



## Driving effect of multiplex factors on Mpox in global high-risk region, implication for Mpox based on one health concept

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### ABSTRACT

Mpox is an ongoing viral zoonotic disease epidemic worldwide. Being different from conventional animal-to-human transmission, the present outbreak is mainly caused by human-to-human transmission of Mpox virus, putting forward the risk of worldwide epidemic. The current spatial distribution characteristics and risk area prediction are urgently needed for preparedness for prevention and control of the disease based on the One Health strategy. In the present study, the global outbreak point of Mpox virus were collected and used to predict potential global risk of Mpox virus with ecological niche model constructed with a combination of ecological, anthropoid, meteorological, and host variables. The results showed that human factors are the key to the risk and prevalence of Mpox. The risk map indicated that Mpox may affect extensive areas worldwide. Europe and North America have the highest risk of Mpox. Although most areas have never recorded Mpox before, there are some high-risk areas in Asia. Our findings highlight population density is the most important contributing factor for high-risk area. Many large cities with dense populations, developed transportation, and high migration rate in the world, are in high risks. At present, the spread of Mpox is highly valued in the world and strict prevention and control measures have been taken. However, under the influence of human factors, Mpox has the potential of a global pandemic. The risk area prediction and main risk factors provide key information for targeted preparedness for prevention and control of Mpox outbreak and avoiding potential global epidemic through the One Health approach.

### 1. Introduction

Mpox is a rare zoonotic disease caused by infection with the Mpox virus [1]. Mpox virus is a member of the Orthopoxvirus genus in the family Poxviridae, members of which include variola virus that causes smallpox. Symptoms of Mpox are similar to those of smallpox, but are milder, and rarely fatal. Mpox was discovered in 1958 when two outbreaks of a pox-like disease occurred in colonies of monkeys kept for

research [2]. Despite being named “Mpox,” the source of the disease remains unknown. Many animal species have been identified to be infected with the Mpox virus, including rope squirrels, tree squirrels, gambian pouched rats, dormice, different species of monkeys, and others [3]. Mpox also shows a trend of cross-host transmission, and the natural reservoir of Mpox and its circulation in nature are still uncertain [4]. However, African rodents and non-human primates (like monkeys) might harbor the virus and infect people. At present, Mpox is mainly

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transmitted by direct contact with the blood, body fluid, skin or mucosal damage of infected animals. Human-to-human transmission may be caused by close contact with respiratory secretions, skin damage of infected persons, or recently contaminated objects, but transmission through droplets and respiratory particles usually requires long-term face-to-face contact [5]. The first human case was recorded in 1970 in the Democratic Republic of the Congo (DRC) [6], and since then the infection has been reported in a number of central and western African countries. Nowadays it affects not only West and Central African countries, but also other regions of the world. In 2022, Mpox cases were reported in the UK, Spain, and elsewhere in Europe, this epidemic has rapidly spread to other countries in the world. As of September 1, 49,974 confirmed cases have been reported by 99 countries in the world, and the number is still growing. To prevent the continuing spread of Mpox virus in the world, especially in those countries that have not yet been reported, spatial distribution characteristics and risk regions are urgently needed. Meanwhile, the One Health approach has been recommended as an ideal preventing and controlling strategy for zoonotic infectious disease, such as Mpox, which highlight the collaborative efforts of multiple disciplines working locally, nationally, and globally, to attain optimal health for people, animals, and our environment. In this study, we did a comprehensive data collection and assessment of the geographical distribution of the current Mpox, conducted a global risk assessment through ecological niche modelling, and found out the key factors for the spread of Mpox virus [7]. This work is expected to help formulate the prevention and control of Mpox virus and prevent its continued spread combined with the One Health strategy.

## 2. Materials and methods

### 2.1. Occurrence and environmental data

The Mpox outbreak locations were collected from the WHO, OIE, and Mpox databases as of September 1, 2022 [8]. To avoid sampling bias, duplicate cases reported by the same area were removed. For environment data, the host datasets were used alongside four fundamental environmental predictor categories relevant for habitat modelling of terrestrial fauna, i.e., climate, terrain, vegetation, and human impact (Table 1) to construct the risk analysis model in this study. Among them, the host datasets contained 2266 present records of Mpox hosts (such as

**Table 1**  
Variable information. Data Layer, source, and Variable of the Prediction Model.

Layer	Source	Variable/proxy
Climate		
Bioclimatic 1–19	<a href="http://worldclim.org/version1">http://worldclim.org/version1</a>	Annual trends, seasonality, extreme or limiting environmental variables
Terrain		
Monthly solar radiation (1–12)	<a href="http://worldclim.org/version1">http://worldclim.org/version1</a>	Topo-climate
Elevation	<a href="https://earthexplorer.usgs.gov">https://earthexplorer.usgs.gov</a>	Climbing distance
Distance to river	<a href="https://www.hydrosheds.org/">https://www.hydrosheds.org/</a>	Water source
Human impact		
Population Density	<a href="https://www.worldpop.org/wprfms/">https://www.worldpop.org/wprfms/</a>	Human-Animal interaction
Distance to road	<a href="http://download.geofabrik.de/">http://download.geofabrik.de/</a>	Human-Animal interaction
Vegetation		
Land cover	<a href="https://maps.elie.ucl.ac.be/CCI/viewer/">https://maps.elie.ucl.ac.be/CCI/viewer/</a>	Animal food and refuge
Soils	<a href="https://soilgrids.org/">https://soilgrids.org/</a>	Vegetation nutrients
Host		
Mpox host density	<a href="https://lucasantini.com/tetradensity-database/">https://lucasantini.com/tetradensity-database/</a>	Host-disease interaction

*Macaca fascicularis*, *Macaca mulatta*, *Papio cynocephalus*, and *Pan troglodytes*), and processed the density layer by Kernel Density tool in ArcGIS. All the spatial data were converted to ASCII raster grids and preprocessed to a spatial resolution of 30 arc-seconds (ca. 1 km<sup>2</sup> at ground level) in UTM-WGS-1984 projected [9].

### 2.2. Spatial distribution model analysis

Risk areas for Mpox outbreak all world were detected using the presence-only maximum entropy ecological niche mode MaxEnt model (version 3.4.1) [10]. In order to reduce the adverse effects of spatial autocorrelation between sample points on the model, the spatial autocorrelation was minimized by filtering all recorded Mpox outbreaks occurred points using the SDM Toolbox v1.1c in ArcGIS 10.6 [11]. In order to reduce the multicollinearity among environmental variables, principal component analysis (PCA) in SPSS 22.0 was used to select the major predictors [11]. The variables with eigenvalues larger than 1.0 and the scree plot criterion or ‘broken stick’ stopping rule for PCA in item-level factoring were adopted. Suppression of unnecessary loading and rotation of factor pattern of variables was used to retain predictors for subsequent analysis in MaxEnt. Next, the least contributing and high standard deviation (SD) variables were eliminated stepwise and using the MaxEnt model [12]. Finally, variance inflation factor (VIF) analysis was conducted to evaluate the multicollinearity among predictors after the reduction. A VIF value below 10 indicates low and acceptable multicollinearity [13].

The filtered Mpox outbreak locations and predictors were then used as input data to construct the Mpox model using the MaxEnt algorithm. The present models were developed using occurrence data and One-thousand background points were then randomly selected as Pseudo-Absence data, representing the distribution of environmental conditions [14]. We divided the selected presence records into 75% training and 25% testing portions to build and validate the models based on 10 bootstrap replicates.

In the model selection process, different combinations of variables and parameters were tested to avoid collinearity, overfitting, and data dredging [15]. ENMTools (version 1.4.4) with AICc was used for model selection. For visualization, the Jenks natural break optimization method was used to classify the model output to identify high-risk areas, followed by map smoothing. We also extracted the highest value, the lowest value, and the average value of the risk of important cities in the world to evaluate the possible prevalence of Mpox in the world.

### 2.3. Modelling performance and variable importance

We use sampling threshold dependent and threshold independent methods to determine the stability of the model. For threshold-independent method, the area enclosed by Receiver operating characteristic curve and abscissa, namely AUC (Area under curve) value, is considered as the best index to evaluate the accuracy of the current model [16]. We also use the Kappa test and correctly classified instances (CCI) as a threshold-dependent validation measure [17,18]. The Kappa statistic normalizes the overall accuracy by the accuracy that might have occurred by chance alone. The percentage of CCI was defined as the rate of correctly classified cells. Sensitivity is the probability of the existence of the correct classification of the model, and specificity is the probability of the absence of the correct classification of the model. So we choose the thresholds of these two criteria are determined using the sensitivity-specificity sum maximization approach.

Further, we extracted the latest monkeypox case information from September 2022 to June 2023, extracted the geographical location of the cases, and then extracted the risk values of the regions for model accuracy verification.

### 3. Results

A total of 42,869 Mpox case were recorded and 671 Mpox virus outbreak locations were collected from the case information. Altogether, 642 recorded Mpox virus outbreak locations points at a distance of at least 10 km away from each other were obtained after filtering (Fig. 1). After limiting multicollinearity by PCA and MaxEnt filtering between and within groups, finally obtained Precipitation of Driest Quarter (Bio17), Mean Temperature of Warmest Quarte (Bio10), Temperature Seasonality (Bio 4), population density, soil, land cover, host density, solar radiation in October and December to construct the final Mpox prediction model. The VIF values among the predictors were 1.008–9.537, which was in line with the low multicollinearity standard (<10). The response curves of the different predictors are shown in Fig. 2, and the relative contributions of each predictor are shown in Table 2.

Mpox high-risk areas all over the world were then predicted using MaxEnt model. To validate the prediction model, AUC was calculated and used for evaluation. The calculated AUC, Kappa and CCI is 0.925, 8.880 and 0.881 respectively, indicating a best prediction, which also validated the robustness of the model. The predicted global high-risk areas by the MaxEnt model is shown in Fig. 3. High-risk areas distributed in Europe and North America are mainly the regions with high incidence at present. The predicted high-risk regions in Africa are mainly concentrated in Central Africa, and Asia's high-risk regions appear in East and South Asia. The southwest of Oceania has a small-scale high-risk region, but the overall risk is greatly smaller than that of other continents.

After extracting the average risk value of major cities in the world, we selected the top 100 rankings, including 40 countries, 30 of which have reported Mpox, and 10 countries have never reported Mpox. At the same time, we present the locations of major cities in the world with global risks, and we can intuitively observe their risks, as shown in Fig. 4. Among the 32 latest cases of monkeypox outbreak, all cases had a risk value >0.3. And 71.88% of cases have a risk value >0.5, located in high-risk areas predicted by the model, proving that the model can effectively predict high-risk areas for monkeypox occurrence (Supplementary Material Table S1).

### 4. Discussion

Mpox has become a disease of global public health importance.

Previously, Mpox was considered a zoonotic disease of wildlife with complex ecology and epidemiology [19]. The global epidemic of Mpox has changed greatly from the previous transmission model: from animal to human transmission in the past to human to human contact transmission now [20]. Moreover, there are many uncertainties in the epidemic trend of Mpox. The traditional epidemiological investigation and prevention and control strategies could no longer prevent the potential global pandemic of the current epidemic [21]. Therefore, the spatial prediction of the model may become an effective means to identify high-risk areas of the disease, One Health approach may be the key to becoming a great significance for prevention and control [22]. This study conducted a global risk assessment of Mpox virus and identified the key factors affecting the rapid global spread of Mpox. The results show that the high risk of Mpox has far exceeded that of previously reported countries, and there are also many high-risk areas in some countries where Mpox virus has not occurred, this also proves that Mpox virus is likely to cause epidemic worldwide.

Our model spatial distribution revealed that Europe and North America has the highest risk distribution, followed by central, Western and Southern Europe. The eastern and northern Europe are at low risk compared to other regions in Europe. Among the European countries, Spain, France, Britain, and Germany have the highest number of confirmed cases. High risk areas in North America are mainly concentrated in the United States, Canada, and Mexico. Recently, the United States is the country with the largest number of cases in the world with over 23,499 confirmed cases, and our model predicted a number of high-risk areas in this country. We also found that countries between North America and South America also have higher risks, which are higher than those in South America excluding Brazil and Peru.

Africa's high-risk areas are mainly concentrated in West Africa, which is also the most likely origin of Mpox virus. Although the number of cases in Africa is small due to the Mpox pandemic, there are still high-risk areas, and prevention and control should be strengthened to prevent a pandemic in this area. Although the number of cases in Asia is small, there are still high risks in East and South Asia, mainly concentrated in Japan, India, Philippines, Thailand, and other countries. Among the risk areas in Asia, our model predicted a high-risk area in southern China. On September 6, Hong Kong, China reported Mpox cases for the first time [23]. There has never been a case of Mpox virus in China before, which also warns us to strengthen monitoring, prevention and control in southern China and urgently needs to formulate prevention and control strategies. China has a large population and a high population density in

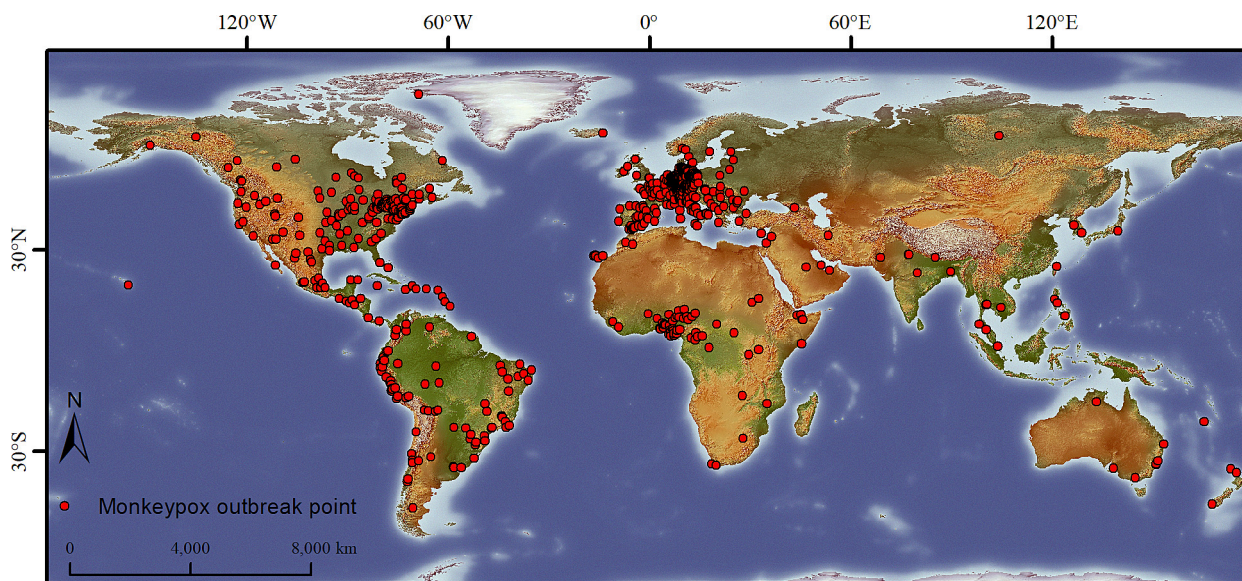
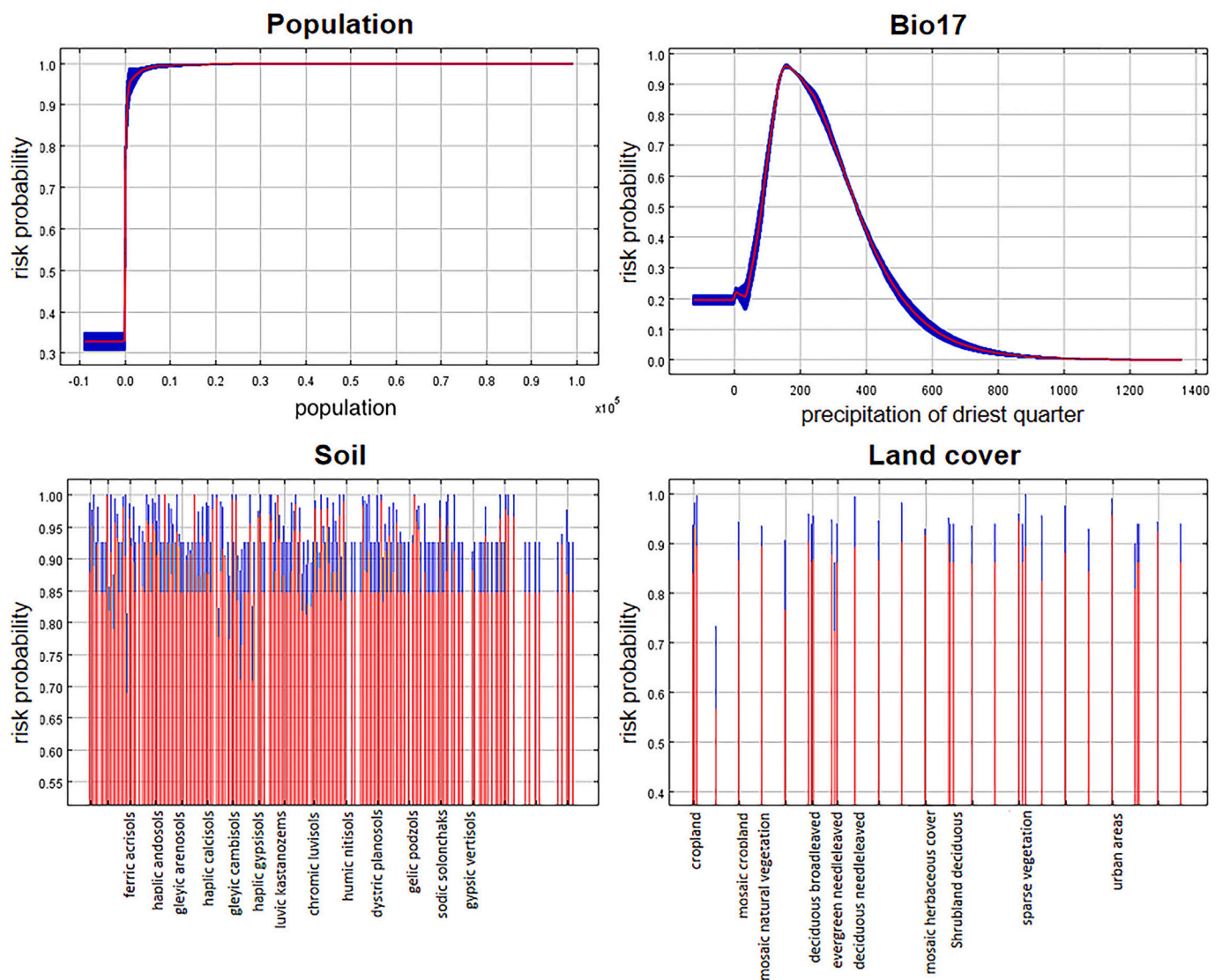


Fig. 1. Geographical distribution of recorded Mpox locations worldwide. Land coloring based on elevation.



**Fig. 2.** The response curves of the model. The curves show the mean response (red) and the mean standard deviation (blue). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the south, once introduced, this disease will have a great impact on public health. The high-risk areas in Oceania are mainly in New Zealand and Southeast Australia, but the overall risk is smaller than that in other continents.

The Population Density is the most important predictor in our model as this factor has the highest contribution rate, this is in tandem with a recent Mpx study in southern Nigeria, Africa. Although the mode of transmission of Mpx is not completely clear, the ongoing outbreak showed that the transmission route has been changed from animal to human transmission to human-to-human transmission, which explained the rapid rising case number worldwide [24]. Recent studies have confirmed that Mpx is mainly transmitted by contact. A patient with Mpx can spread the virus to others from the time symptoms start until the rash has fully healed and a fresh layer of skin has formed. The illness of Mpx typically lasts 2–4 weeks, and during this period, there may be a high risk of transmission [25]. Therefore, human has become the main host of Mpx virus.

Previous mathematical modelling of human-to-human transmission found that Mpx has epidemic potential, with  $R_0 > 1$  [26]. Our results also show that with the increase of population density, diseases show a rapid rising trend, and tend to become stable when the population density reaches its peak. Therefore, in areas with high risk of disease outbreak,

controlling population activities and aggregation, and enabling public health management and vaccination in areas with high population density can effectively control the spread of Mpx virus. At the same time, it is necessary to improve the public's awareness of the Mpx virus, understanding the changing epidemiology of the disease is also the key to formulating prevention and control strategies. On the ecological front, we should try our best to avoid human contact with areas where suspicious host activities are frequent, which reduces the possibility of introducing zoonotic diseases into the scope of human activities [27]. If zoonosis is not introduced repeatedly, human infection will eventually stop occurring.

Given the role of population density, we further extracted the risk values of many cities of the world, including major cities and many provincial capitals. These high-risk cities have high population density, high migration rate, and a large number of transportation hubs. This indicated that population mobility may cause the prevalence of Mpx virus, which is also proved by the high incidence of Mpx in large cities at present. For example, the first Mpx virus patient in the United Kingdom originated from a British resident who went to Nigeria, where the disease is prevalent, and then brought the virus back to the United Kingdom and spread in the United Kingdom [28]. Recently, the first case in Hong Kong, China, was also confirmed to be Mpx virus infection after

**Table 2**

Estimates of relative contributions and the optimum interval of the environmental.

Important Variables	Contribution %	Permutation importance	Interval with the highest risk
Population	44.1	13.1	0.1–1*10 <sup>5</sup> person/km <sup>2</sup>
Bio17	19	3.1	100–400 mm/quarter
Soil Type	12.3	10.1	Haplic Andosols and Gelic Podzols
Land Cover	11.3	2.7	Urban area
Bio4	5	45.2	10–50 (temperature standard deviation)
Solar Radiation 12	3.9	4.2	3000–3500 kJ/m <sup>2</sup> /day
Solar Radiation 10	1.6	18.4	5000–15,000 kJ/m <sup>2</sup> /day
Bio10	1.5	1.6	35–45 °c
Host Density	1.3	1.6	3.87–5.4 individual/km <sup>2</sup>

Shan Gao and Zan Zeng conceptualized the initial hypothesis and conceived and designed the study. Yujia Zhai and Xiangning Feng collected and sorted out the data. Fangyuan Chen edited the figure. Wei Kan and HongLong Xu conducted literature search and participated in the writing part. Shan Gao and Zeng Zan did the statistical analysis and wrote the first draft of the manuscript, Jiahai Lu and Zeliang Chen revised the manuscript. All authors contributed substantially to data acquisition and interpretation, and revision and editing of the manuscript.

entering the country from Philippines. These examples also showed that Mpox virus is easier to spread in large cities with prosperous economy, dense population, and convenient transportation, and causes epidemic. Therefore, it is more necessary to strengthen real-time monitoring of the virus in densely populated areas, especially those areas that have never been reported.

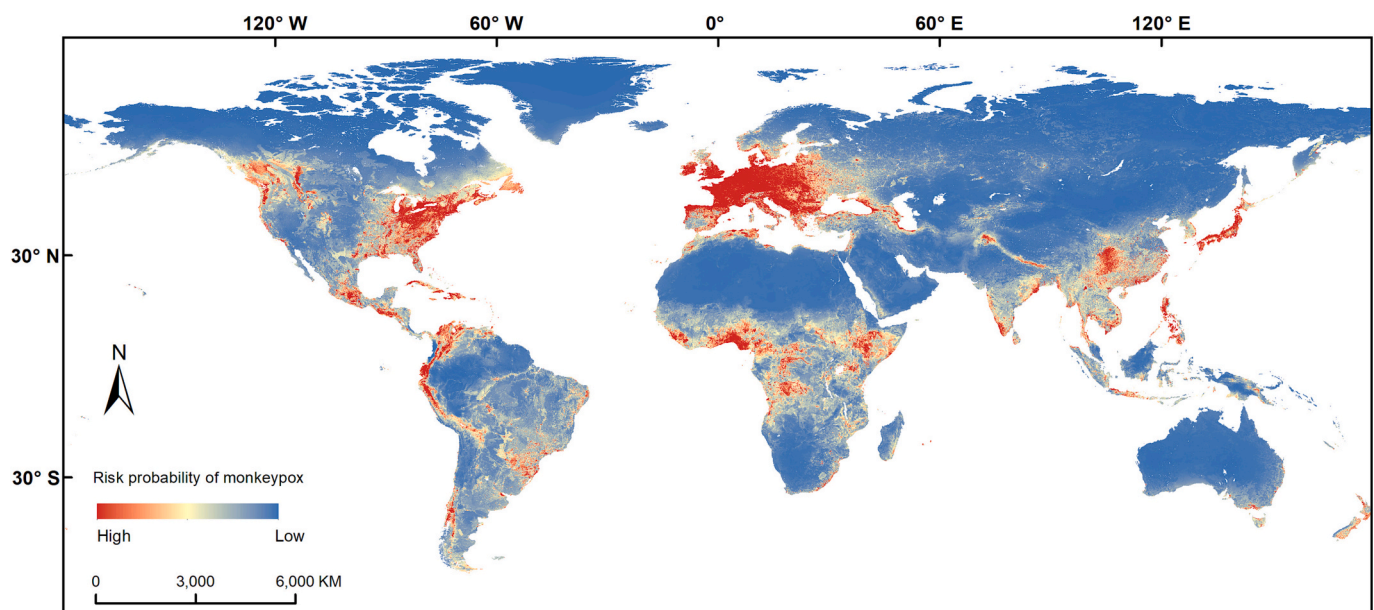
Mpox virus has attracted worldwide attention, but there are still many unanswered questions, that is, how the virus is maintained in nature, this knowledge gap limits our accurate prediction of Mpox. In nature, weather is a factor that affects the prevalence of diseases and thus the risk of Mpox infection [29]. This study also reveals the ecological suitability of Mpox virus in the ecological direction. Although human factors are the leading factor in the risk of Mpox, Mpox virus is also driven by meteorological factors. The result can be inferred that Mpox, as a zoonosis, is a disease with complex seasonal driving. Meteorological factors have always played an important role in the spread of diseases under natural conditions [30]. In this study, we found that

bio17 and bio4 also play an important role in the risk of diseases. Although there is no direct evidence in epidemiology that meteorology can directly affect the spread of diseases, temperature has always been considered to play an important role in the spread of diseases. It can directly affect the infectious power of diseases by affecting the activity of viruses. By analyzing the response curve of bio4, we found that the risk value will change with the change of temperature seasonality standard deviation, which also shows that the transmission of Mpox virus is seasonal in temperature. Secondly, the precipitation in the driest season also affects the disease risk. With the increase of precipitation in the driest season, the disease risk increases rapidly. Although the effect of precipitation on Mpox virus has not been confirmed, naturally-occurring Mpox currently remains confined to the humid forest regions of West and Central Africa, and Mpox in West Africa occurs in a wetter and hotter condition [31]. Therefore, we still need to pay attention to these meteorological variables, because the transmission mode of Mpox virus is not clear.

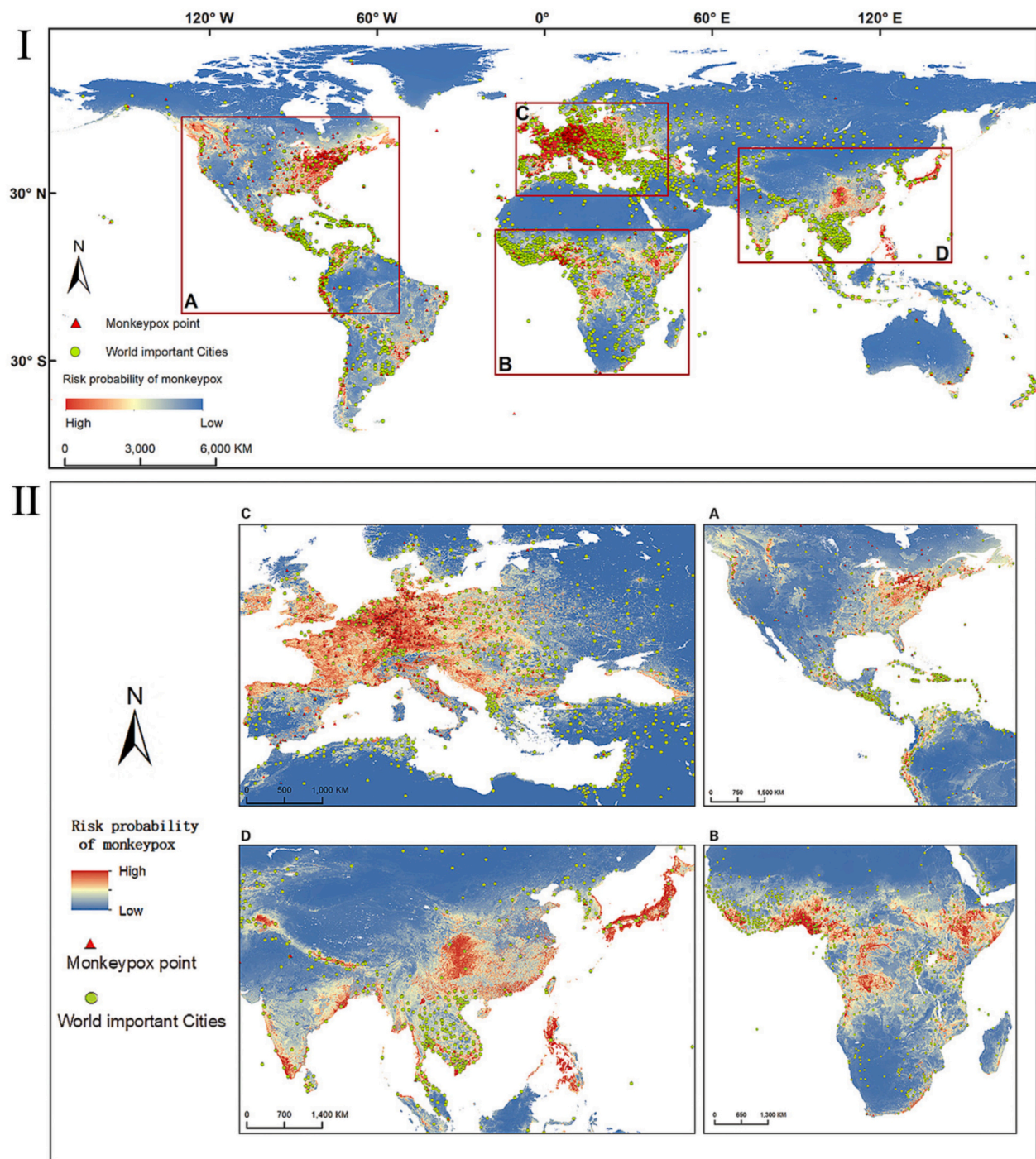
Mpox as a zoonotic disease has been shown to spread from human to human after transmission from wildlife to humans, and Mpox virus can complete the transmission cycle through wildlife hosts in the natural environment. Therefore, Mpox may spread to new areas through human activities and contaminate animals and the environment. Thus, a new chain of transmission is formed in the new area and it becomes a natural epidemic disease. One health philosophy guides us to recognize the interconnectedness of humans, animals and ecosystems, and to work together across disciplines and components to address risks from the animal-human-environment interface [32]. The widespread global outbreak of Mpox warns us of the need for increased surveillance and early warning to address the transmission of monkeypox virus across different interfaces and hosts, including human-animal-environment. There is an urgent need to change the traditional mindset of Mpox. Through multidisciplinary and multisectoral cooperation among veterinary, environmental and human medicine, we should address the public health safety issues caused by the global epidemic of Mpox in order to ensure human-animal-environmental health safety.

## 5. Conclusion

In the present study, risk areas of Mpox were predicted according to present outbreak data. The main transmission route of Mpox virus has been changed from animal-to-human to human-to-human transmission,



**Fig. 3.** Mpox high-risk areas were predicted by the MaxEnt model. This map was made in ArcGIS 10.6 using the resulting rasters produced by MaxEnt.



**Fig. 4.** Typical high-risk regions of Mpox, major cities in the world and outbreak points. The red boxes represent typical high-risk regions, A: America, B: Africa, C: Europe, D: Asia. The red triangle represents the Mpox outbreak point, and the green point represents the major cities around the world. Figure I shows the global scope and figure II shows the local enlargement. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and population density was found to be the most important contributing risk factor. Mpox virus can be transmitted rapidly through population migration in large cities, which may cause a worldwide epidemic and has the potential to become a pandemic. Awareness of the transmission route of the virus and risk areas by public population, preparedness for worldwide epidemic or pandemic are urgently needed. Therefore, based on One Health approach, it may play a key role in the spread of Mpox disease to reveal the relationship between human and animal environment.

#### Author statement

Shan Gao and Zan Zeng conceptualized the initial hypothesis and conceived and designed the study. Yujia Zhai and Xiangning Feng collected and sorted out the data. Fangyuan Chen edited the figure. Wei Kan and HongLong Xu conducted literature search and participated in the writing part. Shan Gao and Zeng Zan did the statistical analysis and wrote the first draft of the manuscript, Jiahai Lu and Zeliang Chen revised the manuscript. All authors contributed substantially to data acquisition and interpretation, and revision and editing of the

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data sources and links have been explained in the manuscript.

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