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## Lagged temperature effect with mosquito transmission potential explains dengue variability in southern Taiwan: Insights from a statistical analysis

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## ABSTRACT

The purpose of this study was to link meteorological factors and mosquito (*Aedes aegypti*) abundance to examine the potential effects of climate variations on patterns of dengue epidemiology in Taiwan during 2001–2008. Spearman's rank correlation tests with and without time-lag were performed to investigate the overall correlation between dengue incidence rates and meteorological variables (i.e., minimum, mean, and maximum temperatures, relative humidity (RH), and rainfall) and percentage Breteau index (BI) level >2 in Taipei and Kaohsiung of northern and southern Taiwan, respectively. A Poisson regression analysis was performed by using a generalized estimating equations (GEE) approach. The most parsimonious model was selected based on the quasi-likelihood based information criterion (QICu). Spearman's rank correlation tests revealed marginally positive trends in the weekly mean ( $\rho = 0.28$ ,  $p < 0.0001$ ), maximum ( $\rho = 0.26$ ,  $p < 0.0001$ ), and minimum ( $\rho = 0.30$ ,  $p < 0.0001$ ) temperatures in Taipei. However, in Kaohsiung, all negative trends were found in the weekly mean ( $\rho = -0.32$ ,  $p < 0.0001$ ), maximum ( $\rho = -0.30$ ,  $p < 0.0001$ ), and minimum ( $\rho = -0.32$ ,  $p < 0.0001$ ) temperatures. This study concluded that based on the GEE approach, rainfall, minimum temperature, and RH, all with 3-month lag, and 1-month lag of percentage BI level >2 are the significant predictors of dengue incidence in Kaohsiung (QICu = -277.77). This study suggested that warmer temperature with 3-month lag, elevated humidity with high mosquito density increased the transmission rate of human dengue fever infection in southern Taiwan.

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### 1. Introduction

Dengue fever is a potentially lethal mosquito-borne disease traditionally found mostly in Central American and Southeast Asia. Over 50 million people living in tropical and subtropical urban and semi-urban areas become infected annually with dengue and up to 500,000 people develop a potentially lethal complication called dengue hemorrhagic fever/dengue shock syndrome (Kyle and Harris, 2008). The high prevalence, lack of a registered vaccine or other prophylactic measures, and the absence of specific treatment of dengue fever pose a grave public health threat globally (Mackenzie et al., 2004; Kyle and Harris, 2008; Phillips, 2008).

The viruses and their predominant mosquito vector, *Aedes aegypti* (yellow fever mosquito), are endemic to most of the tropical and subtropical regions of the world (Gubler, 1998). Efforts to reduce dengue fever are limited to vector control. Unfortunately, traditional mosquito control measures are not succeeding. Substantial effort is being devoted to the development of new strategies to complement

existing vector-control methods (Halstead, 2007). With few exceptions, dengue management strategies have been complicated by the inability to completely eradicate *A. aegypti* from urban settings and the ineffective application of long-lasting vector-control programs (Morrison et al., 2008). This has led to a worldwide resurgence of dengue and has highlighted the urgent need for novel and sustainable disease-control strategies (Phillips, 2008).

Taiwan is located in both subtropical and tropical regions with relatively high temperature and relative humidity year-round, forming an ideal condition for the growth of the vector of dengue fever mosquito. Historical epidemics of dengue in Taiwan had been documented in 1902, 1915 and 1922 in Penghu islet, in 1922 and 1927 in southern Taiwan, 1931 in Tainan, and 1942–1943 in island-wild Taiwan (Bureau of Communicable Disease Control, 1987; King et al., 2000). Dengue hemorrhagic fever cases were taken into account since 1994 in Taiwan (Lei et al., 2002). The most well known dengue outbreak in Taiwan has varied since 1987 in that the higher prevalence has occurred in southern Taiwan (Lei et al., 2002). The most severe one in Taiwan occurred in 1998 (Chao et al., 2004). The largest epidemic occurred in 2002, and there were 52 imported and 5336 indigenous cases in southern Taiwan (Centers for Disease Control, 2002). The outbreak in northern Taiwan occurred in 2008. An

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analysis of the weekly frequency of indigenous dengue cases shows that it peaks around September–December. *A. aegypti* were primarily distributed between southern Putai and northern Hengchun (Lei et al., 2002).

Patterns of infection vary though time owing to extrinsic (e.g., climate (Hopp and Foley, 2001; Wu et al., 2007; Johansson et al., 2009)) and intrinsic (e.g., predictor–prey dynamics between the pathogen and the host population (Ferguson et al., 1999; Hay et al., 2000), and immunity and viral factor (Gubler and Rosen, 1977)) effects. Incidence patterns reflect the complex interaction of all of these factors. The incidence of dengue fever in Taiwan varies widely from year to year, showing nearly a tenfold difference between years, indicating that the presence of nonstationarity and nonlinearity exists in incidence data. Wu et al. (2007) indicated that the weather variability such as monthly maximum, minimum temperature, rainfall, and relative humidity (RH) identified as a meaningful and significant indicators for the increasing occurrence of dengue fever in Taiwan region.

Therefore, there have been some suggestions of a strong link between dengue and climate change (Hales et al., 2002; Bartley et al., 2002; Hopp and Foley, 2001). It is also widely accepted that the distribution and dynamics of vector-borne dengue infections are particularly sensitive to meteorological conditions, by virtue of the sensitivity of the *A. aegypti* vectors themselves to variations in temperature, RH, rainfall, evaporation, and quantities of standing water quality used as breeding sites (Promprou et al., 2005; Chowell and Sanchez, 2006; Wu et al., 2007; Halstead, 2008; Su, 2008; Thammapalo et al., 2008; Johansson et al., 2009).

Specifically, the epidemic behavior of dengue viruses seemingly correlates closely with fluctuations in temperature and rainfall (Halstead, 2008; Johansson et al., 2009). Warmer temperatures can increase or reduce survival rate, depending on the vector, its behavior, ecology, and many other factors. A 2 °C increase in temperature would simultaneously lengthen the lifespan of the mosquito and shorten the extrinsic incubation period of dengue virus, resulting in more infected mosquitoes for a longer period of time (Focks and Barrera, 2007). The association of dengue epidemics with rainfall could be explained by increases in adult survival and feeding activity of the vector mosquito. However, some researches gave contradicting evidence on the relationship of meteorological factors to dengue incidence (Kanchanapairoj et al., 2000).

The objective of this study was to link meteorological factors and mosquito abundance to dengue fever dynamics to investigate the dengue fever distribution in Taiwan. Because mosquito population processes and dengue incubation periods in vectors vary with meteorological conditions (e.g., temperature and moisture conditions), climate-based models of dengue fever are powerful predictors of mosquito distribution patterns and average levels of transmission of dengue parasites by these factors. To improve dengue prevention and surveillance, public health officials need to know much more about the patterns of dengue virus transmission and about the factors that underlie these patterns. Early warning systems and disease prevention programme, therefore, will require models that incorporate meteorological factors.

## 2. Materials and methods

### 2.1. Surveillance data

This study was conducted in Taipei and Kaohsiung because of the major dengue epidemic that occurred in southern Taiwan and the latest clustered epidemic area appeared in northern Taiwan. The largest epidemic occurred in 2002 in that there were 52 imported and 5336 indigenous confirmed dengue cases in the area of Kaohsiung. Recently, the dengue cases appeared frequently in northern Taiwan posing an alarming notice. All weekly confirmed dengue cases were

provided by Taiwan Center of Disease Control (Taiwan CDC) from January 1998 to October 2008 including the indigenous and imported cases. Monthly dengue incidence rates per 100,000 population were estimated from monthly confirmed dengue cases over the specific-year-end population size.

### 2.2. Meteorological factors and mosquito abundance

Taipei city is located in the Taipei basin and around Taipei County with a typical subtropical climate. Kaohsiung city/county is the second largest metropolitan area and is located in southern Taiwan with a tropical climate. All weekly meteorological data for the period of 2001–2008 in Taipei and Kaohsiung were adopted from the observations of 13 and 11 monitor stations of Taiwan Environmental Protection Agency (Taiwan EPA), respectively. The weekly maximum, mean, and minimum temperatures, rainfall intensity, and RH in Taipei and Kaohsiung from 2001 to 2008 were used as the study data. Here the weekly maximum temperature is defined as the weekly average of the daily maximum temperature. We chose the percentage of monthly Breteau index (BI) levels >2 as a vector-borne mosquito density index exhibiting the potential transmission risk. Breteau index is the number of positive containers for *A. aegypti* larvae per 100 houses inspected. However, there are some discontinued measurements of BI levels in specific administrative area. Thus we redefined the percentage monthly BI level >2 to be expressed as the potential transmission frequency in this study. BI level data were obtained from Taiwan CDC.

### 2.3. Statistical analysis

Spearman's rank correlation tests were performed to investigate the overall correlation between dengue incidence rates and meteorological variables (i.e., minimum, mean, and maximum temperatures, RH, and rainfall intensity) together with percentage BI level >2 in Taipei and Kaohsiung from the period of 2001–2008, respectively. We also carried out a cross-correlation analysis without and with time-lag to investigate the lagged effects with a lag of zero to 4 months of the meteorological variables on dengue incidence through observation of statistical significance.

The lagged-time Poisson regression analysis was performed. A basic multivariate Poisson regression model can be written as,

$$\ln(Y_t) = \beta_0 + \beta_1 T_{\max,t-n} + \beta_2 T_{\min,t-n} + \beta_3 T_{\text{mean},t-n} + \beta_4 \text{Rain}_{t-n} + \beta_5 \text{RH}_{t-n} + \beta_6 \text{BI}_{t-n}, \quad (1)$$

where  $Y_t$  is the incidence of dengue confirmed cases at time  $t$ ,  $\beta_0$  is the intercept,  $\beta_1$  through  $\beta_6$  represent coefficients,  $T_{\max}$ ,  $T_{\min}$  and  $T_{\text{mean}}$  are the monthly maximum, minimum, and mean temperatures (°C), respectively, Rain is the rainfall intensity (mm), RH is the relative humidity (%), BI is the percentage BI level >2, and  $t-n$  in the subscript represents the  $n$ -month lag time.

The monthly dengue incidence was modeled using a generalized estimating equations (GEE) approach with a Poisson distribution. The most parsimonious model was selected based on the quasi-likelihood based information criterion (QICu) (Pan, 2001; Lu et al., 2009). The lagged-time Poisson regression analyses were performed by using SAS Version 9.1.3 for Windows (SAS Institute Inc., Cary, North Carolina, USA).

## 3. Results

### 3.1. Data description

There are 6800 and 382 reported dengue cases among the population size of 2,766,421 and 6,400,954 in 2008 with the

population growth rates of 3.28% and 6.22% in Kaohsiung and Taipei, respectively, during 1998–2008. In Taipei, the mean and maximum monthly incidence rates were 0.06 and 0.57 per 100,000 population, whereas nearly 2.64 and 45.41 per 100,000 population in Kaohsiung, respectively. Thus, it suggests that a higher alarming rate may focus on Kaohsiung than that on Taipei when the dengue seasons are coming. The largest scales of dengue fever epidemics in Kaohsiung and Taipei were found in 2002 and 2008, respectively (Fig. 1).

Fig. 2 shows the meteorological data and mosquito index in two regions during 2001–2008. Results show a typical subtropical climate in Taipei with a mean annual temperature of 23.4 °C ( $n=409$ ), the highest temperature of 35.8 °C at summer (June to August), the lowest temperature of 7.4 °C at winter (December to February), a mean annual RH of nearly 74% ( $n=256$ ), and a mean weekly rainfall of 11 mm ( $n=409$ ). However, in Kaohsiung, the results indicate a tropical climate with a mean annual temperature of 25.4 °C ( $n=408$ ), the highest temperature of 35 °C at summer, the lowest temperature of 9.3 °C at winter, a mean annual RH of 72.5% ( $n=262$ ), and a mean weekly rainfall of 14.6 mm ( $n=408$ ). The difference of the subtropical/tropical climate shows that the annual average of temperature, RH and rainfall are respectively only 2 °C, 1.5%, and 3.6 mm. In view of the biological threshold for dengue fever vector (*A. aegypti*), the lowest temperature for pupa to grow into adult/Genotrophic is  $>18$  °C (Hopp and Foley, 2001). In other words, there are 79.8% and 98.9% over the minimum temperature (18 °C) of mean monthly temperature in Taipei and Kaohsiung, respectively.

### 3.2. Cross-correlation analysis without and with time-lag

Spearman's rank correlation tests revealed marginally positive trends in the weekly mean ( $\rho=0.28$ ,  $p<0.0001$ ), maximum ( $\rho=0.26$ ,  $p<0.0001$ ), and minimum temperatures ( $\rho=0.30$ ,  $p<0.0001$ ) in Taipei during the 2001–2008 time periods. However, in Kaohsiung region, all negative trends were found in the weekly mean ( $\rho=-0.32$ ,  $p<0.0001$ ), maximum ( $\rho=-0.30$ ,  $p<0.0001$ ), and minimum temperatures ( $\rho=-0.32$ ,  $p<0.0001$ ), RH ( $\rho=-0.26$ ,  $p<0.0001$ ) and Rainfall ( $\rho=-0.20$ ,  $p<0.0001$ ). Taken together, these results indicate

that temperature plays a key role on dengue fever cases than the other factors. However, the rainfall shows the different trends in two areas may be due in part to the differences of average rainy days, rainfall intensity, and seasonal characteristics in winter and summer in Taipei and Kaohsiung, respectively.

Fig. 3 demonstrates the annual evolution of the average incidence rate and of some meteorological factors of rainfall and temperature on dengue incidence rates. The variation during one year of the arithmetic average weekly rainfall and arithmetic average weekly incidence rates from 2001 to 2008 exhibited the significant time-lag effects in Kaohsiung than that in Taipei (Fig. 3A, B). Fig. 3C, D shows the variation during one year of minimum temperatures on incidence rates in Taipei and Kaohsiung, respectively. Table 1 summarizes the relationships between dengue incidence (2001–2008) and meteorological factors with a lag of zero to 4-month performed by the Spearman's correlation analysis. Monthly minimum temperatures, at lag of zero to 4-month, were both positively associated with the monthly dengue fever cases in Taipei and Kaohsiung with a higher statistical significance ( $p<0.0001$ ). RH was inversely correlated with dengue fever cases at lags of zero and 2-month, although no statistical significance was found. However, monthly percentage BI level  $>2$  was positively associated with dengue fever cases at lags of 1- to 3-month in Kaohsiung only. To illustrate these results, Fig. 4 shows the monthly time-lag effects of meteorological variables and percentage BI level by the Spearman's rank correlation coefficient analysis in Taipei and Kaohsiung, respectively.

### 3.3. Lagged-time Poisson regression analysis

Based on the cross-correlation analysis with time-lag, this study chose the 1-month lag of rainfall, 1-month lag of minimum temperatures, and 4-month lag of RH for Poisson regression analysis in Taipei. However, 3-month lag of rainfall, 3-month lag of minimum temperatures, 3-month lag of RH, and 1-month lag of percentage BI level  $>2$  were chosen for Poisson regression analysis in Kaohsiung (Table 1). Table 2 lists the best-fitting models with the smallest QJCu values to characterize the relationships between monthly dengue

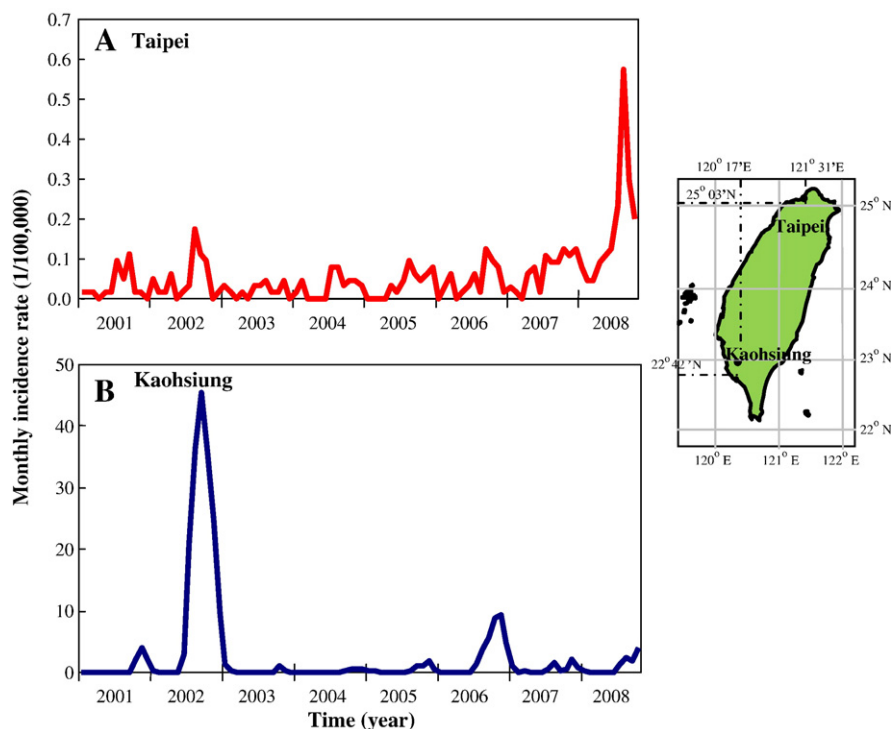


Fig. 1. (A, B) Monthly incidence rates of confirmed dengue cases in Taipei and Kaohsiung from 2001 to 2008, respectively.

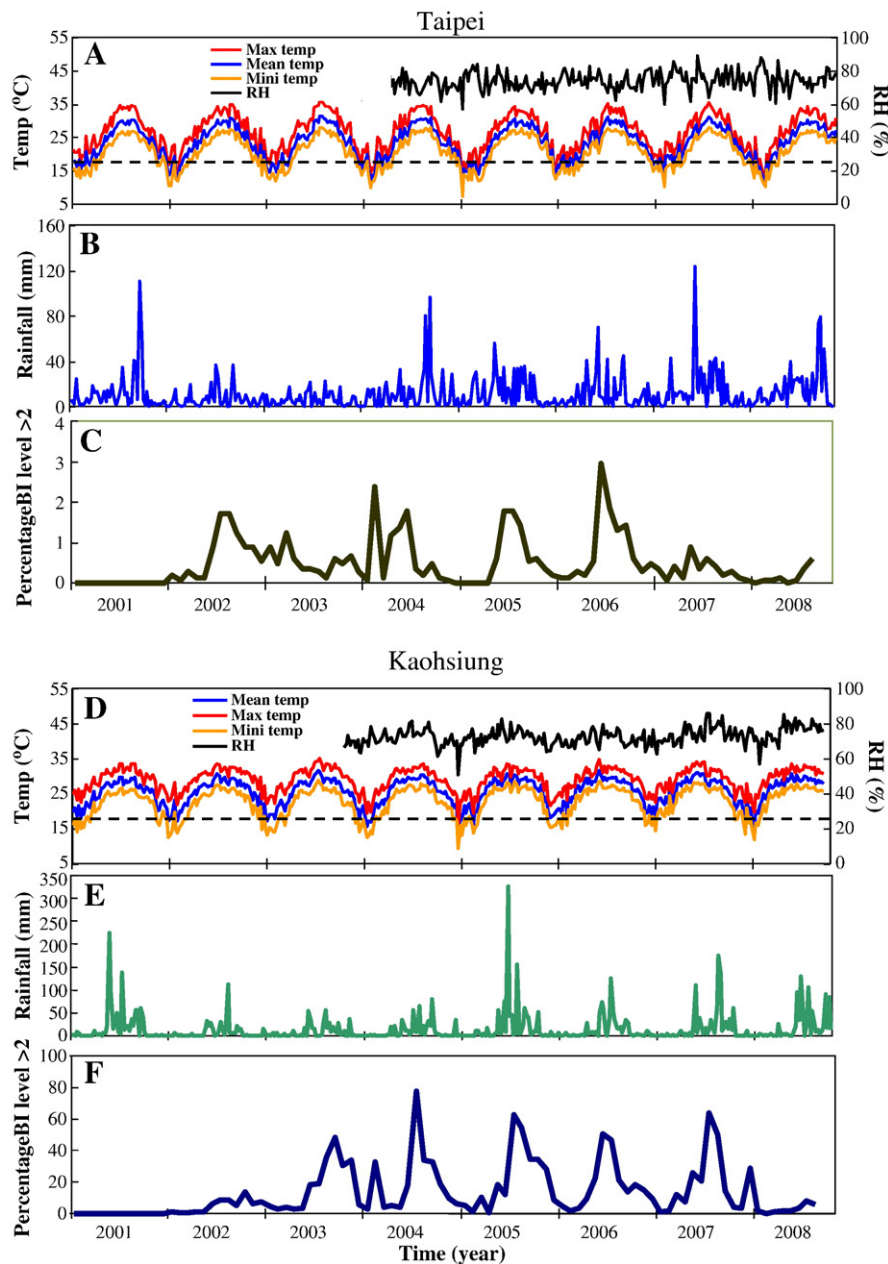


Fig. 2. (A, D) Weekly maximum, mean, and minimum temperatures, RH, (B, E) rainfall, and (C, F) percentage monthly Breteau index (BI) level >2 in Taipei and Kaohsiung from 2001 to 2008, respectively. We chose the frequency of percentage monthly Breteau index (BI) levels >2 as a vector-borne mosquito index exhibiting the potential transmission pattern.

fever cases (2001–2008) and meteorological factors in Taipei ( $QICu = -77.29$ ) and Kaohsiung ( $QICu = -277.77$ ), respectively. Minimum temperature at a lag of 1- and 3-month had a positive effect on dengue incidence in Taipei ( $\beta = 0.1395$ ,  $p < 0.0001$ ) and Kaohsiung ( $\beta = 0.5338$ ,  $p < 0.0001$ ), respectively.

#### 4. Discussion

Potter (2008) recently reported that if global warming continues and the habitat of the mosquito spreads, more than half of the world's population will be at risk. The WHO (2010) reported that explosive outbreaks of dengue hospitalized half a million people in 2009. This study linked climatic factors and mosquito transmission potential to investigate dengue fever dynamics in Taiwan during 2001–2008. By incorporating the climate variables of current and lagged-time effects of temperature, RH, and rainfall intensity together with BI levels into the Poisson regression model, the impacts of major meteorological

factors and mosquito abundance on the dengue fever variability could be quantified.

There were several studies evident that the temperature associated positively with dengue incidence rate (Gubler et al., 2001; Nagao et al., 2003; Arcari et al., 2007; Wu et al., 2007, 2009; Yang et al., 2009a, 2009b). Not only survival rate of mosquitoes but also the life-cycle of the vector including oviposition, hatching, pupation, and emergence processes was evidenced by temperature-dependent effect (Hopp and Foley, 2001; Rohani et al., 2009). Moreover, Yang et al. (2009b) also showed that there were lower mortality rate, higher transition rate, and higher offspring number of mosquitoes in aquatic phase during temperature ranging from 15 to 35 °C. Specifically, temperature could affect the gender of mosquitoes; the females survived more than males in the optimum temperature range of nearly 25 °C (Yang et al., 2009b). Tun-Lin et al. (2000) found that the maximum survival rates of 88–93% were obtained between the optimum temperatures from 20 to 30 °C. In view of the results of



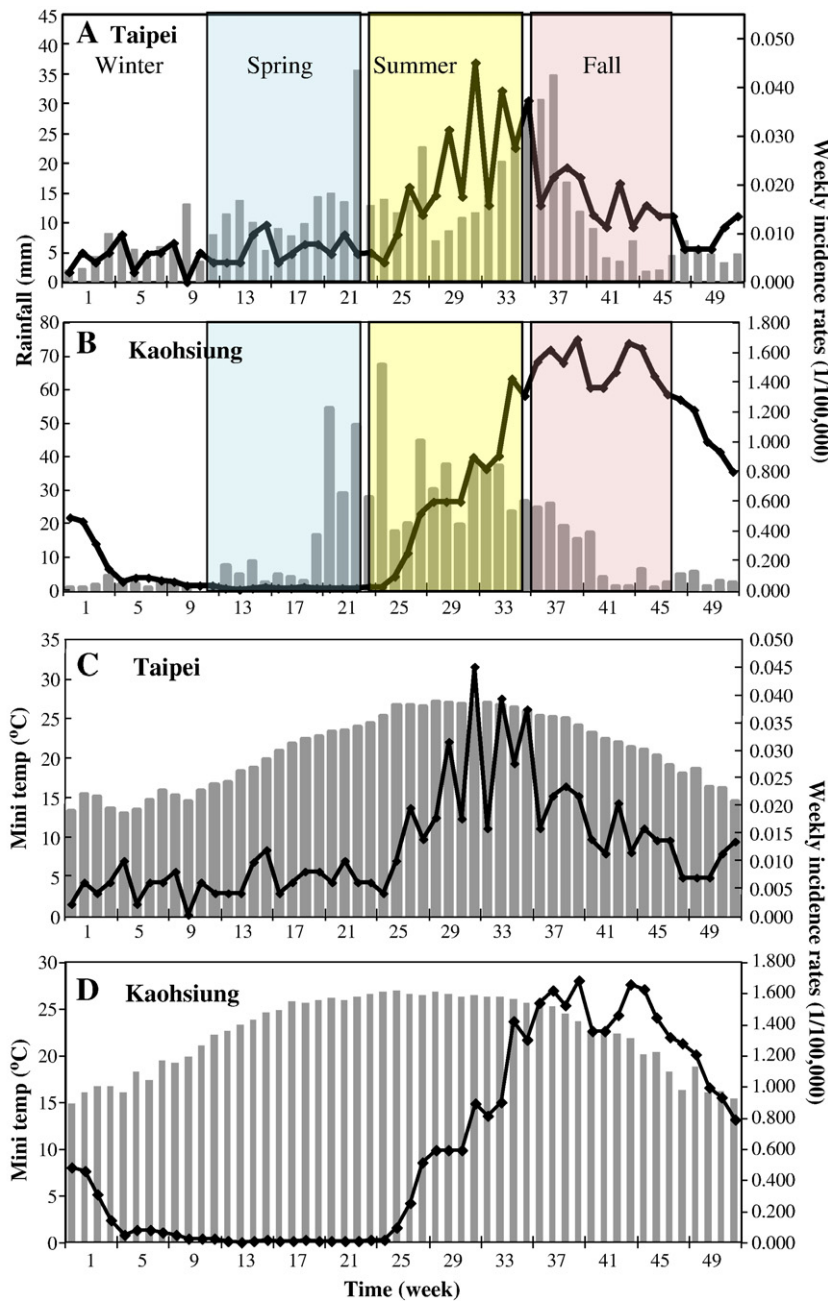
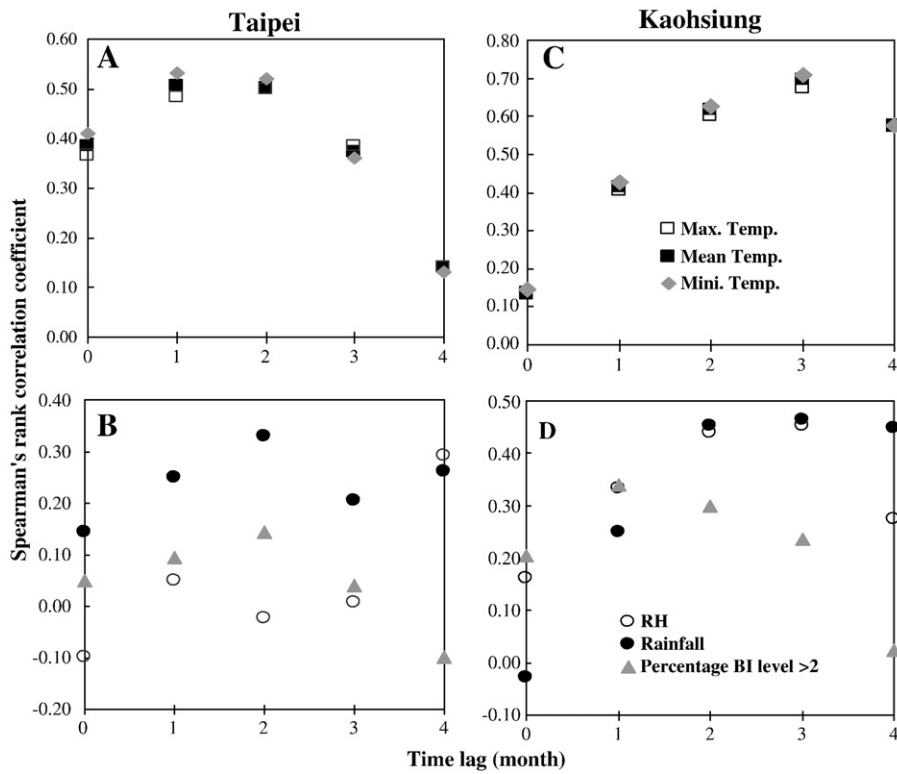


Fig. 3. (A, B) The variation during one year of the averaged weekly rainfall and average weekly incidence rates in Taipei and Kaohsiung, respectively. (C, D) The variation during one year of the averaged weekly minimum temperatures and averaged weekly incidence rates in Taipei and Kaohsiung, respectively.

Table 1  
Results of Spearman's coefficient of rank correlation for time-lag effects<sup>a</sup>.

Time-lag (months)	Mean temperature (°C)	Max temperature (°C)	Mini temperature (°C)	Rainfall (mm)	RH (%)	Percentage BI level >2
<i>Taipei</i>						
0	0.3855**	0.3655**	0.4106***	0.1445	-0.0999	0.0492
1	0.5065***	0.4838***	<b>0.5315***</b>	0.2485*	0.0490	0.0934
2	0.5016***	0.4990***	0.5196***	<b>0.3302**</b>	-0.0246	0.1447
3	0.3726**	0.3850**	0.3615**	0.2052*	0.0079	0.0394
4	0.1399	0.1411	0.1307	0.2622*	<b>0.2919*</b>	-0.0992
<i>Kaohsiung</i>						
0	0.1319	0.1367	0.1470	-0.0268	0.1613	0.2036
1	0.4128	0.4046***	0.4269***	0.2492*	0.3322**	<b>0.3389**</b>
2	0.6154***	0.6004***	0.6252***	0.4528***	0.4394**	0.3001**
3	0.6959***	0.6750***	<b>0.7079***</b>	<b>0.4646***</b>	<b>0.4523***</b>	0.2366*
4	0.5768***	0.5729***	0.5769***	0.4470***	0.2734*	0.0237

<sup>a</sup>Boldface denotes the largest value of correlation coefficient and significance with \* $p < 0.05$ ; \*\* $p < 0.01$ ; and \*\*\* $p < 0.0001$ . All significance levels are assessed at  $\alpha < 0.05$ .



**Fig. 4.** Time-lag effects of meteorological variables (minimum, mean, and maximum temperatures, RH, and amount of rainfall) and percentage BI level >2 on dengue incidence rates in Taipei (A, B) and Kaohsiung (C, D).

Spearman's correlation analysis and Poisson regression models, this present study showed that lagged minimum temperature effect plays a more crucial role on dengue incidence rates than those of the other variables in Kaohsiung and Taipei.

Su (2008) indicated that rainfall is correlated significantly to dengue incidence ( $r^2 = 0.377$ ,  $p < 0.05$ ). No significant correlation, however, was found between dengue incidence and temperature ( $p > 0.05$ ) in the Philippines. On the effects of changes in precipitation, larval habitat and vector population may increase during the period of precipitation to create a new habitat for the vector-borne pathogens and increase adult survival (Focks et al., 1995; Gubler et al., 2001). Consequently, rainfall might be one of the determinants for the vector-borne diseases (Arcari et al., 2007). However, extreme heavy rainfall can still flush mosquito larvae away from breeding sites, eliminating habitats to decrease the vector population (Gubler et al., 2001; Woodruff et al., 2002; Promprou et al., 2005). The monsoon in Kaohsiung primarily occurred from May to September and exhibited less rainfall in autumn and winter.

The impact of time-lag effect on dengue incidence found in this study had also been supported by many studies (Keating, 2001; Depradine and Lovell, 2004; Arcari et al., 2007; Wu et al. 2007). In

Puerto Rico, Keating (2001) found the highest correlation between mean temperature and dengue incidence at a lag period of 3 months. In the small Caribbean island of Barbados, Depradine and Lovell (2004) reported different lag periods having the highest correlation with dengue incidence. They found a 6-week lag for vapor pressure, a 7-week lag for precipitation, and a 12-week lag for minimum temperature. Arcari et al. (2007) examined the monthly incidence data in relation to monthly data for temperature, rainfall, rainfall anomalies, humidity and the Southern Oscillation Index for 1992–2001 in Jakarta. Arcari et al. (2007) reported that a 2-month lag in rainfall and 1-month lag in temperature best explained the variability in the relationships between meteorological variables and dengue incidence rates. However, in Taiwan, Hsieh and Chen (2009) indicated that the highest correlation was between dengue incidence and two meteorological variables: maximum temperature at a lag of 5 weeks ( $r = 0.66$  and  $0.71$ ) and total precipitation at a lag of 7 weeks ( $r = 0.53$ ). Wu et al. (2007) also indicated that dengue incidence in southern Taiwan was strongly associated with temperature and RH. They revealed that a 2-month lag in monthly maximum and minimum temperatures, RH, and monthly rainfall was best explained by the occurrence of dengue fever in Kaohsiung for the period of 1998–2003.

In conclusion, this study suggested that warmer temperature with a 3-month lag, elevated humidity with high mosquito density increased the transmission rate of human dengue fever infection in southern Taiwan. Dengue fever may not threaten to shut down global economy, yet it's a growing killer that deserves some attention of its own.

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**Table 2** Statistics of best-fitting Poisson regression models of the monthly dengue cases (2001–2008) on the meteorological factors and percentage BI level >2.

	Taipei		Kaohsiung	
	$\beta$	$p$	$\beta$	$p$
Rainfall (Lag 1)	0	<.0001	Rainfall (Lag 3)	–0.0009 <.0001
Mini temperature (Lag 1)	0.1395	<.0001	Mini temperature (Lag 3)	0.5338 <.0001
RH (Lag 4)	0.0371	<.0001	RH (Lag 3)	–0.1475 <.0001
			Percentage BI level >2 (Lag 1)	–0.0084 <.0001
QJCu	–77.29		QJCu	–277.77

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