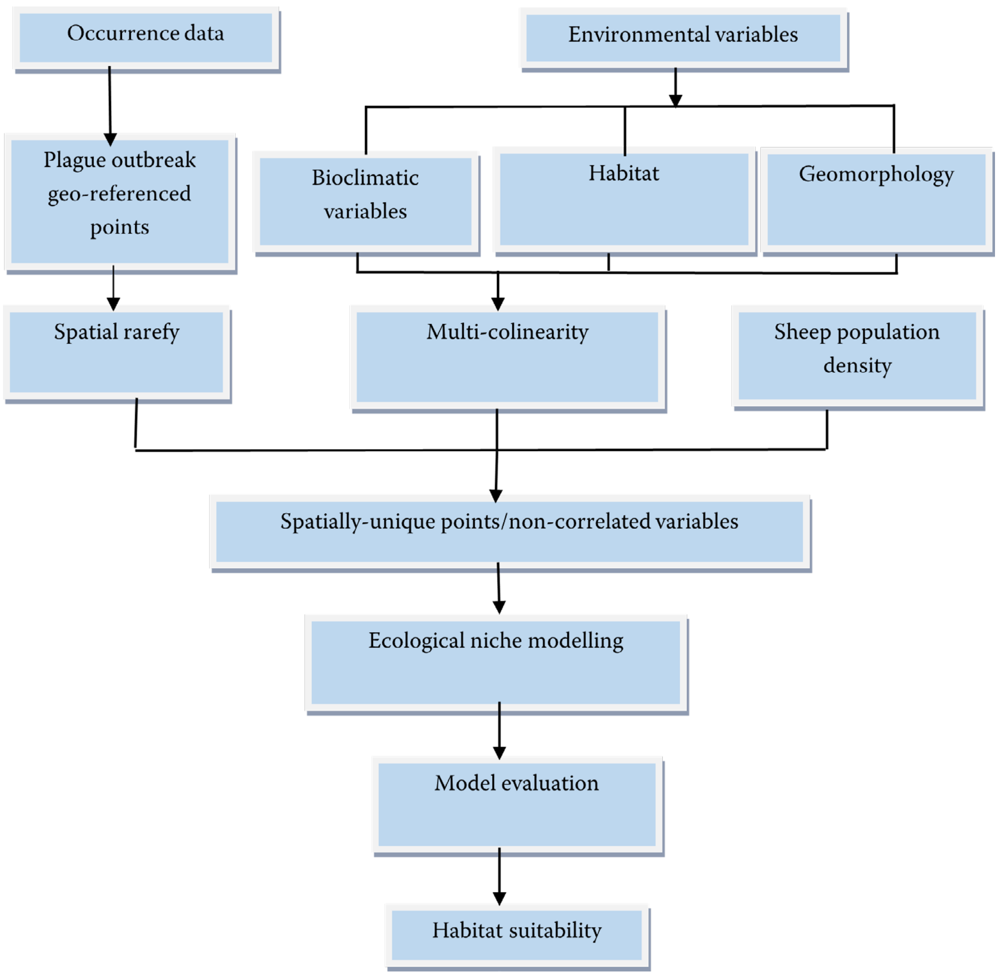

Figure 2. Flowchart for the modelling process with the potential variables

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of grassland and effect of human activities were derived from GlobCover land cover v2.2 (Latham et al. 2014). Also, the amount and productivity of the vegetation were represented by the annual maximum normalised difference of vegetation (NDVI) from 16-day synthetic products from 2004–2014 (available at www.gscloud.cn/search). In addition, the sheep population distribution raster map is available at www.fao.org/livestock-systems.

Data pre-processing

To check the spatial autocorrelation of the presence points, we processed all the points using SDM toolbox v1.1c integrated into ArcGIS v10.3. Filtering was performed by limiting the minimum distance between each pair of occurrence points at 10 km (Pearson et al. 2007; Gao et al. 2022). This helped to address problems associated with spatial sampling bias. Ideally, filtering or thinning removes the fewest records necessary to substantially reduce the effects of sampling bias, while simultaneously retaining the occurrence points with the greatest amount of useful information (Aiello-Lammens et al. 2015; Zeng et al. 2021).

The variable reduction and potential multicollinearity among the environmental variables were checked through a principal component analysis (PCA) (Table 2) using the Statistical Package for Social Sciences software (SPSS v22.0). Multicollinearity may violate statistical assumptions and may alter model predictions (Heikkinen et al. 2006). The non-correlated variables were used for MaxEnt modelling. All the environmental rasters were cut according to the study area using the "extract by mask" tool, verifying that the "processing extent" is the same for each variable within the environment settings to ensure that all the files cover the same area (Jacome et al. 2019).

Table 2. Ranking the number of predictor variables in the principal component analysis

Component	Initial eigenvalues		
	total	% of variance	cumulative %
1	12.571	66.163	66.163
2	3.071	16.165	82.328
3	2.112	11.117	93.446
4	1.058	5.571	99.017

MaxEnt modelling

The maximum entropy (MaxEnt v3.4.1) algorithm was used in this study. The algorithm compares the presence point location with a much larger, unbiased sample of random locations within the area under investigation, the pseudo absence. The MaxEnt model was fitted using bootstrapping runs with a 70/30 partition percentage for the training/testing of the datasets. We selected a random seed to guarantee that the model chooses different sets of presence records for the training and testing per replication. The MaxEnt model parameter settings (auto features, convergence threshold of 0.000 01, the maximum number of background points = 10 000, regularisation multiplier = 1) were used (Phillips and Dudik 2008). The final map was generated using ArcMap v10.2.

To measure the relative contribution of each environmental variable to the predictive model, a jackknife manipulation was performed. The jackknife test help identify the most effective single variable to predict the distribution. There are several methods for assessing the model accuracy, but the most common process involves the use of the area under the curve (AUC) of the receiver operating characteristics (ROC) (Hanley and McNeil 1982; Skowronek et al. 2018) ROC was used to evaluate the discrimination ability of the models and to determine the optimal probability cut-off value for classifying the risk area of plagues. Usually, AUC values of 0.5–0.7 are taken to indicate low accuracy, values of 0.7–0.9 indicate useful applications, and values of > 0.9 indicates high accuracy (Zhao et al. 2013).

RESULTS

Variable assessment

The PCA delivered 4 principal components (PCs) which accounts for 99.02% of the total variance (Table 2), and 45 occurrence data remained and were used for the modelling. Our model, with only two environmental variables (Table 3), was the most discriminative model attaining the highest test AUC of 0.869 with a standard deviation of ± 0.031 when compared with the test AUC in either variable when the variable was used alone or excluded in the model. The two environmental variables,

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Table 3. Contributing variables as predicted by the MaxEnt algorithm

Variable	Contribution (%)	Permutation (%)
Average minimum temperature in September	58.9	76.5
Sheep population density	41.1	23.5

which together contributed to the model, were the average minimum temperature in September (58.9%) and the sheep population density (41.1%). These had the best explanatory power (Table 3, Figure 3).

The plague suitability peaked when the average minimum temperature in September increased from –8 °C to +5 °C, but declined briefly and afterward maintained a constant probability across higher temperatures (Figure 3). The sheep population density response curve showed a gradual upward trend reaching a plateau at about 250 sheep per km^2 (Figure 3).

Figure 4 shows the jackknife test of the variables used in our model. The omission of any of the vari-

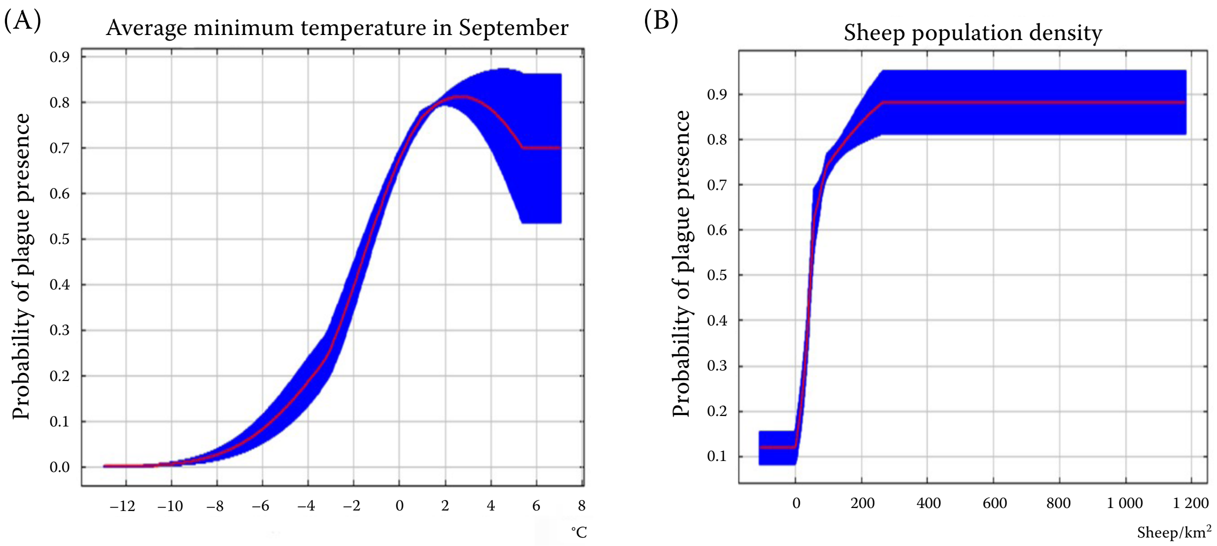

Figure 3. Response of the plague to the average minimum temperature in September (A) and the sheep population density (B) in the QLR (Qinghai Lake region)

The red lines indicate the mean values, while the blue areas denote the standard deviation

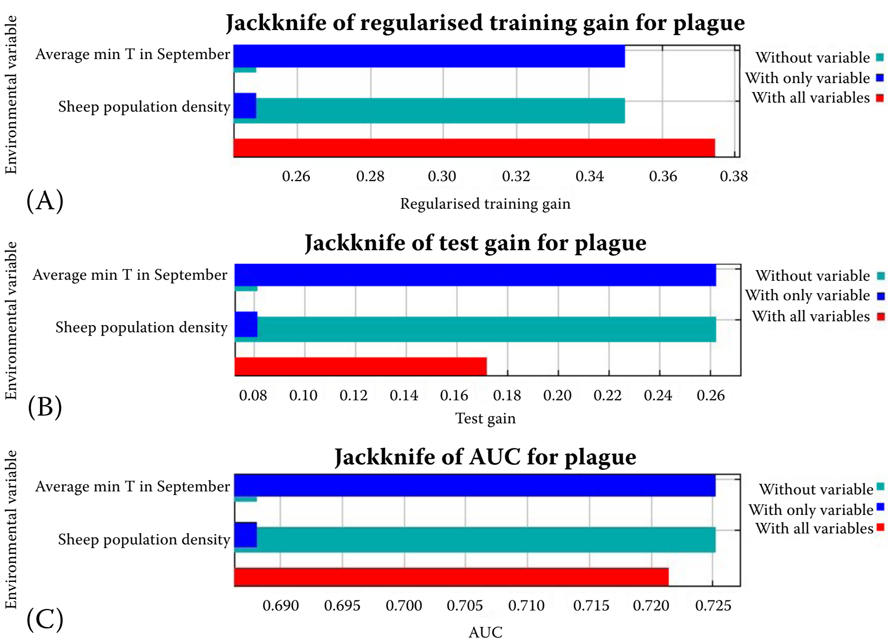

Figure 4. Jackknife tests of the variable importance with (A) the regularised training gain, (B) test gain, and (C) AUC

The light blue bars illustrate the model gain without the variable inclusion, while the solid blue bars show its gain with the variable only

AUC = area under the curve; Min T = minimum temperature

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ables drastically affects the training gain, test gain and test AUC values. The average minimum temperature in September has the highest training gain when each variable was tested as the only environmental variable (0.35), and the lowest values were observed in the sheep population density (0.24). The lowest training gain appeared when the average minimum temperature in September was excluded from the model, while the model had the highest gain when the sheep population density (0.35) was excluded (Figure 4). The average minimum temperature in September had the highest test gain values when it was used as the only environmental variable and the sheep population density has the least test gain. Our model had a high training gain value when the sheep population density was excluded from our modelling process. The exclusion of the average minimum temperature in September variable from the model results in a decline in the test gain.

The output of our jackknife test shows that average minimum temperature in September has a high AUC value of 0.73 when used in isolation compared to the sheep population density whose AUC was not different from the null model (0.5). Our model had an equal AUC value of 0.73 when the sheep population density was excluded from the model and when the average minimum temperature in September was used by itself.

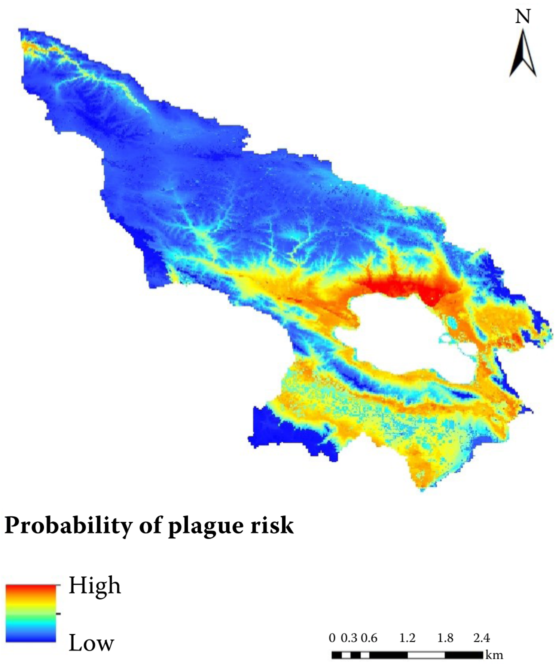

Figure 5. MaxEnt prediction of the plague risk in the Qinghai Lake region

Model evaluation

We used two methods to evaluate the accuracy of our model, namely the area under the curve (AUC) and true skill statistic (TSS). The results show AUC and TSS values of 0.82 and 0.75, respectively; these are considerably higher than the null model of 0.5. These results indicate that the environmental variables used in this study can explain the spatial distribution of the plague.

Potential distribution

The output of the MaxEnt prediction is equivalent to the relative occurrence rate; it shows the relative habitat suitability for each pixel. The map produced from averaging the raw output captures the lowland areas around the Qinghai Lake basin with the highest suitability, particularly in the northern part of Qinghai Lake (Figure 5). Gangcha county stands out from the entire area of interest as having a high probability of plague occurrence, while Haiyan, Gonghe and Tianjun counties have a moderate probability of plague risk. A low probability of occurrence can be seen in the northern part of the Qinghai Lake region.

DISCUSSION

Environmental and climatic variables are important factors influencing the ecology of plague. Variables, such as the temperature, precipitation, and humidity, play a vital role in vector-borne disease transmission by altering the vector and pathogen development, which will invariably influence the distribution of both disease hosts and habitats (Gage et al. 2008). However, variable patterns in the species-specific mortality and timing of outbreaks between and within ecosystems have made it challenging to understand plague epidemiology and to predict the disease occurrence. Despite this, our study reveals that risk epidemics in the QLR depend on the following environmental variables: the average minimum temperature in September and the sheep population density. Evidently, the plague presence exhibits a significant response to temperature increases. These results are consistent with other studies that have examined the role of the temperature and other climatic variables on plague

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outbreaks in human and animal populations (Stapp et al. 2004; Collinge et al. 2005).

Temperature is a critical variable in plague risk prediction. Specifically, while warmer temperatures may stimulate plague activity generally, temperatures above 35 °C are associated with a negative effect on the flea fecundity, survival, and behaviour (Hinnebusch et al. 1998; Parmenter et al. 1999). Other variables, which do not satisfy our variable selection criteria, but have been documented as predictors, include the landcover such as mosaic cropland/natural vegetation, grassland, urban areas, and water bodies. Moreover, most preferably, the alpine desert/semi-desert grassland, such as the alpine meadow, alpine grassland, and alpine shrub (Tian 2000) are suitable for the enzootic plague, while habitats with luxurious vegetation seemed unsuitable for the enzootic plague.

Our findings of the temperature and livestock population density agree with Assefa et al. (2021) in that the temperature influences the spread of infectious diseases in many ways. A lower temperature may favour the microorganism's survival in the environment for more prolonged periods causing outbreaks in the small ruminant population. Another previous study indicated that a higher temperature negatively affects the distribution of host animals (Qian et al. 2014).

The identification of sheep population density by the MaxEnt model as the most important predictive variable shows the availability of a susceptible host, which is acceptable logic for spreading- and maintaining plague. Therefore, a higher density of sheep carries a higher risk of increasing the number of plague outbreaks in the QLR.

The low-elevation areas in this study are mainly distributed around the Qinghai Lake basin. Our suitability map shows that the increasing elevation was linearly associated with the increased probability of plague. The reason for such a threshold is not entirely clear. Still, it may coincide with the generally increasingly favourable habitat conditions for the host species in areas with an increasing altitude from sea level. Also, at lower elevations, the forest and thick grass could be harmful to plague hosts, while at higher elevations, there would be lack of food (Qian et al. 2014). The shared distribution of rodents, fleas, and human beings increases the danger of infection and epidemic potential of the plague, especially for farmers who live within the higher probability areas (Nyirenda et al. 2017; Goldberg et al. 2020), such as those identified in our map.

In the Qinghai Lake region, most human plague outbreaks stemmed from contact with infected marmots or foxes in the Qinghai province (Ji 1988). Secondly, human-related activities and land cover change, such as the conversion of forests to farmlands, might enlarge the rodent habitats and increase the human plague risks (Duplantier et al. 2005). Lastly, transhuman migration may account for the introduction and spread of plague, as these factors increase the potential of transmitting infected fleas, rodents, or patients.

In this study, we predicted the plague occurrence in the Qinghai Lake region based on the reported occurrence plague outbreaks. The average minimum temperature in September and the sheep population density were identified as important contributing features governing the habitat suitability for plague in the QLR.

Our model identifies potential plague risk areas which can help public health authorities decide where to allocate scarce plague surveillance resources.

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Conflict of interest

The authors declare no conflict of interest.

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