Letter to the Editor

The Relationship between Japanese Encephalitis and Environmental Factors in China Explored Using National Surveillance Data*

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Japanese encephalitis (JE) is a serious public health issue. This study was undertaken to better understand the relationship between JE distribution and environmental factors in China. JE data from 2005 to 2010 were retrieved from National Notifiable Disease Report System. ArcGIS, remote sensing techniques, and *R* software was used to exhibit and explore the relationship between JE distribution and environmental factors. Our results indicated that JE cases were mostly concentrated in warm-temperate, semitropical and tropical zones with annual precipitation > 400 mm; Broad-leaved evergreen forest, shrubs, paddy field, irrigated land, dryland, evergreen coniferous forest, and shrubland were risk factors for JE occurrence, and the former five were risk factors for counties with high JE incidence. These findings will inform the effective allocation of limited health resources such as intensive vaccination, surveillance and training in areas with high environmental risk factors.

Key words: Japanese encephalitis; Environmental factors; Landscape

Japanese encephalitis (JE) is severe vector-borne encephalitis caused by JE virus (JEV) identified in about 24 countries. Available data showed an estimated 68,000 clinical JE cases occurred annually worldwide with about 30% case-fatality rate in patients with encephalitis[1]. In China, JE has been classified as a notifiable disease since the 1950s. JE case numbers peaked in 1966 with 150,000 cases (morbidity > 15/100,000) and 1971 with 174,932 cases (morbidity > 20/100,000)[2]. Although JE incidence showed a decreasing trend, JE was one of the top 10 diseases with high fatality rate of more than 30 notifiable diseases in China in recent years. By now, JE remains a considerable threat to health[3] because of its high fatality rate and protracted and severe sequelae.

As a mosquito-borne virus, circulation among pigs and mosquitoes is an important mode of JEV transmission. Humans are dead-end hosts infected by mosquito bite. More than 30 types of mosquitoes from five genera are potential JEV carriers, but *Culex tritaeniorhynchus* is the primary vector in China. Mosquito's life history as well as human abundance and activities can be affected by environmental factors. This study aimed to explore the relationship between JE distribution and environmental variables (precipitation, temperature, elevation, and landscape) using JE national surveillance data and environmental factors at county level.

JE clinical diagnosis cases and lab-confirmed cases[4] data from 2005 to 2010 for mainland China were retrieved from National Notifiable Disease Report System (NNDRS) with approval. The data extraction and use were all anonymized to protect patient privacy and confidentiality. Annual precipitation and air temperature data from 2005 to 2010 were obtained from the China Meteorological Administration. Raster maps for annual average precipitation and air temperature with a 1-km grid were generated using the inverse distance weighting method[5,6]. The annual precipitation data were

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divided into four levels: < 200, 200-400, 400-800, and > 800 mm, representing arid, semi-arid, semi-humid and humid areas, respectively. The annual average air temperature was classified into five zones: frigid-temperate, mid-temperature, warm-temperate, semitropical, and tropical. The elevation data extracted from a previously described digital elevation model (DEM) with a 1:100,000 scale were converted to a raster map with a 1-km grid[7]. Using the DEM and a map of the administrative units, the average elevation of each county was calculated. According to this, counties were divided into five levels: < 200, 200-500, 500-1,000, 1,000-4,000, and > 4,000 m. Landscape data produced based on remote sensing images in 2005 with 250-meter spatial resolution were obtained from the Institute of Remote Sensing and Digital Earth, Chinese Academy of Sciences. It was classified into six major class types, including forest, grassland, farmland, settlement, wetland and desert, and the major classes were then classified into 25 secondary class types[8]. The landscape of each county was represented by the type of land cover with the largest portion. For example, if a county was covered by 80% meadow grassland, 15% typical grassland and 5% rural settlement, the landscape was classified as meadow grassland. ArcGIS software (ESRI, USA) and remote sensing techniques was used to generate and exhibit environmental factors at county level. JE incidence was calculated according to the corresponding population. Based on six-digit county geocodes, JE cases at county level were demonstrated on the maps with different environmental factors to make geographic and spatial visualization.

R software [R Core Team (2016), Austrica. URL https://www.R.project.org/.] was used for statistical analysis. Chi-square test was used to compare JE distribution in relation to different environmental factors, including precipitation, air temperature, elevation, and landscape. To further explore the relationship between JE and landscape, counties were divided into three categories: 1) JE non-endemic counties (counties without JE cases reported), 2) JE low-endemic counties (JE cases reported in any one to four years of six years between 2005 and 2010), and 3) JE high-endemic counties (JE cases reported in any five years of six years between 2005 and 2010). The latter two combined to JE endemic counties. The comparison of endemic *vs.* non-endemic counties and high-endemic *vs.* low-endemic counties were conducted in each forest, grassland, farmland and settlement sub-factors by univariate analysis. To further explore the potential factors, variables with $P < 0.2$ in univariate analysis were included in multivariable logistic regression model with backward stepwise method. Statistical significance was set at $P < 0.05$. Odds ratio (*OR*s) and corresponding 95% confidence intervals (*CI*s) were presented.

JE case numbers and incidence decreased from 7,643 cases and 0.58 case per 100,000 population respectively, in 2006 to 2,541 and 0.19/100,000 respectively, in 2010, showing a decreasing trend with occasional fluctuation over the study period. In line with an increased national emphasis on the detection of JE, the proportion of lab-confirmed cases increased from 29.3% (in 2005) to 76.2% (in 2010). Table 1 showed the annual JE case numbers, incidence and laboratory confirmation proportion.

Average annual incidence of JE positively correlated with precipitation. The highest average yearly incidence (0.45/100,000) was observed in humid areas which was much higher than in semi-humid (0.13/100,000), semi-arid (0.02/ 100,000), and arid areas (only 0.001/100,000). The *OR* for humid areas (104.3) was also much higher than for other areas. Semitropical zones had the highest JE incidence (0.44/100,000), followed by warm-temperate (0.22/100,000), tropical (0.18/ 100,000), and mid-temperature zones (0.06/ 100,000). Few JE cases occurred in frigid-temperate

Table 1. Annual Incidence of Japanese Encephalitis from 2005 to 2010 in Mainland China

Year	Cases, *n*	Incidence, per 100,000 Population	Fatal Cases, *n*	Male, %	Female, %	Laboratory Confirmed, %*
2005	5,097	0.39	214	61.2	38.8	29.3
2006	7,643	0.58	463	62.1	37.9	48.6
2007	4,430	0.33	227	59.8	40.2	60.0
2008	2,975	0.23	142	61.0	39.0	51.5
2009	3,913	0.30	172	60.3	39.7	64.7
2010	2,541	0.19	92	59.7	40.3	76.2

Note. *The proportion of laboratory confirmed cases in the total annual JE cases.

zones. Areas with 1,000-2,000 m elevation had the highest JE incidence (0.74/100,000). At < 2,000 m elevation, JE incidence increased as elevation increased. JE incidence then decreased to 0.28/100,000 in areas with 2,000-4,000 m elevation. Table 2 showed JE incidence and *ORs* in different environmental factors, which reflected that JE cases were mostly concentrated in warm-temperate, semitropical, and tropical zones with annual precipitation > 400 mm.

Comparing non-endemic and endemic areas, univariate analysis showed that evergreen coniferous forest (*OR*: 3.09, 95% *CI*: 2.19, 4.44), broad-leaved evergreen forests (*OR*: 2.34, 95% *CI:* 1.73, 3.18), shrubs (*OR*: 10.52, 95% *CI*: 5.53, 22.46), shrubland (*OR*: 2.48, 95% *CI*: 1.32, 5.00), paddy field (*OR*: 2.31, 95% *CI*: 1.80, 3.00), and irrigated land (*OR*: 1.88, 95% *CI*: 1.51, 2.34) were the landscape risk factors for JE endemicity (Supplementary Table S1 available in www.besjournal.com). Landscape risk factors for high-endemicity, compared with low-endemicity were shrubs (*OR*: 3.26, 95% *CI*: 2.30, 4.63) and dryland (*OR*: 2.53, 95% *CI*: 1.89, 3.40) (Supplementary Table S2 available in www.besjournal.com).

Landscape variables with *P* < 0.2 in Table S1 and Table S2 was included in multivariable logistic regression analysis to make further analysis for JE occurrence and high endemicity, respectively. Meanwhile, considering paddy field was a risk factor for JE endemic, it was also included in risk factor analysis of JE high endemicity. The results (Supplementary Table S3 available in www.besjournal.com) showed that evergreen coniferous forest (*OR*: 5.80, 95% *CI*: 4.02, 8.36), broad-leaved evergreen forests (*OR*: 4.41, 95% *CI*: 3.19, 6.10), shrubs (*OR*: 19.64, 95% *CI*: 10.16, 37.97), shrubland (*OR*: 4.94, 95% *CI*: 2.63, 9.27), paddy field (*OR*: 4.24, 95% *CI*: 3.19, 5.63), irrigated land (*OR*: 3.44, 95% *CI*: 2.67, 4.43) and dryland (*OR*: 1.34, 95% *CI*: 1.05,1.72) were risk factors for JE occurrence; broad-leaved evergreen forests (*OR*: 1.74, 95% *CI*: 1.21, 2.50), shrubs (*OR*: 5.29, 95% *CI*: 3.63, 7.72), paddy field (*OR*: 1.69, 95% *CI*: 1.23, 2.32), irrigated land (*OR*: 1.58, 95% *CI*: 1.16, 2.13) and dryland (*OR*: 4.06, 95% *CI*: 2.91, 5.67) were risk factors associated with JE high-endemicity (Supplementary Table S4 available in www.besjournal.com).

Table 2. Japanese Encephalitis in Different Environmental Factors

Environmental Factors	**Average Yearly Incidence, 2005-2010, Cases per 100,000 Population**	***OR*# (95% *CI*)**
Annually Precipitation, mm		
< 200* (arid)	0.00	-
200-400 (semi-arid)	0.02	3.036 (1.160, 7.943)
400-800 (semi-humid)	0.13	17.323 (7.576, 39.609)
> 800 (humid)	0.45	104.304 (45.596, 238.604)
Temperature Zone		
Frigid-temperate*	0.00	-
Mid-temperature	0.06	10.037 (5.937, 16.971)
Warm-temperate	0.22	36.847 (21.607, 62.837)
Semitropical	0.44	135.225 (81.751, 223.678)
Tropical	0.18	46.685 (22.605, 96.416)
Elevation, m		
< 200	0.18	3.366 (2.412, 4.698)
200-500	0.37	3.889 (2.715, 5.57)
500-1,000	0.66	4.805 (3.275, 7.049)
1,000-2,000	0.74	2.834 (1.982, 4.053)
2,000-4,000*	0.28	-
> 4,000	-	-

Note. *Reference group. #*OR* represents the probability of JE cases occurring in county-level administrative units. Compared with reference group from corresponding environmental factors, *OR* was calculated.

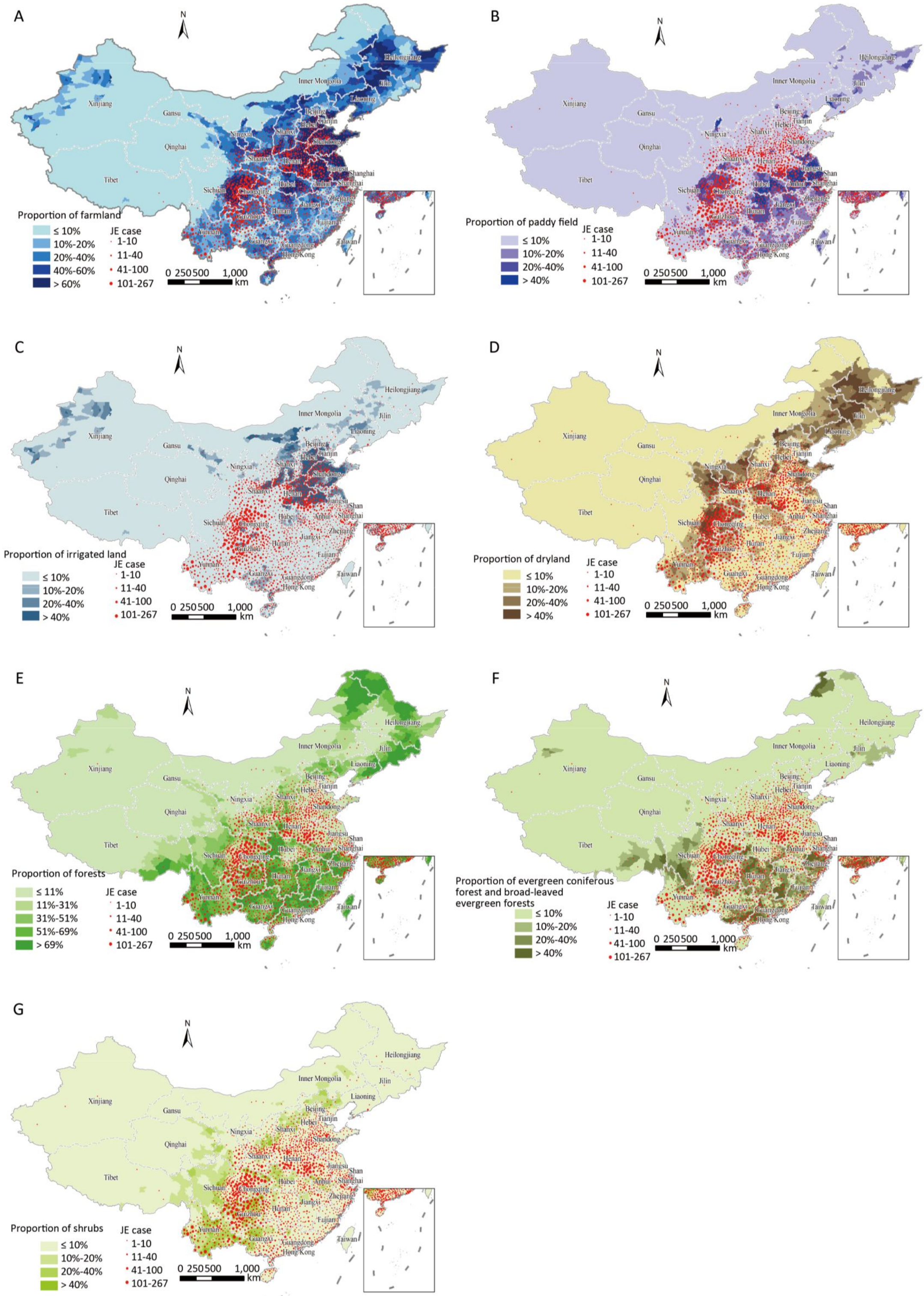

Figure 1. Japanese encephalitis distribution in different landscape. (A) JE distribution in farmland, (B) JE distribution in paddy field, (C) JE distribution in irrigated land, (D) JE distribution in dryland, (E) JE distribution in forests, (F) JE distribution in evergreen coniferous forest and broad-leaved evergreen forests, (G) JE distribution in shrubs.

Vector-borne diseases are strongly influenced by environmental factors. For general public health professionals' better understanding, here, we used traditional epidemiological method combined with GIS and remote sensing techniques to explore and visualize the association between JE distribution and environmental factors (especially landscape) at county level. Furthermore, considering JE incidence decreasing in China (0.09/100,000 in 2016, 0.39/100,000 in 2005) which may be attributed to China's expanded immunization targeted eligible children since 2008[9], we used JE data from 2005 to 2010 to avoid as much as possible the influence of expanded immunization. Our results showed that some environmental factors were significantly associated with JE distribution.

Climate and elevation affects vector-borne diseases' distribution through influencing mosquitoes' life history as well as human abundance and activities. Our study verified again that the climate factors of precipitation and temperature significantly influenced observed JE human infection distribution, and showed that the majority of JE cases in China distributed in counties of warm-temperate, semitropical, and tropical areas with annual precipitation > 400 mm. Almost all JE cases distributed in areas with elevation < 4,000 m. As a good example, Tibet was actually a JE-free area with average elevation > 4,000 m, however JEV was isolated from mosquitoes[10] at a specific area with lower elevation in Motuo county of Tibet. All these reminded public health workers especially in JE-free areas (Xinjiang, Qinghai, and Tibet) should pay more attention to lower elevation areas.

JE is a vector-borne disease, and is spatially affected by the distribution of both its vectors and hosts. Study of the relationship between JE distribution and landscape at county level in China were lack. Our results indicated that JE distribution was closely associated with landscape, and that JE cases mainly occurred in agricultural and forest areas. The landscape of some JE high prevalence provinces such as Sichuan (mainly dominated by paddy field and dry farmland), Henan (mainly irrigated farmland), Yunnan (mainly shrubs) also, in turn, supported our results to a certain extent. Dryland, an unconventional risk factor for JE, was also identified as risk factor in this study, which may be related to pig farming in dry farmland.

Our results should be interpreted based on the studies' limitations: firstly, the most appropriate and available landscape classification data used here were generated in 2005, which might lead a lag compared to JE data from 2005 to 2010. Secondly, because of unavailable pig population and density data across China, we did not included JEV host - pigs' information into this study. Thirdly, except environmental factors mentioned above, as a vector-borne and vaccine preventable disease, JE distribution can also be affected by other non-environmental factors including vaccination coverage and observation/reporting biases. In this study, we just focused on environmental variables to make a preliminary and general study of the environmental risk factors for JE distribution. For further study, we will in-depth focus on more risk factors such as pig farming, vector distribution, and vaccine influence at some specific areas. Our results implied that JE prevention and control should break administrative area division, and should pay more attention to the areas division based on environmental factors.

In conclusion, JE distribution was strongly correlated with precipitation, air temperature, elevation, and specific types of farmland and forest. The provision of this JE distribution-related environmental information to stakeholders will, in turn, enable the reasonable and effective allocation of limited health resources. For example, JE control measures (e.g. vaccination, JE case management and mosquito control) should be strengthened in high-risk environmental areas with JE cases; in high-risk areas without JE cases intensified surveillance for JEV and JE cases is recommended.

No conflict of interest to declare.

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Supplementary Table S1. Univariate Analysis of Landscape Risk for Japanese Encephalitis in Endemic Counties Compared with Non-endemic Counties in Mainland China

Major Class Types	Secondary Class Types	*OR* (95% *CI*)	*P* Value (Chi square test)
Forest	Evergreen coniferous forest	3.09 (2.19, 4.44)	< 0.001
	Broad-leaved evergreen forests	2.34 (1.73, 3.18)	< 0.001
	Deciduous coniferous forest	0.43 (0.20, 0.90)	0.014
	Deciduous broadleaved forest	0.47 (0.31, 0.70)	< 0.001
	Mixed coniferous and broad leaved forest	0.63 (0.40, 0.99)	0.031
	Shrubs	10.52 (5.53, 22.46)	< 0.001
Grassland	Meadow grassland	0.20 (0.11, 0.34)	< 0.001
	Typical grassland	0.51 (0.36, 0.72)	< 0.001
	Desert grassland	0.06 (0.02, 0.13)	< 0.001
	Alpine meadow	0.001 (0.06, 0.02)	0.130
	Alpine steppes*	-	-
	Shrubland	2.48 (1.32, 5.00)	0.003
Farmland	Paddy field	2.31 (1.80, 3.00)	< 0.001
	Irrigated land	1.88 (1.51, 2.34)	< 0.001
	Dryland	0.62 (0.5, 0.76)	< 0.001
Settlement	Urban constructive land	0.44 (0.32, 0.60)	< 0.001
	Rural settlement*	-	-

Note. *Indicates that this landscape type was not the predominant landscape in any administrative unit.

Supplementary Table S2. Univariate Analysis of Landscape Risk for Japanese Encephalitis in High-endemic Counties Compared with Low-endemic Counties in Mainland China

Major Class Types	Secondary Class Types	*OR* (95% *CI*)	*P* Value (Chi square test)
Forest	Evergreen coniferous forest	0.95 (0.68, 1.32)	0.770
	Broad-leaved evergreen forests	0.55 (0.39, 0.79)	0.005
	Deciduous coniferous forest	0.58 (0.10, 1.20)	0.400
	Deciduous broadleaved forest	0.97 (0.48, 1.85)	0.920
	Mixed coniferous and broad leaved forest	0.26 (0.08,0.68)	0.003
	Shrubs	3.26 (2.30, 4.63)	< 0.001
Grassland	Meadow grassland	0.53 (0.13, 1.65)	0.250
	Typical grassland	0.52 (0.26, 0.98)	0.036
	Desert grassland*	-	-
	Alpine meadow*	-	-
	Alpine steppes*	-	-
	Shrubland	1.17 (0.61, 2.16)	0.600
Farmland	Paddy field	0.92 (0.69, 1.21)	0.520
	Irrigated land	0.84 (0.64, 1.08)	0.160
	Dryland	2.53 (1.89, 3.40)	< 0.001
Settlement	Urban constructive land	0.22 (0.09, 0.46)	< 0.001
	Rural settlement*	-	-

Note. *Indicates that this landscape type was not the predominant landscape in any administrative unit.

Supplementary Table S3. Multivariable Logistic Regression Analysis of Landscape Risk for Japanese Encephalitis in Endemic Counties Compared with Non-endemic Counties in Mainland China

Landscape	***OR* (95% *CI*)**	***P* Value**
Evergreen coniferous forest	5.80 (4.02, 8.36)	< 0.001
Broad-leaved evergreen forests	4.41 (3.19, 6.10)	< 0.001
Shrubs	19.64 (10.16, 37.97)	< 0.001
Shrubland	4.94 (2.63, 9.27)	< 0.001
Paddy field	4.24 (3.19, 5.63)	< 0.001
Irrigated land	3.44 (2.67, 4.43)	< 0.001
Dryland	1.34 (1.05, 1.72)	< 0.001

Supplementary Table S4. Multivariable Logistic Regression Analysis of Landscape Risk for Japanese Encephalitis in High-endemic Counties Compared with Low-endemic Counties in Mainland China

Landscape	***OR* (95% *CI*)**	***P* Value**
Broad-leaved evergreen forests	1.74 (1.21, 2.50)	0.003
Shrubs	5.29 (3.63, 7.72)	< 0.001
Paddy field	1.69(1.23, 2.32)	0.001
Irrigated land	1.58 (1.16, 2.13)	0.003
Dryland	4.06 (2.91, 5.67)	< 0.001