

Time series analysis of Japanese encephalitis and weather in Linyi City, China

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Received: 30 March 2010/Revised: 18 September 2010/Accepted: 2 December 2010/Published online: 10 February 2011
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Abstract

Objectives To examine the relationship between meteorological factors and epidemiological pattern of Japanese encephalitis in Linyi City during 1956–2004.

Methods Autoregressive integrated moving average (ARIMA) models were used to evaluate the relationship between monthly JE incidence and weather factors. Logarithmic transformation was applied to the JE incidence series to assure the normality and homogeneity of variance of the residuals. The effect of mass vaccination on JE incidence was also evaluated using a transfer function in the time series analysis.

Results The analysis suggested that monthly average temperature [$\beta = 0.0574$, 95% confidence interval (CI) = (0.0172, 0.0976)] and relative humidity [$\beta = 0.0082$, 95% CI = (0.0004, 0.0158)] were positively associated with the logarithmic incidence of Japanese encephalitis after adjusting for mass vaccination in this area.

Conclusions Weather variables might be treated as possible predictors of Japanese encephalitis incidence for regions with similar geographic, weather, and socio-economic conditions to Linyi, China.

Keywords Japanese encephalitis · Time series analysis · Vaccination · Weather · Linyi City · China

Introduction

Japanese encephalitis (JE) is a viral disease that infects animals and humans, transmitted by mosquitoes, with the potential to significantly increase and expand in response to climate change (Gubler 1998; Zarocostas 2008; Kovats 2010; Vineis 2010). It is estimated that three billion persons live in countries where the JE virus is endemic worldwide (Erlanger et al. 2009); at present it is widely distributed in the South and South-East Asian countries, including Japan, China, Malaysia, Indonesia, India, and Bangladesh, etc. (Parida et al. 2006; Li et al. 2009), and it has recently spread to new territories (Van Den Hurk et al. 2006; Erlanger et al. 2009).

Analyses of the historical data from the recent past can elucidate how variations in weather factors affect transmission pattern of Japanese encephalitis. The findings can be applied in a modeling exercise to estimate the future patterns (Hsu et al. 2008; Forastiere 2010; Kovats 2010). The world has undergone a general increase in ambient temperature by 0.6°C over the past century (Houghton et al. 2001), followed by a range of ecological consequences (Walther et al. 2002; Kjellstrom et al. 2010). The possible relationship between global climate change and transmission of Japanese encephalitis and its geographic spread has been discussed (Nicholls 1993; Bi et al. 2003;

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Bi et al. 2007). The relationship between climate and Japanese encephalitis may be highly dependent upon the local environmental factors, and it is not always possible to extrapolate to a broader scale. Investigations that examine the consistency of local weather conditions and Japanese encephalitis in different environmental and regional contexts can improve our understanding of the linkages between weather variables and JE transmission and provide a stronger scientific foundation for predicting future transmission patterns (Bosello et al. 2006).

Since the first report in 1949, JE epidemics have occurred in China for over 50 years (Wang et al. 2007a). Human cases of Japanese encephalitis occur in all Provinces in mainland China except for Tibet, Xinjiang and Qinghai Provinces (Wang et al. 2004). In China, the main reservoir hosts of this disease are pigs (Li et al. 2009); recently, bats were found to be a possible reservoir in southern China (Cui et al. 2008; Wang et al. 2009b). Mosquitoes, mostly *Culex tritaeniorhynchus*, are the main vectors of JE in China (Li et al. 2009). Although mass vaccination has been extensively applied in China since the 1970s, there are still about 8,000 human cases reported in China every year, and an increasing trend has been observed in recent years (Wang et al. 2004). The fatality of Japanese encephalitis in China varies across regions, ranging from 2.16 to 25.71% during 1991–2005 according to a national wide analysis (Guo et al. 2006). In 2006, an outbreak occurred in Shanxi Province causing 19 deaths (Wang et al. 2007b).

Factors affecting transmission of the disease probably include seroincidence rate of JE among pigs, mass vaccination, rainfall, temperature, humidity, population immunity, the species of mosquitoes to be infected and their ecological settings and related control measures, and the level of social and economic development (Guo et al. 2006; Bi et al. 2007). In endemic areas, residents usually have immunity by vaccination or naturally acquired, which can reduce the risk of illness for a certain period. Along with the development of global trade and international tourism, combined with the global climate change, more and more geographic locations became JE epidemic areas; because travelers from endemic areas can bring the virus and geographical expansion of the vector mosquitoes makes the transmission possible (Ritchie and Rochester 2001; van den Hurk et al. 2009). It is important to study the impact of weather variability on the transmission of Japanese encephalitis because global warming might change the patterns of temperature and precipitation (Houghton et al. 2001; Anyamba et al. 2006), which may influence the development of mosquitoes and the virus, as well as people's behavior. For example, proper temperature is an important ecological component in the transmission of JE because it affects the development and infection cycle of

both the mosquito and the virus (Bi et al. 2003). Humidity is also essential for the propagation and development of the mosquitoes (Thomson 2009).

We have used spatial and temporal analysis techniques to study the relationship between weather variability and the transmission of malaria, hemorrhagic fever with renal syndrome and dengue fever in China (Lin et al. 2007; Tian et al. 2008; Lin et al. 2009; Lu et al. 2009). Few studies, however, have been done on the effect of weather variability on Japanese encephalitis, which is still a serious infectious disease in China and nearby countries (Wang et al. 2007b; Morita 2009). The present study examines the effect of weather variables, along with mass vaccination, on the incidence of Japanese encephalitis in the city of Linyi, Shandong Province, China over the period 1956–2004.

Methods

Linyi is the biggest city of Shandong Province in northern China. It is located at 117°24'E to 119°11'E and 34°22'N to 36°22'N (Fig. 1). The population is about ten million according to the fifth population census of China; over 95% of the population is of Chinese Han ethnicity. Linyi is a rural city with farming and agriculture as the main industry. Linyi has a warm temperate continental monsoon climate. Summers are hot and rainy and winters are cold and dry.

Japanese encephalitis is a legally notifiable infectious disease in China (Wang et al. 2009a). As an official disease surveillance organization, the Centre for Disease Control and Prevention (CDC) of Linyi City has kept relatively complete JE incidence records for approximately half a century. A JE case was routinely reported according to two definitions: (1) presentation with clinical symptoms related to encephal meningitis, combined with fever, malaise, nausea, convulsion, headache or flaccid paralysis; or (2) asymptomatic but highly suspected by a physician, or conforming to epidemiological evidence. Monthly weather data, including monthly total rainfall, average temperature and relative humidity were retrieved from China Meteorological Data Sharing Service System for the corresponding years 1956–2004. All residents in Linyi City during the period 1956–2004 were treated as the study population. Annual populations for the study period were estimated by interpolation based on the national population census records.

Autoregressive integrated moving average (ARIMA) models were used to evaluate the relationship between monthly JE incidence and weather factors. Logarithmic transformation was applied to the JE incidence series to assure the normality and homogeneity of variance of the

Fig. 1 Location of Linyi City in China. The current study examined the relationship between meteorological factors and epidemiological pattern of Japanese encephalitis in Linyi City during 1956–2004



residuals. The effect of mass vaccination on JE incidence was also evaluated using a transfer function in the time series analysis (Helfenstein 1991; Upshur et al. 1999). Mass vaccination began in Linyi since 1970. Without information on the detailed time frame of the vaccination strategies, we simply treated vaccination as an indicator variable, coded as 0 for pre-1970 and 1 for post-1970, respectively. Transfer functions have two possible parameters. The first parameter, ω , is the magnitude of the asymptotic change in level after intervention. The second parameter, δ , reflects the onset of the change, the rate at which the post-intervention series approaches its asymptotic level. The ultimate change in level is represented by the equation

$$\text{Level change} = \frac{\omega}{1 - \delta}$$

Both ω and δ are tested for significance in the analysis. If the null hypothesis that ω is 0 is retained, there is no impact of intervention. If ω is significant, the size of the change is ω . The δ coefficient varies between 0 and 1. When δ is 0, the onset of the impact is abrupt. When δ is significant but small, the series reaches its asymptotic level quickly. The closer δ is to 1, the more gradual the onset of change (Tabachnick and Fidell 2007; Pridemore and Snowden 2009).

An ARIMA model was first applied to the predictor variable, and then to the dependent variable before the two series were cross-correlated to determine whether an association existed. Modeling with ARIMA involves the estimation of a series of parameters to account for the inherent dynamics in the time series, including the trends

and autoregressive and moving average processes (Diggle 1990). The general model introduced by Box and Jenkins (Box and Jenkins 1976) includes autoregressive and moving average parameters, and explicitly includes differencing in the formulation of the model. An ARIMA (p , d , q) model comprises three types of parameters: the autoregressive parameters (p), number of differencing passes (d), and moving average parameters (q). The multiplicative seasonal ARIMA (p , d , q) (P , D , Q)s model is an extension of the ARIMA method to time series in which a pattern repeats seasonally over time. Analogous to the simple ARIMA parameters, the seasonal parameters are: seasonal autoregressive (P), seasonal differencing (D), and seasonal moving average parameters (Q). The length of the seasonal period is represented by s .

Each of the weather series at lags of 0–3 months and vaccination series, respectively, were fitted into the seasonal ARIMA model of monthly JE incidence to screen for potential predictors of JE incidence. Cross-correlation plots were also used as guidance in selecting the lagged effect of weather variation on JE transmission. Those input series significantly associated with JE incidence, with a p value <0.10 , were singled out to fit the best multivariate ARIMA model. The Ljung-Box Q test was applied to ascertain whether the residual series were white noise. The conditional least squares method was applied in the ARIMA procedure of SAS (SAS Institute, Inc., Cary, NC, USA). The selection of ARIMA processes was conducted using Akaike's information criterion (AIC), which measures how well the model fits the series.

Results

The temporal trend of incidence rates of Japanese encephalitis in Linyi between 1956 and 2004 is plotted in Fig. 2. There were totally 43,517 cases reported in Linyi over the study period. Figure 2 shows a major incidence peak in August of 1966, with an incidence of 93.69 per 100,000, which corresponded to an annual mean temperature increase in that year. Besides the major epidemic peak, several minor peaks were also observed, mainly before the year of 1975; and then the incidence has been declining over the recent decades. As shown in Fig. 2, there was an obvious seasonal distribution of the disease, with most cases occurring in summer and autumn, from July to October. Augmented Dickey–Fuller test with no lagged differences and with one lagged difference indicated that the logarithmic JE incidence was a stationary time series. No differencing was needed to meet the stationarity requirement for ARIMA analysis. Figure 3 shows the plots of cross-correlation between the prewhitened weather variables (monthly mean temperature and relative humidity) and the logarithmic JE incidence. The cross-correlation was the strongest at a lag of 0 month.

Table 1 shows the results for two models: Model A without weather variables and Model B with weather variables. Both the likelihood ratio test and AIC value comparison indicated that the addition of the weather variables significantly improved the model fit. The seasonal moving average parameter in Model B was 0.7057; the standard and seasonal autoregression parameters were 0.4077 and 0.9834, respectively, all of which were statistically significant. A total of 3 input series were found to be significantly associated with JE incidence. Two input series, monthly average temperature ($\beta = 0.0574$,

$p = 0.0042$) and relative humidity ($\beta = 0.0082$, $p = 0.0333$) at a 0-month lag, were positively associated with JE incidence. Another input series, mass vaccination, was inversely associated with JE incidence ($\omega = -0.0059$, $p = 0.0031$). The intervention effect of vaccination on the JE incidence was found to be gradual and permanent as indicated by a parameter δ close to 1. The combinations of monthly average temperature, rainfall, relative humidity, and vaccination were added to the multivariate models as input series. Of all the models tested, the seasonal ARIMA (1, 0, 1) (1, 0, 1)₁₂ model fits the data best according to the AIC and goodness-of-fit criteria. The best fitting model includes monthly average temperature, relatively humidity and vaccination as the predicting variables for the JE incidence.

Discussion

Vector-borne diseases are associated with the meteorological conditions for two reasons: the extrinsic reason related to the mosquito's sensitivity to weather conditions and the intrinsic reason related to the host pathogen population dynamics (Hay et al. 2000). It is essential to investigate the relationship at the regional and local levels. Time series analysis method has been used extensively to study the effect of weather variability on vector-borne diseases (Luz et al. 2008; Tian et al. 2008; Lu et al. 2009). In the current study, we used the time series method to examine the effects of weather variability and vaccination on JE incidence in the rural city of Linyi for the period 1956–2004. The results indicate that an increase in monthly average temperature and relative humidity is associated with an increase of JE incidence, which is in general

Fig. 2 The monthly Japanese encephalitis incidence rate (1/100,000) in Linyi City, China, 1956–2004

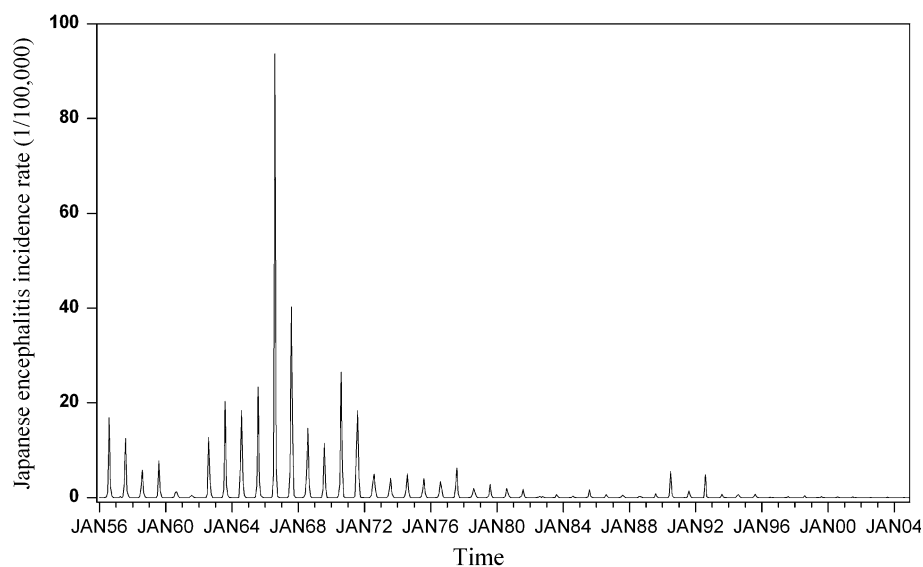


Fig. 3 Cross-correlation between the prewhitened weather variables (monthly mean temperature and relative humidity) and the logarithmic Japanese encephalitis incidence rate (1956–2004) in Linyi City, China. The shaded areas represent the 2 standard error range of the cross-correlation function. CCF: cross-correlation function

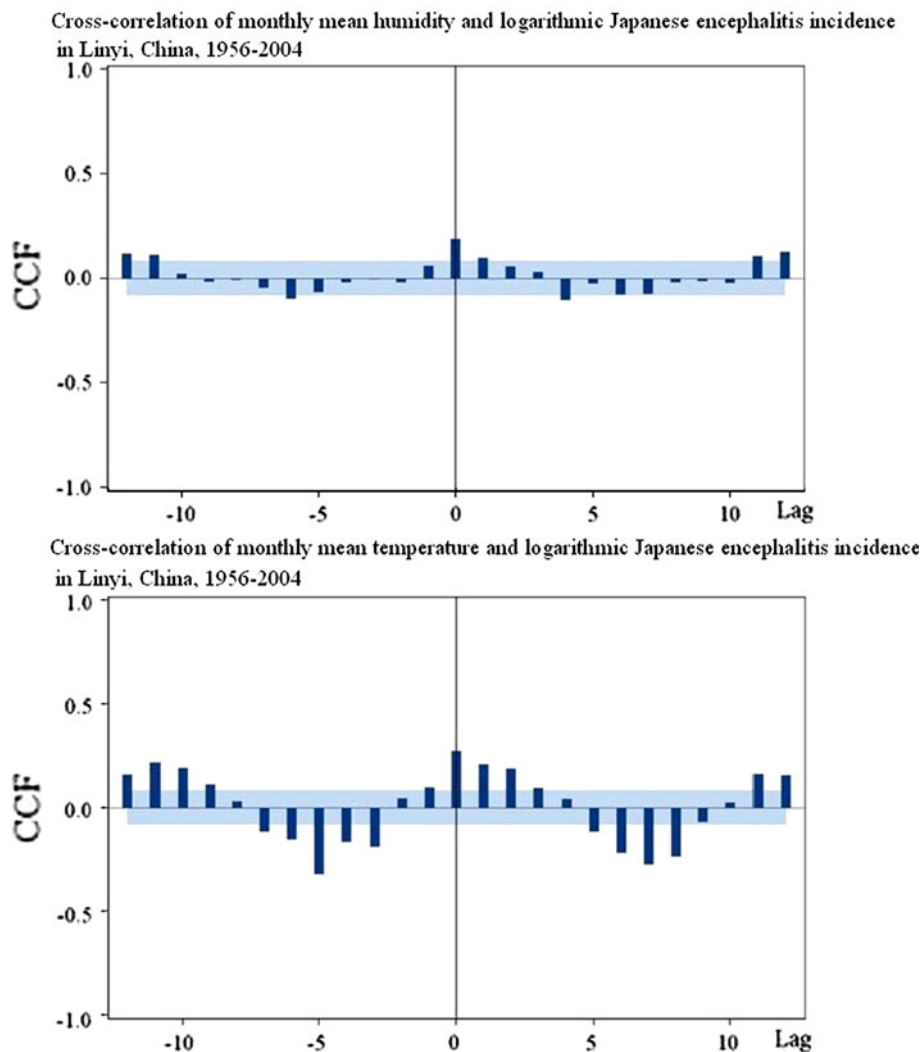


Table 1 ARIMA regression of the logarithmic monthly Japanese encephalitis incidence (1956–2004) on weather and vaccination factors in Linyi, China

	Model A			Model B		
	β	SE	p	β	SE	p
Seasonal moving average	0.7099	0.0321	<0.0001	0.7057	0.0333	<0.001
Auto-regression	0.4052	0.0381	<0.0001	0.4077	0.0382	<0.001
Seasonal auto-regression	0.9889	0.0039	<0.0001	0.9834	0.0058	<0.001
Vaccination						
Size of change (ω) ^a	-0.0060	0.0031	0.0553	-0.0059	0.0031	0.0534
Onset of change (δ) ^b	0.9989	0.0023	<0.0001	0.9990	0.0022	<0.0001
Temperature				0.0574	0.0201	0.0042
Humidity				0.0082	0.0038	0.0333
Log likelihood		-604.6			-599.0	
AIC		1221.2			1213.9	

ARIMA autoregressive integrated moving average

^a The magnitude of effect of vaccination on the occurrence of Japanese encephalitis

^b The speed of the change of the occurrence of Japanese encephalitis due to the vaccination

agreement with other studies (Mogi 1983; Bi et al. 2007). The effect of vaccination was adjusted for in the time series analysis.

Although Japanese encephalitis has been under control in China, especially after mass vaccination program since the 1970s, there are still around 8,000 cases being notified annually (Guo et al. 2006). Many risk factors can affect the disease transmission pattern: weather factors such as rainfall, temperature, and humidity can affect the breeding of the mosquito vectors; other factors include pig density and vaccine coverage rate and related control measures and residential housing conditions, etc. (Bi et al. 2007; Hsu et al. 2008). It is important to study the impact of weather conditions on the transmission of Japanese encephalitis because global warming might change the patterns of temperature and precipitation, which may influence the growth and distribution of the mosquitoes, and thus the virus as well (Yang et al. 2009).

Monthly mean temperature was found to be associated with the elevated JE incidence in the temperate City of Linyi, China. On a secular scale, the major JE incidence peak in 1966 also corresponded to an annual mean temperature increase. The association between temperature and JE incidence is biologically plausible because temperature can affect three aspects of JE transmission: (1) the survival and reproduction rates of *Culex tritaeniorhynchus*; (2) the intensity, particularly the biting rate, of *Culex tritaeniorhynchus* activity; and (3) the development, survival, and reproduction rates of the JE virus within *Culex tritaeniorhynchus*. Higher temperatures, within limits, can lead to more rapid development of larvae, shorter times between blood meals, and faster incubation times for viral infections within mosquito populations. As a result, increases in temperature allow mosquito populations to reach higher density faster, and to be maintained for longer time, thereby increasing the opportunities for viral transmission to human beings.

Relative humidity is an important factor in the transmission of JE; it is an important component of the living condition of mosquitoes, and it also directly affects evaporation rates of mosquito breeding sites, so the development and breeding of the mosquitoes have some relationship with the relative humidity (Dow and Gerrish 1970; Tong et al. 2002). In the current study, the time series regression found a positive association between the relative humidity and the JE incidence. Generally, in places with higher humidity, mosquitoes can survive longer and spread further, which allows them to have a higher chance of feeding on an infected animal and transmitting a virus to humans or other animals (Tong and Hu 2001).

Rainfall is generally expected to be associated with the JE incidence while it fails to enter the best fitting predictive model in the current study. Provided that rainfall has a

linear dose–response effect on fluctuations in mosquito density, and thus JE incidence, this effect would emerge also in fluctuations in the monthly data after filtering out the seasonal component. Within some limits, more rainfall can provide more breeding sites for the mosquitoes, and lengthen their life, which helps the virus spread cycle and transmission of the infection to humans. In some studies, however, rainfall was found to be inversely related to JE incidence (Mogi 1983), because heavy rainfall or even storms might destroy existing breeding sites of mosquitoes or their larvae, interrupt the development of mosquito eggs or larvae, or simply flush the eggs or larvae out of the breeding sites (Tian et al. 2008).

The finding on time lag 0 of climate variables for the JE incidence in Linyi suggests that it takes less than 1 month for temperature and humidity to affect occurrence of JE in humans. In Linyi, the pigs were usually kept at homes, which, along with the high density of mosquitoes, may facilitate the spread the virus from pig population to human beings and account for the shorter duration.

Seasonal dependence (seasonality) is apparent in the time series of JE incidence in the current study area. Seasonality is one type of autocorrelation, which refers to the correlation of a time series with its own past and future values. Cross-correlations are correlations between the two time series shifted in time relative to one another. In the presence of autocorrelation in the individual series, the estimated cross-correlation function may be distorted (Diggle 1990). Prior to the examination of interdependency between the predictor variables and JE incidence, seasonal autocorrelation has to be removed by prewhitening (Tian et al. 2008). Successful modeling using a seasonal ARIMA model in this study was the basis for the examination of the effects of weather variability and vaccination program on JE transmission.

In the evaluation of the association between weather factors and JE incidence in Linyi, China, the effect of vaccination was adjusted for in the multiple time series analysis. Among all the factors, vaccination plays a very important role in the transmission and related control measurements of Japanese encephalitis (Burchard et al. 2009; Li et al. 2009). Because no specific treatment for the disease has been available yet, and vector control is not feasible in some resource-poor countries, the World Health Organization (WHO) recommends Japanese encephalitis vaccine as the single most effective preventive measure. In Linyi, the vaccination began in the year of 1970 among the susceptible population, mainly infants and children. Overall, an inverse association between the mass vaccination and this disease was noted and the effects were found to be gradual and permanent, which may be explained by the steady development of an immunity barrier in the population.

The present study has a few limitations. First, sporadic or epidemic JE cases were not specified in the incidence database. Second, vaccination was treated as a simple binary variable due to the lack of detailed time frame of different vaccination schemes and vaccination coverage rates over the decades. Lastly, potential confounding factors such as urbanization, changes in agricultural practices, water impoundment, changes in pig husbandry may have influenced JE incidence and may have been associated with the weather factors examined in this study. Due to the lack of historical data, these factors were not adjusted for in the regression modeling.

In conclusion, monthly average temperature and relative humidity are positively associated with the JE incidence in the temperate rural city of Linyi, China. The effect of vaccination in reducing JE incidence is gradual and permanent. These findings should be considered in the prevention and control of Japanese encephalitis in locations with similar geographic, weather, and socio-economic conditions to Linyi, China.

Acknowledgments This study was supported by the National Natural Science Foundation of China (grant No. 30771873) and partially supported by the social welfare research special program of the Ministry of Science and Technology, China (grant No. 2003DIA6N009). One of the authors (HLL) thanks the studentship support by a grant from the NSFC/RGC Joint Research Scheme sponsored by the Research Grants Council of Hong Kong and the National Natural Science Foundation of China (Project No. N_CUHK454_08).

Conflict of interest The authors declare that they have no competing interests.

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