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Short-term effects of floods on Japanese encephalitis in Nanchong, China, 2007–2012: A time-stratified case-crossover study

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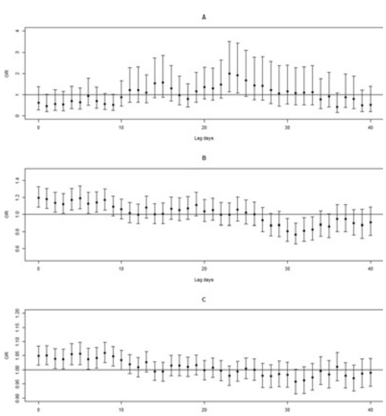
HIGHLIGHTS

- A case-crossover study was used to quantify the impact of floods on JE.
- Floods significantly increased the number of JE cases from lag 23 to lag 24.
- Results will provide recommendations to take measures to prevent JE infection.

GRAPHICAL ABSTRACT



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ABSTRACT

This time-stratified case-crossover study aimed to quantify the impact of floods on daily Japanese encephalitis (JE) cases from 2007 to 2012 in Nanchong city of Sichuan Province, China. Using conditional logistic regression analysis, we calculated the odds ratios (ORs) and 95% confidence intervals (CIs) at different lagged days, adjusting for daily average temperature (AT) and daily average relative humidity (ARH). A total of 370 JE cases were notified during the study period, with the median patient age being 4.2 years. The seasonal pattern of JE cases clustered in July and August during the study period. Floods were significantly associated with an increased number of JE cases from lag 23 to lag 24, with the strongest lag effect at lag 23 (OR = 2.00, 95% CI: 1.14–3.52). Similarly, AT and ARH were positively associated with daily JE cases from lag 0 to lag 8 and from lag 0 to lag 9, respectively. Floods, with AT and ARH, can be used to forecast JE outbreaks in the study area. Based on the results of this study, recommendations include undertaking control measures before the number of cases increases, especially for regions with similar geographic, climatic, and socio-economic conditions as those in the study area.

1. Introduction

Japanese encephalitis (JE) is a serious mosquito-borne viral encephalitis that is endemic in Asia and northern Australia (Wang and Liang,

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2015). In Asia alone, it is estimated that 67,900 cases of JE have occurred annually, with a 20–30% case-fatality rate (Centers for Disease and Prevention, 2013). In China, >2 million cases of JE were reported between 1950 and 2011, representing a considerable burden on the Chinese health authorities (Gao et al., 2014). Approximately 30–50% of cases who survive the infection can experience severe neurological and mental sequelae (Li et al., 2014).

The JE virus (JEV) is mainly transmitted by the mosquito *Culex tritaeniorhynchus* (Erlanger et al., 2009), which prefers to breed in pools of stagnant water (such as in rice paddy fields) (Solomon et al., 2000). The principle amplifying hosts are pigs and wading birds; humans are considered to be a dead-end host for this virus due to the transient and low titer of viremia in humans (Vaughn and Hoke, 1992). Humans can be infected with JEV when living or travelling in close proximity to the enzootic cycle of the virus (Solomon et al., 2000). Transmission of JEV is predominant in rural agricultural areas, often associated with rice cultivation and flooding irrigation in the monsoon season (Ahmad et al., 2015; Phukan et al., 2004). Rainfall is one of the most important contributors to JE cases; appropriate breeding sites are available after a monsoon rain for mosquitoes to lay their eggs, with a suitable relative humidity to prolong mosquito survival, of at least 50–60% (Reiter, 2001). As the mosquito numbers increase, so does the carriage of JEV and the rate of infection of pigs, followed by infections in humans (Solomon et al., 2000).

Little is known about the quantitative impact of floods, as natural disasters related with rainfall, on cases of JE. Flooding, which is defined as an overflow of surface runoff that submerges towns and farmland (Ding et al., 2014), is the most common natural disaster in both developed and developing countries. The Intergovernmental Panel on Climate Change (IPCC) projects that the areas affected by monsoon systems globally will increase during the 21st century, with monsoon precipitation likely to intensify, thereby causing or amplifying flood events (Patz et al., 1996). Therefore, this study was undertaken to examine the relationship between floods and JE in Nanchong city of Sichuan Province, China, to better understand the impact of floods on mosquito-borne diseases.

2. Materials and methods

2.1. Data collection

The study period covered 6 years (2007–2012), during which time 2181 cases were notified in Sichuan Province (Fig. 1); most of these cases were notified in Nanchong city, which is located in northeastern Sichuan Province (between longitude 105°27′–106°58′E and latitude 30°35′–31°51′N). Therefore, we chose Nanchong city as the study site.

Nanchong city has an area of 12,500 km^2 and total population of 7.59 million (Fig. 1). The city has a mid-subtropical monsoon climate, with an annual average temperature of 17 °C, a total 1350 h of sunshine, and 1100 mm of rainfall. The main crops are rice, corn, and wheat. In 2014, pig farmers bred a total of 6.3 million pigs. The principle production modes in Nanchong, such as growing rice and raising pigs, provide

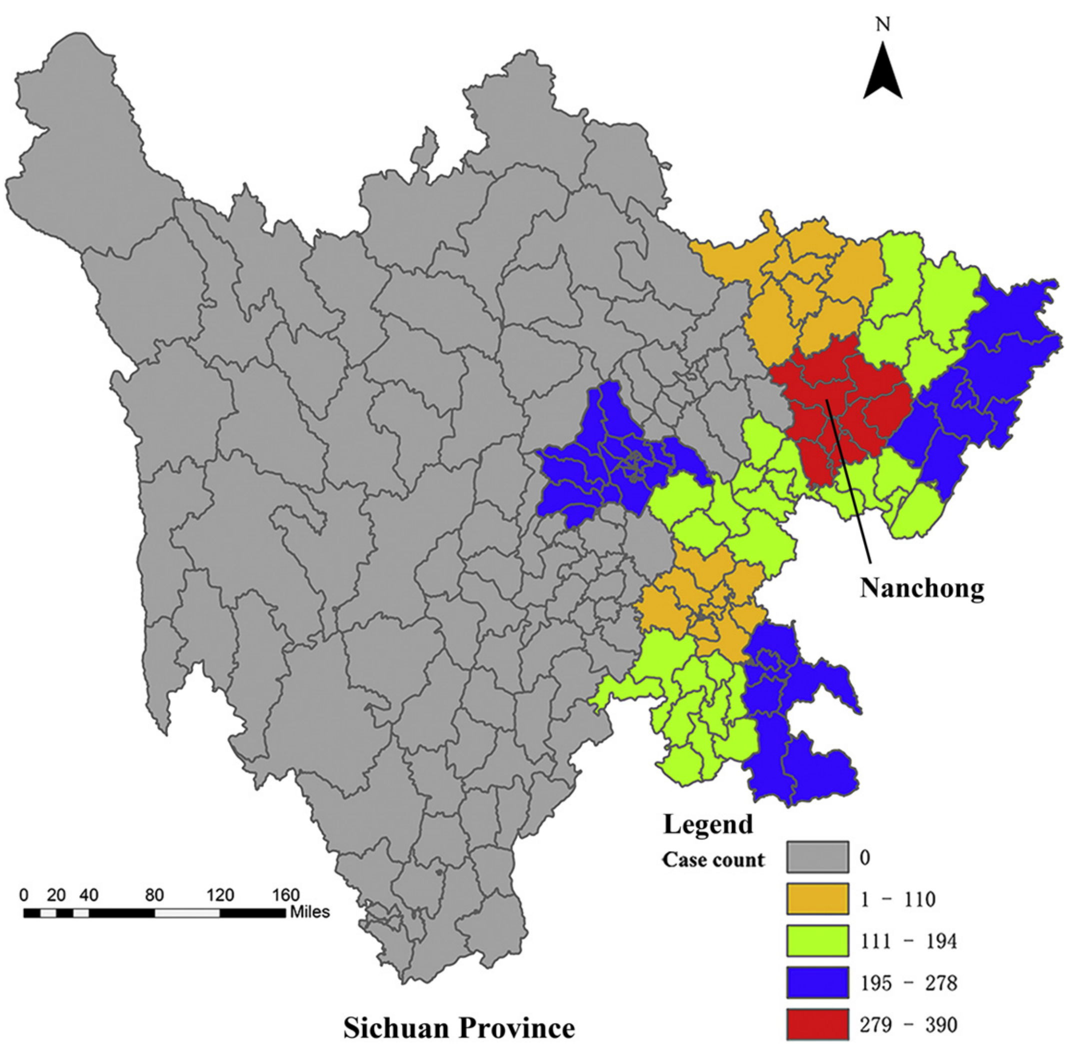

Fig. 1. Reported Japanese encephalitis cases in Sichuan Province, China, 2007–2012.

favorable breeding sites for *C. tritaeniorhynchus* and the ability to transmit JEV from pigs.

In China, the reporting system for cases of JE has been mandated by law since 1951 (Wang and Liang, 2015). JE is a notifiable Class-B communicable disease, and all clinical and hospital doctors are required to report every JE case to the local Centers for Disease Control and Prevention through the National Notifiable Disease Report System within 24 h (National Health and Family Planning Commission (Producer), 2006). Most reported cases were based on clinical diagnosis. The main clinical symptom of JE is encephalomeningitis, combined with fever, malaise, nausea, convulsion, headache, or flaccid paralysis. Several asymptomatic but highly suspected cases have serological confirmation.

For the present study, cases of JE were collected daily from the China Center for Disease Control and Prevention, and the following information was obtained: age, sex, disease name, disease classification, and dates of morbidity and mortality.

Data on floods were collected from the Yearbook of Meteorological Disasters in China. Cumulative rainfall of >80 mm for three consecutive days was defined as a flood. Because all floods are described as city-wide in the yearbook, all areas in the city were considered exposed when a specific flood occurred (Song, 2010, 2011, 2012, 2013; Xiao, 2008, 2009).

Data for the following meteorological variables were provided by the China Meteorological Data Sharing Service System (http://cdc.nmic.cn/home.do): daily average temperature (AT), daily average relative humidity (ARH), and daily rainfall (RF). The mean AT, ARH, and RF values from the two meteorological stations in Nanchong were used.

2.2. Statistical analysis

Descriptive analyses were performed for the distribution of daily JE cases and meteorological factors. Because all of the floods and 94.9% of the cases of JE occurred in the summer (July and August; whole year vs. summer: 390 vs. 370) during the study period, data analysis was restricted to these two months.

Second, we used a time-stratified case-crossover design to quantify the effect of floods on the risk of JE. The case-crossover design was developed from the case-control design to estimate the association between short-term exposure and the risk of an adverse health event (Maclure, 1991). Only cases are required for such a study. For each individual case, exposure at the 'index' time (the hazard period prior to the event) is compared with exposure at other control (or "referent") times. Using within-person comparisons, time-independent confounders are controlled by design, rather than by statistical modeling. More importantly, with the proper selection of referents, time-dependent confounders (for example, if the referents are restricted to the same month as the index time) can also be controlled (Janes et al., 2005a, 2005b). The morbidity data for every day of the six summers during the study period were selected as the index days in our time-stratified approach. The days falling on the same day of the week within the same month as the index day were selected as referent days (i.e., one index day was matched with three or four referent days). A dummy variable was used to represent flooding days (1) and non-flooding days (0). The association between the JE morbidity rate and flood status was estimated using odds ratios (ORs) and 95% confidence intervals (CIs), which were produced using conditional logistic regression with a weight equal to the number of cases on that index day. Meteorological variables that could influence the incidence of JE were adjusted in the multiple conditional logistic regression model. Several studies have explored the association between JE and climate variation. For example, temperature is an important factor in the transmission of JE because it can not only affect the development of mosquitoes but also enhance the growth of virus in an amplifying host and vector (Patz et al., 1996; Rueda et al., 1990). In addition, relative humidity directly affects evaporation rates of mosquito breeding sites, which results in a greater chance of a mosquito feeding on an infected animal and transmitting the virus to humans or other animals (Bi et al., 2007; Lin et al., 2012). Therefore, we included AT and ARH in the final model when analyzing the effect of floods on the morbidity of JE. Additionally, considering the incubation period of JE and habitual characteristic of mosquitoes, lagged effects (lag 0 to lag 40) were assessed using the same methods. All statistical analyses were performed using R 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Descriptive analysis for the disease and meteorological data

According to the Yearbook of Meteorological Disasters in China, nine floods (2007: 5 July to 7 July, 16 July to 19 July; 2008: 21 July to 23 July; 2009: 10 July to 11 July, 1 August to 3 August; 2010: 17 July to 19 July, 21 August to 23 August; 2012: 4 July to 5 July, 31 August) occurred in Nanchong city, with 42 million people affected and 145 killed (Fig. 2). The floods affected 0.4 million hectares of crops, and the economic damage was estimated at approximately 4.5 billion Yuan (US $0.72 billion) (Song, 2010, 2011, 2012, 2013; Xiao, 2008, 2009).

Most JE cases occurred in July and August, indicating a distinct seasonal pattern of JE morbidity (Fig. 2). The AT distribution, but not the ARH distribution, had the same peak as the JE cases. The distribution of daily JE cases and meteorological factors in Nanchong are shown in Table 1. A total of 370 notified JE cases were identified by the local hospitals, with 26 deaths, in the summer months during the study period (mean number of cases, 1.0; range, 0–8). The median age was 4.2 years (range, 5 months to 13 years), with a male: female ratio of 1.3:1.

The mean daily AT during the study period was 27.2 °C, and the mean daily ARH was 76.5% (range, 49.0–97.5%).

3.2. Conditional logistic regression analysis

In the conditional logistic regression multivariate model, floods were positively related with the morbidity of JE cases from lag 23 to lag 24, with the strongest lag effect at lag 23 (OR = 2.00, 95% CI: 1.14–3.52; Fig. 3). Similarly, AT and ARH were positively related with daily JE cases from lag 0 to lag 8 and from lag 0 to lag 9, respectively.

4. Discussion

To the best of our knowledge, this is the first epidemiological study to assess the impact of floods on JE. The results suggest that exposure to flood can increase the incidence of JE. Therefore, floods can be considered early warning signals for the number of JE cases, allowing earlier action in the course of the epidemic or increasing the available time to implement control measures before the number of cases becomes excessive, especially for regions with similar geographic, climatic, and socio-economic conditions as those in Nanchong city.

In the present study, JE predominantly affected children younger than 4.2 years old, which is consistent with previous research conducted in many other regions (Lopez et al., 2015; Phukan et al., 2004). For example, in northeast India, most JE cases were aged 7–12 years (34.2%) (Phukan et al., 2004). In northern Thailand, the estimated incidence of JE was up to 40 per 100,000 for people aged 5–25, decreasing to almost zero for those aged >35 years (Solomon et al., 2000). This phenomenon could be attributed to the weak resistance to JEV in children, as well as the tendency for children to play outdoors at twilight when swarms of mosquitoes are active. The number of human JE cases is determined by multiple factors, among which the percentage of protective antibody-positivity in humans plays the greatest role (Tsai, 2000). As a result, a robust JE vaccination program should be implemented among the young population.

There was a distinct seasonal distribution of daily JE cases in Nanchong city during the study period, which was probably related

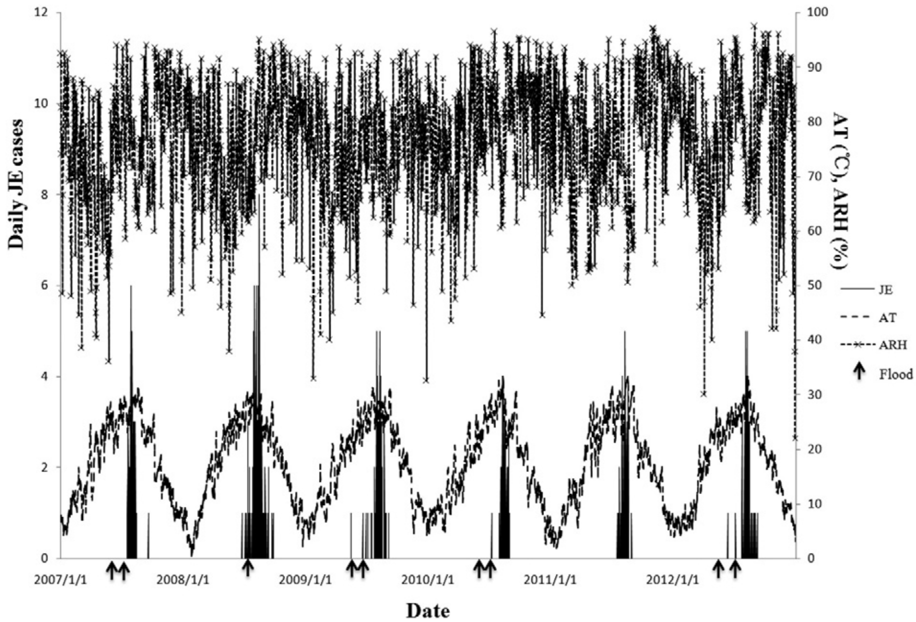

Fig. 2. Daily incidence of Japanese encephalitis and meteorological factors in Nanchong, 2007–2012. JE, Japanese encephalitis; AT, average temperature; ARH, average relative humidity.

with mosquito growth and development, the propagation of the virus in mosquitoes, and increased contact between humans and mosquitoes during the rainy and hot summer (Bi et al., 2003). JE cases were positively correlated with AT and ARH from lag 0 to lag 8 and from lag 0 to lag 9, similar to the findings of other studies that examined the impact of environmental factors on the incidence of JE elsewhere in China (Bai et al., 2013; Bi et al., 2003; Bi et al., 2007; Hsu et al., 2008; Lin et al., 2012). In theory, high temperatures could lead to more rapid development of larvae and reduce the extrinsic incubation period for viral infections within mosquitoes. As a result, the higher temperature in summer allows mosquito populations to grow faster and to have a higher survival rate, thereby increasing the likelihood of JEV transmission. In addition, activities such as biting and egg laying are also likely to be accelerated in higher temperatures, affecting the transmission rate (Bi et al., 2007; Reiter, 2001). Relative humidity is also an important factor for the transmission of JE. With suitable relative humidity, mosquitoes can survive longer and disperse further. The regression analysis indicated that JE is positively associated with floods from lag 23 to lag 24, with the strongest lag effect at lag 23 (OR = 2.00, 95% CI: 1.14–3.52). A certain amount of precipitation during the floods not only provides the medium for breeding but also increases the relative humidity that enhances the longevity of adult mosquitoes, which in turn facilitates the transmission of JEV to humans (Bai et al., 2013; Bi et al., 2003; Bi et al., 2007). The relationship between rainfall and cases of JE has been confirmed in various geographic regions. In Indonesia, the seasonal abundance of two JE vector species (*C. tritaeniorhynchus* and *Culex gelidus*) was significantly correlated with rainfall (Suroso, 1989). A time-series analysis conducted over the period 1980–1996 in eastern China found that monthly precipitation had a significant relationship with the transmission of JE, with a 1-month lag (Bi et al., 2003). In another study in the Jinan metropolitan area, monthly total rainfall had a positive effect on the monthly notification of JE, with a 2-month lag (Bi et al., 2007). Similar findings have been also found in Taiwan and India (Borah et al., 2013; Hsu et al., 2008). However, testing of flooded water for mosquito larvae and monitoring of mosquito density after floods were not performed in the present study. Therefore, whether the flooded water was suitable for breeding of *C. tritaeniorhynchus* needs to be clarified in additional studies.

Table 1
Description of cases of Japanese encephalitis, collected daily, and meteorological factors from July to August 2007–2012, in Nanchong.

	Mean ± SD	Minimum	P_{25}	Median	P_{75}	Maximum
JE	1.0 ± 1.4	0.0	0.0	0.0	2.0	8.0
AT	27.2 ± 2.7	20.2	25.3	27.5	29.2	33.3
ARH	76.5 ± 9.7	49.0	69.5	75.8	84.0	97.5

SD, standard deviation; P_{25}, 25th percentile; P_{75}, 75th percentile; JE, Japanese encephalitis; AT, average temperature; ARH, average relative humidity.

The 23-day lag between floods and JE cases in the present study indicates that it took only 23 days for JEV to infect human beings. In general, water can become stagnant within 1 day after a flood. The duration from egg development to adult mosquitoes is about 9–15 days (Ding et al., 2014). Then, JEV-infected *C. tritaeniorhynchus* can transmit the virus to humans, with an incubation period for JE of approximately 4–21 days (Gong, 1980). Once JE infection is confirmed, doctors must report it to the local CDC within 24 h. Therefore, approximately 15–38 days are required for the JEV to complete its infection process. Therefore, the short duration in the current study is biologically plausible. Both a high density of pig breeders and mosquito population can facilitate the achievement of the threshold density of the mosquito population (Hsu et al., 2008). Besides, the floods could indirectly affect the intermediate stage of JEV infection through providing proper environmental conditions (i.e. rainfall, humidity and temperature) for adult mosquitoes' activity, rather from the beginning of the infection process (Borah et al., 2013; Tian et al., 2015). Given a lack of research studying the relationship between JE and flood or rainfall on a daily basis, more studies should be done to confirm the lag period found in the present study.

One main advantage of the present study is the investigation of the impact of floods on JE cases on a daily basis in Nanchong, Sichuan Province. A daily scale is more suitable for disease control and prevention by providing more timely information for diseases with short incubation periods (Chen et al., 2014).

Several limitations must also be acknowledged. First, a number of variables could also influence the incidence of JE during days of flooding, including the activity and numbers of vector mosquitoes, location of pig farms, bodies of water surrounding houses, and rice cultivation; this information was not available from our data sources. Second, the levels of JEV activity in nature are not reflected directly by the number of JE cases in countries with strong JE vaccination programs, in which most of the population has protective immunity (Kurane et al., 2013); this could lead to underestimating the association between floods and JEV. Third,

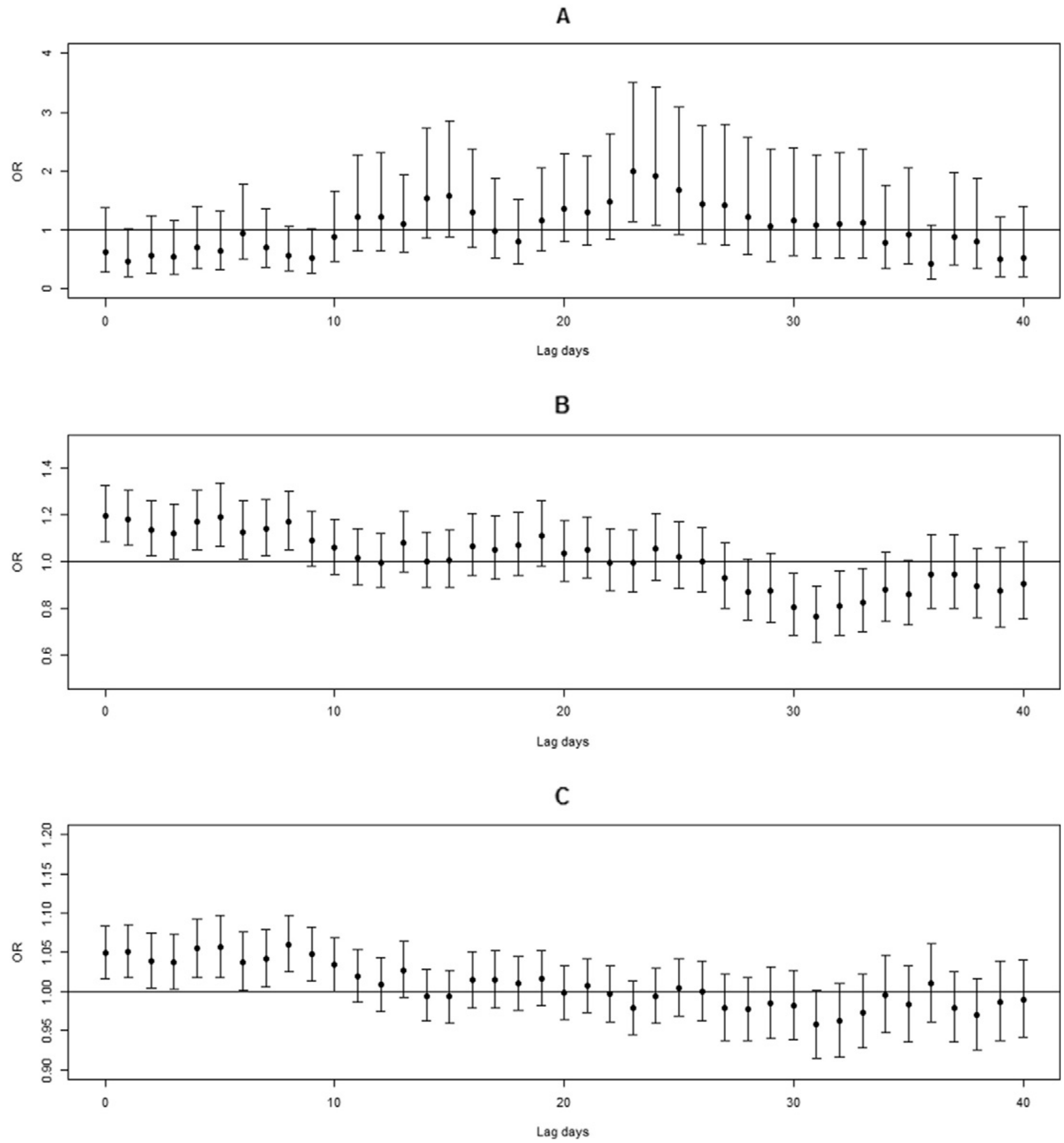

Fig. 3. Odds ratio (OR) estimates of floods (A), daily average temperature (B), and daily average relative humidity (C) on the risk of Japanese encephalitis in different lagged days from July to August 2007–2012, in Nanchong.

under-reporting is an inevitable issue in disease surveillance systems. The notified cases might be only those with serious symptoms who chose to visit doctors in hospitals, which could also lead to underestimation of the risk of JE ascribed to floods. Last, more recent data should be included, when they are available.

In conclusion, our study confirmed that floods, together with AT and ARH, can be used to forecast JE outbreaks in the study area. Therefore, public health actions should be undertaken after floods to reduce future JE cases.

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Conflict of interest

None.

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