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Regional response of dengue fever epidemics to interannual variation and related climate variability

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Abstract Dengue is a major international public health concern and one of the most important vector-borne diseases. The purpose of this article is to investigate the association among temperature, rainfall, relative humidity, and dengue fever by incorporating the lag effect and examining the dominant interannual model of the modern climate, the El Niño Southern Oscillation (ENSO), in the southern region of Taiwan. We built a linear Poisson regression model by including linear time treads and statistical indicators, verified with disease data in the 2004–2013 period. Here we showed that regional climatic factors in association with the interannual climate variability expressed by the ENSO phenomenon had a significant influence on the dynamics of urban dengue fever in southern Taiwan. The 2–4-month lag of statistical indicators of regional climate factors together with the 4-month lagged Pacific surface temperature (SST) anomaly in the proposed Poisson regression model could capture the regional dengue incidence patterns well. The statistical indicators of mean and coefficient of variation of temperature showed the greatest impact on the dengue incidence rate. We also found that the dengue incidence rate increased significantly with the lag effect of the warmer SST. The ability to forecast regional dengue incidence in southern Taiwan could permit pretreatment of mosquito habitats adjacent to human habitations with highly effective insecticides that would be released at the time of the high-temperature season.

Keywords Dengue · Mosquito · Climate variability · Interannual variation · Statistical indicator · Vector-borne diseases

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1 Introduction

Recently, Bhatt et al. (2013) estimated that there were nearly 390 million (95 % credible interval 284–528) dengue infections annually in 2010 considering that up to 96 million (67–136) manifest apparently with any level of clinical or subclinical severity. On the other hand, Asia bore 67 (47–94) million apparent infections (~70 %) of this burden (Bhatt et al. 2013). The high prevalence, lack of a registered vaccine or other prophylactic measures, and absence of specific treatment make dengue fever 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).

Southern Taiwan is located in the tropical region with relatively high temperature and relative humidity (RH) year round, ideal conditions for the growth of the vector of dengue fever, the mosquito. Historical epidemics of dengue in Taiwan were documented in Penghu Islet in 1902, 1915,

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and 1922; in the southern regions of Taiwan in 1922, 1927, and 1931; and in island-wide Taiwan during 1942–1943 (Chen et al. 1987; King et al. 2000), whereas dengue hemorrhagic fever cases have been taken into account since 1994 (Lei et al. 2002). The most well-known dengue outbreaks in Taiwan have varied since 1987 in that the prevalence has been higher in southern Taiwan with *A. aegypti* primarily distributed between southern Putai and northern Hengchun (Lei et al. 2002). In general, dengue epidemics have occurred in Taiwan annually for the past decade, and the largest epidemic occurred in southern Taiwan in 2002 with 52 imported and 5,336 indigenous cases that peaked around September–December (Centers for Disease Control of Taiwan 2002).

There have been some suggestions of a strong link between dengue and climate change (Patz et al. 2005; McMichael et al. 2006). It is also widely accepted that the distribution and dynamics of vector-borne dengue infections are particularly sensitive to climatic conditions, by virtue of the sensitivity of the *A. aegypti* vectors themselves to variations in temperature, RH, rainfall, vapor pressure, evaporation, and quantities and qualities of the standing water used as breeding sites (Hales et al. 2002; Promprou et al. 2005; Chowell and Sanchez 2006; Wu et al. 2007; Halstead 2008; Su 2008; Thammapalo et al. 2008; Johansson et al. 2009; Yu et al. 2011; Bhatt et al. 2013). Focks and Barrera (2007) indicated that a 2 °C increase in temperature would simultaneously lengthen the lifespan of the mosquito and shorten the extrinsic incubation period of the dengue virus, resulting in more infected mosquitoes for a longer period of time. Wu et al. (2007) indicated that the weather variability such as monthly maximum and minimum temperature, rainfall, and RH was a meaningful and significant indicator for the increasing occurrence of dengue fever in the Taiwan region.

Halstead (2008) and Johansson et al. (2009) indicated that the epidemic behavior of dengue viruses was also likely closely correlated with fluctuations in the temperature and rainfall. Chen et al. (2010) suggested that warmer temperature with a 3-month lag and elevated humidity with high mosquito density increased the transmission rate of human dengue fever infection in southern Taiwan. Lambrechts et al. (2011) revealed that short-term temperature fluctuations had a significant impact on dengue virus transmission by *A. aegypti* females.

Recent studies also suggested that the El Niño Southern Oscillation (ENSO), a major source of interannual climate variability, drives the interannual variation of dengue incidence (Hales et al. 1996, 1999; Gagnon et al. 2001; Kovats et al. 2003; Cazelles et al. 2005; Brunkard et al. 2008; Tipayamongkholgul et al. 2009; Hu et al. 2010; Earnest et al. 2012). The Southern Oscillation Index (SOI) is the most commonly used index for the ENSO phenomena. This index compares the normalized atmospheric pressure difference between Darwin in Australia and Tahiti in the Southern Pacific, and it is expressed as a standardized deviation from the norm. Strong negative anomalies are associated with the El Niño event. During ENSO events, there are significant changes in the amount and intensity of rainfall in the tropics, especially over Southeast Asia and northern South America (Dai and Wigley 2000). In southern Taiwan, the correlations between local dengue fever and the ENSO have been demonstrated through time series analysis (Lai 2011; Yu et al. 2011).

Recent studies addressing the risk of critical transitions in complex dynamic systems, ranging from climate to ecosystems, revealed that statistical indicators can be used as early warning signals to capture the predictability and detectability (Carpenter and Brock 2006; Livina and Lenton 2007; Dakos et al. 2008; Guttal and Jayaprakash 2008; Biggs et al. 2009; Scheffer et al. 2009; Takimoto 2009; Dakos et al. 2010; Drake and Griffen 2010; Lenton 2011). The leading indicators representing generic early warning signals in the climate system and ecosystem processes include the coefficient of variation (Martinerie et al. 1998; Carpenter and Brock 2006; Guttal and Jayaprakash 2008), skewness (Guttal and Jayaprakash 2008; Takimoto 2009), autocorrelation (Dakos et al. 2008; Takimoto 2009), spatial correlation (Dakos et al. 2010), and a composite index comprising all previous statistical signatures (Drake and Griffen 2010).

The coefficient of variation is a measurement of dispersion for a set of samples that can reflect the system stability and vulnerability in a dynamic process (Carpenter and Brock 2006). Skewness is a measurement of asymmetry that can also be seen as an indicator for judging the resilience of a dynamic system (Guttal and Jayaprakash 2008). Kurtosis is a measurement of peakedness and has similar properties as skewness (Joanes and Gill 1998). In cross-correlation of a signal, autocorrelation can reflect the self-similarity in a data set, and the spatial correlation can receive a signal gain for two time-dependent state variables (Dakos et al. 2008, 2010).

Although it has been suggested that weather conditions are correlated with dengue infections, the consistency in respect to their interactions (e.g., positive or negative relation) has not been demonstrated. Additionally, a traditional epidemiology study is not well suited for capturing and understanding variance or extreme events. Until recently, it was still difficult to identify the relationship between regional and global climate and dengue fever outbreaks in any particular epidemic region. The purpose of this article was to investigate the association between regional climate variables, including temperature, RH, and rainfall, and dengue fever by incorporating the lag effect and examining the dominant interannual model of the modern climate, the ENSO, based on the data from Kaohsiung in southern Taiwan where the disease was endemic in the 2004–2013 period. We built a linear generalized model by including linear time trends and statistical indicators by considering different hypotheses for the roles of environmental driving variables and the inherent disease dynamics in producing the interannual variability of dengue incidence.

We thought that time-varying climatic conditions were associated with dengue incidence. The statistical properties of climatic variables can be seen as the leading indicators to predict dengue incidence. Therefore, these statistical properties embedded in time-dependent climate variables can be further tested. The concept of dengue prediction was based on previous studies that used a statistical indicator as an early warning signal for critical transitions. This study supposed that statistical indicators can be seen as the leading indicators and can further be used to predict dengue incidence. Thus, the indicators can be seen as risk warning signals to predict dengue incidence. Since climatic variables and ENSO have been confirmed as factors that affect the dengue epidemic, there may be some impact factors in these time-varying fluctuations.

2 Methods

2.1 Background

The main focus of dengue fever epidemic activity in Taiwan is Kaohsiung. Moreover, the epicenter of the 2002 dengue epidemic was Kaohsiung. Kaohsiung, a typical tropical city, is situated on the southwestern coast of Taiwan (22°48′N–23°47′N, 120°176′E–121°05′E). Moreover, Kaohsiung is a densely populated region (nearly 2.78 million persons within a total area of 3,000 km^2) with very high suitability for dengue transmission. In Kaohsiung, the average temperatures (SD) during spring (March to May), summer (June to August), fall (September to November), and winter (December to February) were 25.38 (0.12), 28.85 (0.03), 26.64 (0.10), and 20.59 (0.08) °C in the 2005–2010 period, respectively, with the relative humidity (RH) ranging from 77 to 83 %. The lowest and highest accumulative rainfall occurred in the winter (0.5 mm) and summer (2,137 mm) (Taiwan Central Weather Bureau, http://www.cwb.gov.tw/eng/index.htm).

2.2 Study data

Time-series data of monthly confirmed dengue cases in Kaohsiung in the 2004–2013 period were obtained from the Centers for Disease Control of Taiwan (http://www.cdc.gov.tw/english/index.aspx). This study calculated the dengue incidence rate (per 100,000 population) by monthly confirmed dengue cases, including both inpatients and outpatients over the year-end resident population numbers in Kaohsiung. The resident population data were adopted from Department of Statistics, Ministry of the Interior, Taiwan (http://www.moi.gov.tw/stat/english/index.asp). The daily mean meteorological data for temperature, rainfall, and RH in the 2004–2013 period were adopted from the observations of eight monitoring stations of the Taiwan Environmental Protection Agency (http://www.epa.gov.tw/en/index.aspx). Of the eight monitoring stations, four are located in Kaohsiung City, including

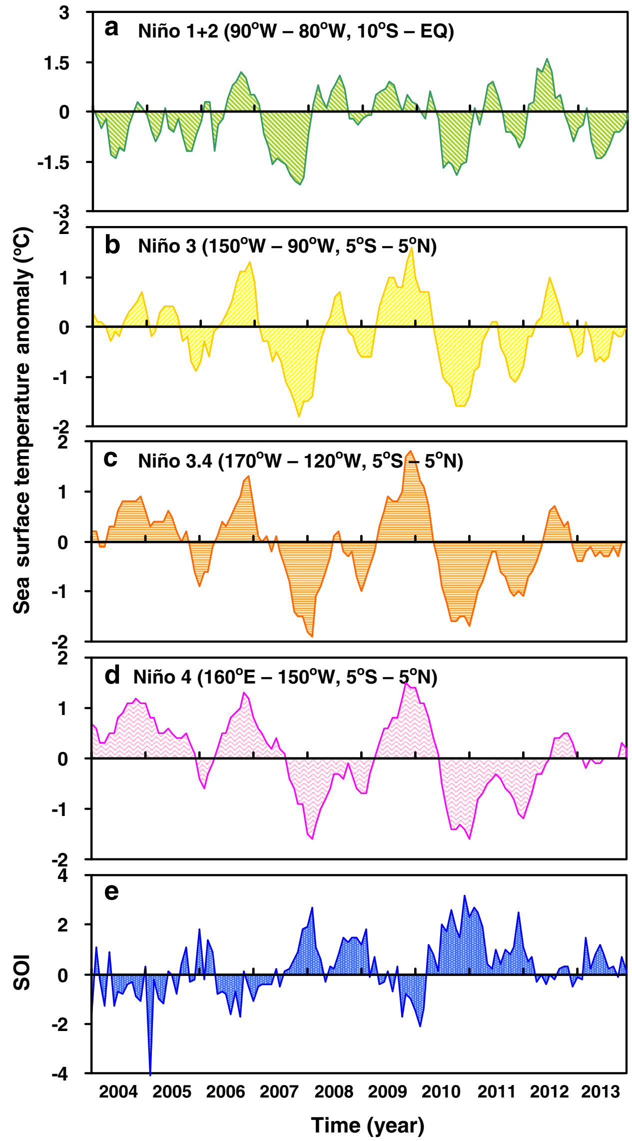

Fig. 1 Time series of the sea surface temperature anomaly (SSTA) indices for **a** Niño 1 + 2, **b** Niño 3, **c** Niño 3.4, and **d** Niño 4 and **e** the Southern Oscillation Index (SOI) in the 2004–2013 period, respectively

Nanzih, Zuoying, Cianjin, and Siaogang, whereas the others are in Linyuan, Meinong, Renwu, and Daliao in Kaohsiung County.

We used the SOI and sea surface temperature anomaly (SSTA) as proxies for ENSO variability adopted from the openly available databases of the National Oceanic and Atmospheric Administration (http://www.cpc.ncep.noaa.gov/data/indices). We utilized monthly means of four SSTA indices: (1) Niño 1 + 2 (90°W–80°W, 10°S–EQ), (2) Niño 3 (150°W–90°W, 5°S–5°N), (3) Niño 3.4 (170°W–120°W, 5°S–5°N), and (4) Niño 4 (160°E–150°W, 5°S–5°N) in the 2004–2013 period (Fig. 1). These indices measure the sea surface temperature (SST) in different locations in the Pacific Ocean, with Niño 1 + 2 measured furthest east and Niño 4 measured furthest west. These four indices differ in both the magnitude and timing of their variations, but are correlated with one another.

2.3 Statistical analyses

In this study, six statistical indicators including the mean, coefficient of variation (CV), skewness, coefficient of autocorrelation (CA), coefficient of spatial correlation (CS), and kurtosis were used. The CV can be calculated as the ratio of the sample standard deviation (sd) and sample mean ($\bar{x}$) as: CV = sd/$\bar{x}$. The sample skewness can be calculated by using the estimator $g_1 = m_3/m_2^{3/2}$ where m_2 is the sample variance sd^2 and m_3 is the sample third central moment. The CA corresponding to each sampling date can be calculated as the Pearson correlation coefficient (r) between the meteorological data at subsequent sampling times t and $t + \Delta t$ over all samples. Here we calculated the CA at 1 month lag. On the other hand, this study used CS to examine the spatial correlation of the meteorological data between Kaohsiung City and County. The CS of each month can be calculated by Spearman's rank correlation coefficient between meteorological data at two areas. Kurtosis describes the shape in a random variable probability distribution that can be calculated as m_4/sd^4 where m_4 is the sample fourth central moment.

Spearman's rank correlation tests were performed to examine the correlation between climate variables and dengue incidence rate and further to investigate the lagged effects with a lag of 0–4 months of leading indicators for meteorological and ENSO data in Kaohsiung in the 2004–2012 period.

Given the evidence for the roles of seasonality, meteorological factors characterized by statistical indicators, and the ENSO, we used a Poisson regression model to assess the characteristics of the dengue fever epidemic in Kaohsiung in the 2004–2012 period. The model was fitted to the data to estimate dengue fever trends and can be written as:

$$\begin{aligned} Y(t) = \exp\Big\{ & \beta_0 + \beta_1 t + \beta_2 t^2 + \beta_3 \sin\left(\frac{2\pi t}{12}\right) \\ & + \beta_4 \cos\left(\frac{2\pi t}{12}\right) + \beta_5 L_{\mathrm{Temp},t-n} + \beta_6 L_{\mathrm{Rain},t-n} \\ & + \beta_7 L_{\mathrm{RH},t-n} + \beta_8 SOI_{t-n} + \beta_9 \mathrm{SSTA}_{t-n} \Big\}, \end{aligned} \tag{1}$$

where $Y(t)$ represents the expected dengue incidence rate at time t, β_0 stands for the intercept, β_1 and β_2 stand for the coefficients for the linear and quadratic time trend, β_3 and β_4 stand for the coefficients for seasonality, β_5 through β_7 represent the coefficients for statistical indicators of temperature (°C), rainfall (mm), and RH (%), respectively, and β_8 and β_9 represent the coefficients for SOI and SSTA. The term in the subscript represents the n-month lag time.

Equation (1) is one simple expression of generalized linear models that do not require prior knowledge of the shape of the response function. To ensure robustness, the model was tested by validating dynamic dengue incidence time series in 2013 based on data of dengue incidences, meteorological factors, and the ENSO in the 2004–2012 period.

Statistica® software (version 6.0, StatSoft, Tulsa, OK, USA) was used to perform Spearman's rank correlation tests and other related statistical analyses. The Poisson regression model was used in the open-source language R (version 2.11.1, The R Foundation for Statistical Computing, Vienna, Austria). The Akaike information criterion (AIC) was also used to assess model fit and can be expressed as $n \times \ln(\text{residual sum of squares}/n) + 2\,k$ where n is the number of observations and k is the number of parameters.

3 Results

3.1 Time series of dengue fever and statistical indicators of climate

Figure 2a shows the time series of the dengue fever incidence rate, mean temperature, rainfall, and RH in the 2004–2013 period. The mean and maximum monthly dengue incidence rates were 2.27 and 21.67 per 100,000 population in Kaohsiung in the 2004–2013 period. On the other hand, the mean monthly temperature was 25.31 °C with the highest temperature being 31.01 °C in July and lowest temperature being 15.98 °C in January, whereas the mean monthly RH was 73.88 % with the highest rainfall being 1235.18 mm in August. Generally, dengue incidence rates increased with increasing temperature and rainfall (Fig. 2a).

Figure 2b–p shows the analysis results of statistical indicators for CV, skewness, kurtosis, CA, and CS,

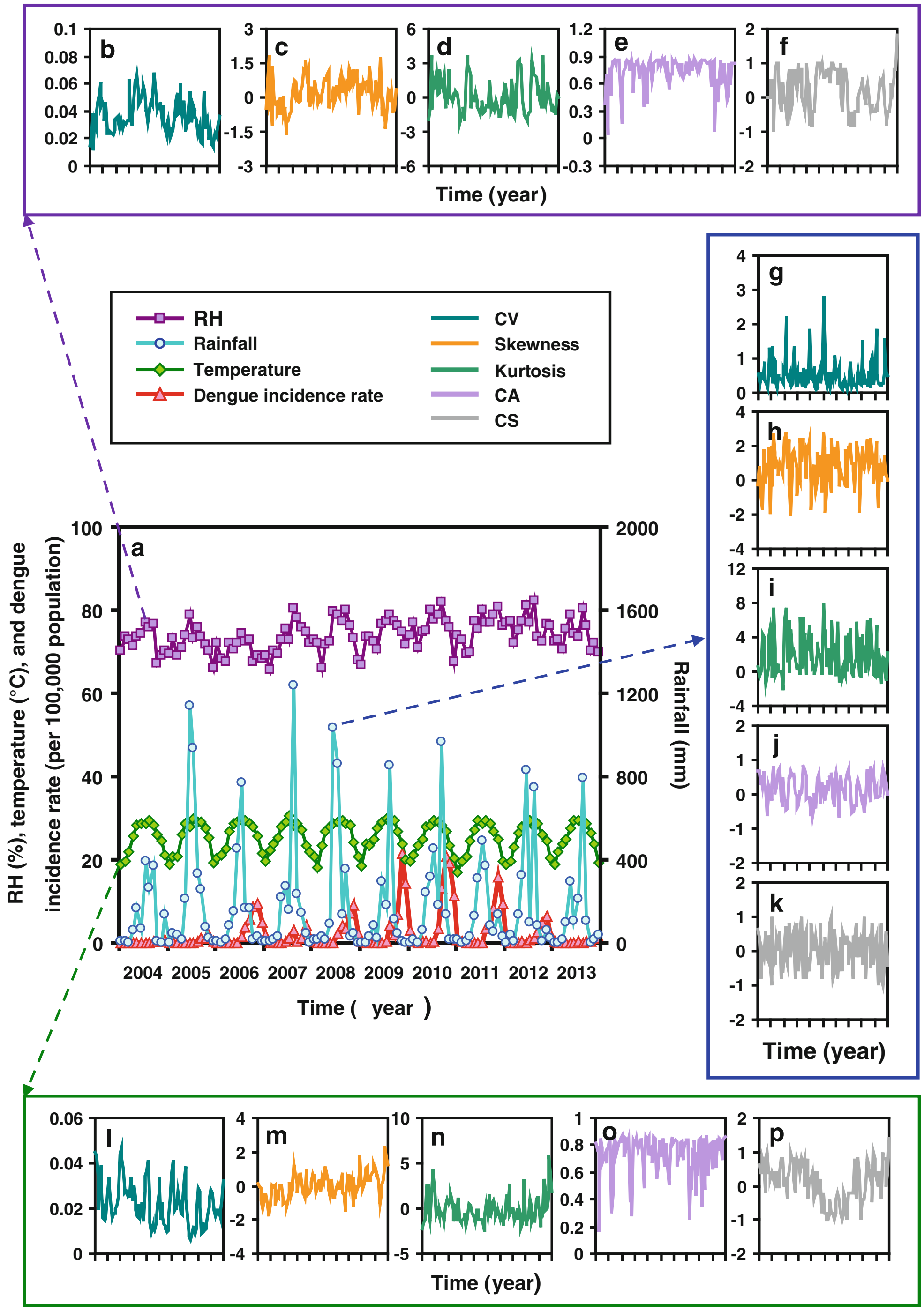

Fig. 2 Monthly relative mean humidity (RH), rainfall, and temperature (**a**) used to estimate the coefficient of variation (CV) (**b, g, l**), skewness (**c, h, m**), coefficient of spatial (CS) correlation (**d, i, n**), coefficient of autocorrelation (CA) (**e, j, o**), and kurtosis (**f, k, p**) in the 2004–2013 period, respectively

respectively. The results showed that the statistical indicators for the CV of temperature (Fig. 2l) and RH (Fig. 2b) were all less than 0.1, indicating temperature and RH had a higher consistency. The CV of temperature is higher in winter (December–February) and lower in summer (June–August). This study also found that the CV of temperature showed seasonality and increased as the temperature decreased. Rainfall had higher CV values (Fig. 2g), demonstrating that rainfall data had higher dispersion. Moreover, the autocorrelation of rainfall showed a random distribution (Fig. 2j). Negative and positive correlations were both found in the CS for all climate variables (Fig. 2f,

Table 1 Spearman's correlation coefficient (ρ) for the relationship between statistical indicators of climate variables and dengue incidence varied with 0–4-month lag times

Time lag (month)	Statistical indicators					
	Mean, $\bar{x}$	CV, $\hat{v}_t$	Skewness, $\hat{w}_t$	CS, $\hat{x}_t$	CA, $\hat{y}_t$	Kurtosis, $\hat{z}_t$
Temperature						
0	0.031	0.012	0.077	−0.233*	0.028	0.023
1	0.425***	−0.264**	0.050	−0.161	−0.078	0.061
2	**0.684*****	−0.445***	0.019	−0.065	−0.235*	0.003
3	**0.796*****	**−0.563*****	0.033	−0.008	−0.198*	0.001
4	**0.696*****	**−0.509*****	−0.042	0.011	−0.090	−0.020
Rainfall						
0	−0.020	−0.020	0.040	0.048	0.179	0.015
1	0.295**	−0.140	0.043	0.101	0.188*	0.029
2	**0.589*****	−0.278**	0.012	0.174	0.230*	0.073
3	**0.678*****	−0.289**	−0.041	0.190*	0.197*	−0.016
4	**0.617*****	**0.604*****	−0.335***	−0.003	−0.023	−0.070
Relative humidity						
0	0.199*	0.230*	0.244**	0.097	0.156	0.039
1	0.407***	0.115	0.330***	−0.018	0.231*	−0.162
2	**0.525*****	0.054	0.278**	−0.029	0.191*	−0.344***
3	**0.537*****	−0.060	0.197*	−0.053	0.126	−0.400***
4	0.356***	−0.066	−0.121	0.136	−0.430***	0.141

Boldface indicates that the leading indicators with $\rho > 0.5$ were selected in the Poisson regression model

CV coefficient of variation, *CS* coefficient of spatial correlation, *CA* coefficient of autocorrelation

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Table 2 Spearman's correlation coefficient (ρ) for the dengue incidence rate between the Southern Oscillation Index (SOI) and sea surface temperature anomaly (SSTA) varied with 0–4-month lag times

Time lag (months)	SOI	SSTA			
		Niño 1 + 2 (90°W–80°W, 10°S–EQ[a])[b]	Niño 3 (150°W–90°W, 5°S–5°N)	Niño 4 (160°E–150°W, 5°S–5°N)	Niño 3.4 (170°W–120°W, 5°S–5°N)
0	0.072	−0.016	0.032	0.042	0.029
1	0.044	0.063	0.152	0.134	0.077
2	−0.085	0.154	0.229*	0.174	0.077
3	−0.133	0.248**	0.274**	0.175	0.045
4	−0.080	0.326***	0.249**	0.130	−0.002

[a] Equator

[b] Geographic coordinate system

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

k, p), indicating that a difference in meteorological trends existed between Kouhsiung City and Kouhsiung County.

3.2 Cross-correlation analysis

The interactions among climate variables, seasonality, and ENSO in the 2004–2012 period are listed in Table S1. The result showed that there was no significant collinearity ($\rho > 0.8$) among all seasonality and statistical indicators of temperature, rainfall, and RH. However, the SSTA (Niño 3.4) had obvious interactions in SSTA (Niño 3) ($\rho = 0.89$) and SSTA (Niño 4) ($\rho = 0.94$).

Table 1 summarizes the correlations between the dengue fever incidence rate and statistical indicators of meteorological data during 2004–2012 by Spearman's rank correlation tests, which varied with 0–4-month lag times. The results indicated that the correlations of mean for temperature and rainfall had significant 2-, 3-, and 4-month lag effects ($\rho > 0.5$, $P < 0.001$). The CV of temperature with 3 ($\rho = -0.563$, $P < 0.001$) and 4 ($\rho = -0.509$, $P < 0.001$) month lags showed a significant influence on dengue incidence, whereas a significant correlation of CV for rainfall was found in 4-month lag ($\rho = 0.604$, $P < 0.001$). The correlations for RH showed that the mean had 2 ($\rho = 0.525$, $P < 0.001$) and 3 ($\rho = 0.537$, $P < 0.001$) month lag effects. However, the correlations of skewness, CS, CA, and kurtosis for all climate variables were less than 0.5. Overall, the statistical indicators of

Table 3 Poisson regression models used in this study

Poisson regression model[a]	r^2	AIC	
$Y(t) = \exp\begin{bmatrix}\beta_0 + \beta_1 t + \beta_2 t^2 + \beta_3 \sin(2\pi t/12) + \beta_4 \cos(2\pi t/12) \\ + \beta_5 \bar{x}_{\mathrm{Temp},t-2} + \beta_6 \bar{x}_{\mathrm{Temp},t-3} + \beta_7 \bar{x}_{\mathrm{Temp},t-4} + \beta_8 \hat{v}_{\mathrm{Temp},t-3} \\ + \beta_9 \hat{v}_{\mathrm{Temp},t-4} + \beta_{10} \bar{x}_{\mathrm{Rain},t-2} + \beta_{11} \bar{x}_{\mathrm{Rain},t-3} + \beta_{12} \bar{x}_{\mathrm{Rain},t-4} \\ + \beta_{13} \hat{v}_{\mathrm{Rain},t-4} + \beta_{14} \bar{x}_{\mathrm{RH},t-2} + \beta_{15} \bar{x}_{\mathrm{RH},t-3} + \beta_{16} \mathrm{SSTA}_{1+2,t-4}\end{bmatrix}$	0.861	24.68	(T1)
$Y(t) = \exp\begin{bmatrix}\beta_0 + \beta_1 t + \beta_2 t^2 + \beta_3 \sin(2\pi t/12) + \beta_4 \bar{x}_{\mathrm{Temp},t-2} \\ + \beta_5 \bar{x}_{\mathrm{Temp},t-3} + \beta_6 \bar{x}_{\mathrm{Temp},t-4} + \beta_7 \hat{v}_{\mathrm{Temp},t-3} + \beta_8 \hat{v}_{\mathrm{Temp},t-4} \\ + \beta_9 \bar{x}_{\mathrm{Rain},t-2} + \beta_{10} \bar{x}_{\mathrm{Rain},t-3} + \beta_{11} \bar{x}_{\mathrm{Rain},t-4} + \beta_{12} \hat{v}_{\mathrm{Rain},t-4} \\ + \beta_{13} \bar{x}_{\mathrm{RH},t-2} + \beta_{14} \bar{x}_{\mathrm{RH},t-3} + \beta_{15} \mathrm{SSTA}_{1+2,t-4}\end{bmatrix}$	0.861	21.62	(T2)
$Y(t) = \exp\begin{bmatrix}\beta_0 + \beta_1 t + \beta_2 t^2 + \beta_3 \sin(2\pi t/12) + \beta_4 \bar{x}_{\mathrm{Temp},t-2} \\ + \beta_5 \bar{x}_{\mathrm{Temp},t-3} + \beta_6 \bar{x}_{\mathrm{Temp},t-4} + \beta_7 \hat{v}_{\mathrm{Temp},t-3} \\ + \beta_8 \hat{v}_{\mathrm{Temp},t-4} + \beta_9 \bar{x}_{\mathrm{Rain},t-3} + \beta_{10} \bar{x}_{\mathrm{Rain},t-4} + \beta_{11} \hat{v}_{\mathrm{Rain},t-4} \\ + \beta_{12} \bar{x}_{\mathrm{RH},t-2} + \beta_{13} \bar{x}_{\mathrm{RH},t-3} + \beta_{14} \mathrm{SSTA}_{1+2,t-4}\end{bmatrix}$	0.861	19.75	(T3)
$Y(t) = \exp\begin{bmatrix}\beta_0 + \beta_1 t + \beta_2 t^2 + \beta_3 \sin(2\pi t/12) + \beta_4 \bar{x}_{\mathrm{Temp},t-2} + \beta_5 \bar{x}_{\mathrm{Temp},t-3} \\ + \beta_6 \bar{x}_{\mathrm{Temp},t-4} + \beta_7 \hat{v}_{\mathrm{Temp},t-3} + \beta_8 \hat{v}_{\mathrm{Temp},t-4} + \beta_9 \bar{x}_{\mathrm{Rain},t-3} \\ + \beta_{10} \bar{x}_{\mathrm{Rain},t-4} + \beta_{11} \hat{v}_{\mathrm{Rain},t-4} + \beta_{12} \bar{x}_{\mathrm{RH},t-3} + \beta_{13} \mathrm{SSTA}_{1+2,t-4}\end{bmatrix}$	**0.860**	**18.90**	**(T4)**
$Y(t) = \exp\begin{bmatrix}\beta_0 + \beta_1 t + \beta_2 t^2 + \beta_3 \sin(2\pi t/12) + \beta_4 \bar{x}_{\mathrm{Temp},t-2} \\ + \beta_5 \bar{x}_{\mathrm{Temp},t-3} + \beta_6 \bar{x}_{\mathrm{Temp},t-4} + \beta_7 \hat{v}_{\mathrm{Temp},t-4} + \beta_8 \bar{x}_{\mathrm{Rain},t-3} \\ + \beta_9 \bar{x}_{\mathrm{Rain},t-4} + \beta_{10} \hat{v}_{\mathrm{Rain},t-4} + \beta_{11} \bar{x}_{\mathrm{RH},t-3} + \beta_{12} \mathrm{SSTA}_{1+2,t-4}\end{bmatrix}$	0.860	19.36	(T5)

The best fitting model is highlighted in bold

AIC Akaike information criterion

[a] $Y(t)$ is the expected dengue incidence rate; β_0 is the intercept; β_1 and β_2 are the coefficients for the linear time trend and quadratic time trend; β_3 and β_4 are the coefficients for seasonality; β_5 through β_{16} represents the fitted coefficients for various statistical indicators; *Temp* is the temperature; *RH* is the relative humidity; $SSTA_{1+2}$ is the sea surface temperature anomaly (Niño 1 + 2); $\bar{x}$is the mean; $\hat{v}$ is the coefficient of variation; $t-2$, $t-3$, and $t-4$ in the subscript represent the 2-, 3-, and 4-month time-lag, respectively

mean and CV of regional climate variables were strongly correlated with dengue epidemics in Kaohsiung.

Spearman's rank correlation analysis indicated a positive trend in the 4-month lag of SSTA (Niño 1 + 2) ($\rho = 0.326$, $P < 0.001$) in Kaohsiung in the 2004–2012 period (Table 2). The results also revealed that the dengue incidence rate is marginally significant together with effect of ENSO, implying that the dengue incidence rate increased with effect of the ENSO. Nevertheless, no strong association existed between the dengue incidence rate and SOI with 0–4-month lag times ($\rho < 0.5$, $P > 0.05$) (Table 2).

3.3 Poisson regression analysis

Based on the interactions among analysis of the climate variables, seasonality, and ENSO (Table S1) and the cross-correlation analysis with time lag (Tables 1, 2), we considered the climate factors with Spearman's correlation coefficient $\rho > 0.5$ for the Poisson regression model to capture the dengue incidence trends. However, the ENSO variable with the highest ρ value was selected in the Poisson regression model.

Although we found strong collinearity in Niño 3.4 between Niño 3 and Niño 4 (Table S1), the correlations among dengue incidence rate, Niño 3, Niño 3.4, and Niño 4 were less than 0.5 (Table 2). Thus, a total of 12 statistical indicators were chosen in the Poisson regression model (Table 3, Eq. T1) in that five indicators were temperature including 2-, 3-, and 4-month lags of the mean as well as 3- and 4-month lags of the CV. The four indicators selected from rainfall were 2-, 3-, and 4-month lags of the mean and a 4-month lag of the CV. The other three indicators were mean RH with 2- and 3-month lags as well as a 4-month lag of the SSTA (Niño 1 + 2).

In the Poisson regression model selection procedure, we used Eq. (T1) as the reference model and deleted the most insignificant variables one by one based on the P value to obtain other models. A model with the lowest AIC value was selected. Table 3 indicates that the Poisson regression model of Eq. (T4) gave the best model fit as judged by the AIC. Equation (T4) had the lowest AIC value of 18.9 and could significantly estimate the dengue incidence trends in

Table 4 Fitting coefficients in the Poisson regression model of Eq. (T4)

Parameter	Fitted coefficient
Intercept	$-23.830 \pm 4.036^{a***}$
t	$0.107 \pm 0.018^{***}$
t^2	$-0.001 \pm 0.0001^{***}$
$\sin(2\pi t/12)$	$1.065 \pm 0.383^{**}$
$\bar{x}_{\mathrm{Temp},t-2}$	$0.549 \pm 0.123^{***}$
$\bar{x}_{\mathrm{Temp},t-3}$	0.169 ± 0.141
$\bar{x}_{\mathrm{Temp},t-4}$	$0.245 \pm 0.096^{*}$
$\hat{v}_{\mathrm{Temp},t-3}$	3.976 ± 5.817
$\hat{v}_{\mathrm{Temp},t-4}$	$23.150 \pm 6.376^{***}$
$\bar{x}_{\mathrm{Rain},t-3}$	0.00031 ± 0.00028
$\bar{x}_{\mathrm{Rain},t-4}$	0.00032 ± 0.00027
$\hat{v}_{\mathrm{Rain},t-4}$	-0.390 ± 0.449
$\bar{x}_{\mathrm{RH},t-3}$	-0.078 ± 0.045
$\mathrm{SSTA}_{1+2,t-4}$	-0.055 ± 0.076

Temp is the temperature; *RH* is the relative humidity; $SSTA_{1+2}$ is the sea surface temperature anomaly (Niño 1 + 2); $\bar{x}$ is the mean; $\hat{v}$ is the coefficient of variation; $t-2$, $t-3$, and $t-4$ in subscript represent the 2-, 3-, and 4-month time lag, respectively

[a] Mean ± SE

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

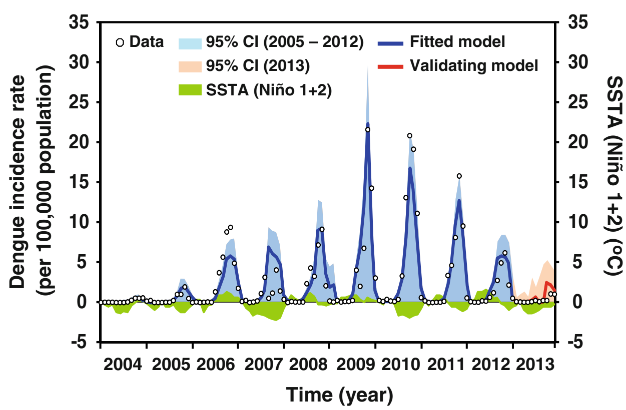

Fig. 3 Validated time series of the monthly dengue incidence rate in 2013 by the Poisson regression model based on data in the 2004–2012 period

Kaohsiung in the 2004–2012 period ($r^2 = 0.86$, AIC = 18.9). The fitted coefficients of the Poisson regression model are listed in Table 4. To assess the prediction performance of the present model, the Poisson regression model (Eq. T4) was tested by validating the time-series dynamics of dengue incidence in 2013 based on data from 2004 to 2012. Figure 3 shows that our predictions with 95 % CIs could capture the observed data in Kaohsiung during 2013.

The individual impact of factors on the dengue incidence rate in Kaohsiung using sensitivity analysis is illustrated in Fig. 4. In addition to the time trends of t and t^2, we found that the mean temperature with a 2-month lag ($P < 0.001$) and the CV of temperature with a 4-month lag ($P < 0.001$) were the most significant factors for the dengue incidence rate in Kaohsiung. Although the SSTA (Niño 1 + 2) showed a weak association with dengue incidence ($\rho = 0.326$, Table 2), the SSTA (Niño 1 + 2) was still an indispensable factor for capturing dengue incidence patterns (Table 3, Eq. T4). We also found that a large and significant increase in the dengue incidence rate was strongly associated with the lag effects of warmer SSTA (Niño 1 + 2) values occurring respectively in 2008, 2009, 2011, and 2012 (Fig. 3).

4 Discussion

4.1 Dengue fever trends with climate variability

Our study showed that the regional climatic factors of temperature, rainfall, and RH in association with the interannual climate variability expressed by the ENSO phenomenon had a significant influence on the dynamics of urban dengue fever in southern Taiwan. We revealed that a 2–4-month lag of the mean and CV of regional climatic factors together with the 4-month lag SSTA (Niño 1 + 2) could significantly capture the dengue incidence trends in Kaohsiung in the 2004–2012 period. We have also shown that (1) the mean with a 2-month lag and CV with a 4-month lag for temperature were the most significant factors in relation to dengue fever in Kaohsiung in the 2004–2012 period, (2) 4-month lagged SSTA (Niño 1 + 2) was an indispensable factor for capturing dengue incidence patterns, and (3) the dengue incidence rate increased with the effect of the ENSO.

Hales et al. (1996) revealed that dengue fever epidemics were moderately strong positively correlated with the SOI ($\rho = 0.58$, $P = 0.002$). Gagnon et al. (2001) showed a strong link between dengue incidence and the ENSO in French Guiana, Indonesia, Colombia, and Surinam. Cazelles et al. (2005) pointed out a strong association between the monthly dengue incidence and El Niño 2–3-year periodic mode in Thailand. Brunkard et al. (2008) found that for the SST increase, every 1 °C (El Niño region 3.4) could result in a 19.4 % increase in 18-week lagged dengue incidence in the Texas-Mexico border region.

Tipayamongkholgul et al. (2009) indicated that the ENSO played an important role in driving dengue epidemics across the regions of Thailand. The western Pacific, Singapore, and Thailand all show positive trends in the association between dengue fever and El Niño (Tipayamongkholgul et al. 2009; Earnest et al. 2012). Earnest et al. (2012) further found that the weekly mean

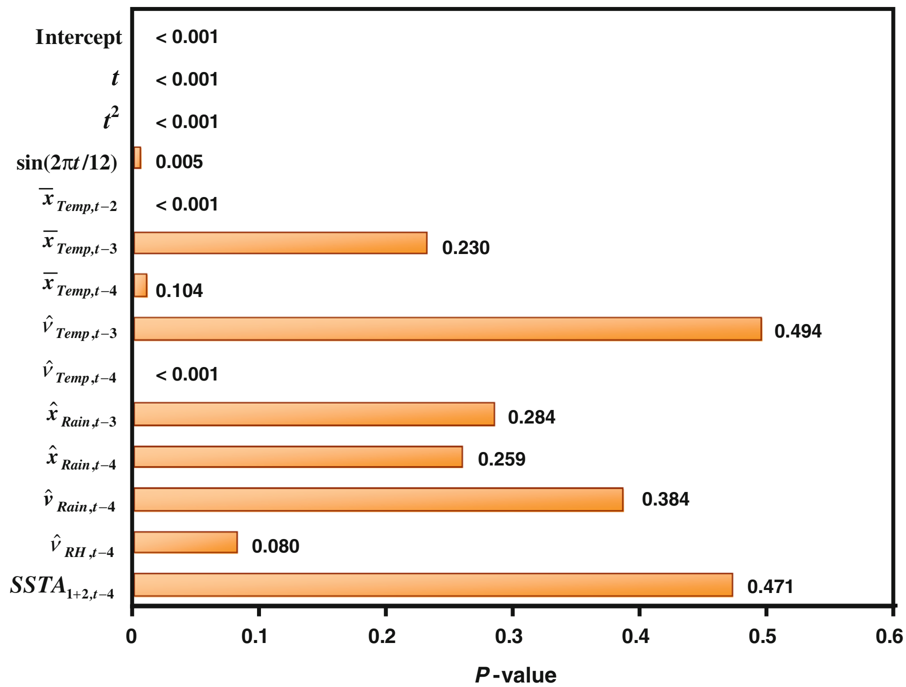

Fig. 4 Sensitivity analysis showed significant factors (*P* value) for the the dengue incidence rate (*symbol* meaning: *Temp* is the temperature, *RH* is the relative humidity, $SSTA_{1+2}$ is the sea surface temperature anomaly (Niño 1 + 2), $\bar{x}$ is the mean, and $\hat{v}$ is the coefficient of variation; $t-2$, $t-3$, and $t-4$ in the subscript represent the 2-, 3-, and 4-month time lag, respectively)

temperature and RH together with the SOI were strongly and independently correlated with dengue incidence. However, Johansson et al. (2009) found no systematic link between the multi-annual dengue incidence and ENSO in Puerto Rico, Mexico, and Thailand.

The effect of El Niño on dengue epidemics is probably due to a warming effect on the local temperature, which in turn reinforces the replication of the dengue virus and the biting rate of the mosquito vector, *A. aegypti* (Watts et al. 1987; Scott et al. 2000). We indicated that recent dengue outbreaks occurring in the densely populated urban settings of southern Taiwan during 2006 and 2009 were strongly associated with a warmer SSTA (Niño 3). Thus, our study suggests that an increase in regional temperature mediates the influence of the ENSO on the dengue incidence rate. Higher ambient temperature would lead to higher water temperatures in shallow bodies of water, such as ponds and rivers, in the estuary of Kaohsiung City.

This suggests that *A. aegypti* has adapted well to urban settings in Taiwan, as it has in much of the tropics, subtropics, and temperate regions of the world, after its origin in sylvan Africa in the absence of human populations (Christophers 1960). This also implicates that *A. aegypti* has adapted to regional climate conditions in southern Taiwan with the highest temperature of 30.42 °C in July and mean monthly RH of 73.29 % with the highest rainfall of 1,229.3 mm in August. Thus, in southern Taiwan the occurrence of the majority of dengue incidences during elevated temperature and warmer SSTA (Niño 1 + 2) periods strongly suggests that temperature alone was a major driving factor in urban transmission by *A. aegypti*. In addition to the mean temperature, we also found that the CV of temperature could also be an early warning signal for dengue outbreaks. The variation in the amplitude of temperature fluctuations had a significant association with the strength of dengue transmission and risk of mosquito-borne disease (Lambrechts et al. 2011). Mosquitoes lived longer and were more likely to become infected under moderate temperature fluctuations, which is typical of the higher dengue virus transmission than under large temperature fluctuations.

However, the rainfall and RH are also important factors in the spread of dengue fever. Wiwanitkit (2006) revealed the possible influence of rainfall on the prevalence of dengue. The influences of changes in rainfall, larval habitat, and vector population may increase during the period of low rainfall to create a new habitat for vector-borne pathogens and increase adult survival; nevertheless, excess rainfall can eliminate the larval habitat by flooding (Gubler et al. 2001; Chen et al. 2010). Moreover, RH affects the longevity, mating, dispersal, feeding behavior, and oviposition of mosquitoes (McMichael et al. 1996; Bi et al. 2007).

4.2 Limitations and implications

Our study only focused on the impact of climate variability and seasonality on the dynamics of urban dengue fever. Our study did not consider older patients, secondary dengue infection, diabetes, and the mosquito density index (Figueeiredo et al. 2010; Lin et al. 2010). Dengue incidence in Kaohsiung was found predominantly in those aged

55–64 and older. The average annual incidence rates were 36.3 (21.9) per 100,000 population and 30.6 (21.3) per 100,000 population among those aged 55–64 and >64 years old, respectively; in the 2005–2010 period, there was a 1.3–1.6 times higher than average incidence of 22.8 (13.3) at the same time. Our Poisson regression model did not take into account the dengue virus serotypes and geographical-environmental and socioeconomic variation factors in order to assess the dengue fever epidemics in Taiwan. The Dengue virus serotypes are non-climate-related factors that could partly influence the increase in dengue cases (Hii et al. 2012). The major dengue virus serotypes in Kaohsiung were attributed to serotypes 2 (73.3 %) and 3 (22.7 %) in the 1998–2007 period (Tsai et al. 2009).

Reiter et al. (2003) indicated that people with high socioeconomic levels usually use more air conditioning; this could effectively reduce their contact with vector mosquitoes, and the low temperature and dry environment could inhibit their survival and transmission rates. On the other hand, international travel, such as commercial ships and air travel, has a potential influence on the distribution of vectors (Kyle and Harris 2008). Kaohsiung is the largest international port in Taiwan. Moreover, changes in population density, travel, dengue vaccination, and new dengue virus strains are important factors that lead to the occurrence of new dengue epidemics and need to be considered (Shepard et al. 2004; Wilder-Smith and Gubler 2008; Earnest et al. 2012). The linkage of dengue, climate changes, and socio-environmental factors on dengue transmission should be considered seriously. Future work will examine the relative importance of the various serotypes and geographical and socio-environmental factors to dengue incidence.

This study showed that the predicted dengue incidence rates were highly coherent with the observed data, indicating the proposed model was capable of forecasting the disease. We also showed that our model was capable of predicting the large dengue outbreaks that occurred in the 2005–2012 period, and this capacity had a relevant implication for public health. Therefore, the predictors in this study may allow an opportunity to anticipate outbreaks using model-based forecasts. Therefore, we find that our lagged Poisson model may make a dengue early warning system practically operational. Our results also suggest that more efforts to forecast climate variability are likely to prove valuable for early warnings for dengue.

Hu et al. (2010) suggested that a SOI-based epidemic forecasting system could provide a predictive tool for dengue fever surveillance, prediction, and risk management in Queensland, Australia. Our analysis suggests that the Pacific SST anomalies and 2–4-month lags of statistical indicators of temperature, rainfall, and RH can capture and predict regional dengue outbreaks well. Tsai et al. (2012) also indicated that the mosquito population increased about 7 days after a bout of rain in Taiwan. Therefore, the ability to forecast regional dengue incidence in southern Taiwan can permit pretreatment of mosquito habitats adjacent to human-inhabited areas with highly effective insecticides that will be released in the high-temperature season.

There are some related activities that may occur in addition to the environmental variables during these periods of global and local climate change: (1) increased temperature and extended seasonality of mosquito activity could signify an expansion in the range of dengue virus vectors, (2) climate change could also facilitate the introduction or reintroduction of new vectors and diseases, (3) mosquito populations may decline during the summer because of decreased precipitation, increased evaporation, and immature mortality at high temperatures, (4) mosquitoes that rely on more permanent water sources may be less affected by drying conditions and thereby gain a larger role as disease vectors, and (5) local area microclimate, seasonality, and surrounding vegetation can also influence mosquito species composition.

Although these results provide an important new understanding of the potential effects of climate change on dengue virus vector ecology, they have some important limitations: (1) suitable validation data are not available, (2) there are a lack of long-term and continuous mosquito surveillance data, (3) mosquito response to climate variables may change in time and between places as a result of evolutionary pressures, and (4) limited test data from mosquito trapping and inaccuracies in climate change projections are limited. Our model also does not account for species interactions or for the effects of human interventions, such as pesticide use, water storage, or large-scale irrigation. Therefore, it is difficult, if not impossible, to incorporate above-mentioned items into our analysis scheme. However, in future work, it is necessary to advance validation and develop location-specific predictions of mosquito population dynamics to improve the integration of model output and mosquito observations.

In conclusion, this study showed that dengue fever outbreaks in southern Taiwan can be explained by regional temperature-, rainfall-, RH-, and ENSO-driven changes. Our Poisson regression model results also demonstrated that there was a 2–4-month time gap between regional climate factors and the dengue incidence rate. Thus, we suggest that there is a need for public health authorities to take advantage of climate observations and analyses in times of climate variability on a monthly basis. Our lagged Poisson model also can alert public health authorities to the need to introduce mitigation planning at the month of increasing temperature and decreasing temperature variation, including pretreatment of mosquito habitats by a mixed control strategy of adulticide and larvicide methods (Burattini et al. 2008), vaccination, and public awareness in the region to prevent or minimize the emergence and re-emergence of dengue fever. Moreover, because strong ENSO events, which have a broad influence, may be predictable up to 1–2 years in advance (Chen et al. 2004), use of our findings may improve regional preparedness for dengue epidemics and other vector-borne disease transmission.

References

Bhatt S, Gething PW, Brady OJ et al (2013) The global distribution and burden of dengue. Nature 496:504–507

Bi P, Zhang Y, Parton KA (2007) Weather variables and Japanese encephalitis in the metropolitan area of Jinan city, China. J Infect 55:551–556

Biggs R, Carpenter SR, Brock WA (2009) Turning back from the brink: detecting an impending regime shift in time to avert it. Proc Natl Acad Sci USA 106:826–831

Brunkard JM, Cifuentes E, Rothenberg SJ (2008) Assessing the roles of temperature, precipitation, and ENSO in dengue re-emergence on the Texas-Mexico border region. Salud Publica Mex 50:227–234

Burattini MN, Chen M, Chow A et al (2008) Modelling the control strategies against dengue in Singapore. Epidemiology and Infection 136:309–319

Carpenter SR, Brock WA (2006) Rising variance: a leading indicator of ecological transition. Ecol Lett 9:308–315

Cazelles B, Chavez M, McMichael AJ, Hales S (2005) Nonstationary influence of El Niño on the synchronous dengue epidemics in Thailand. PLoS Med 2:e106

Centers for Disease Control, Department of Health, ROC (Taiwan) (2002) Statistics of communicable diseases and surveillance report in Taiwan area, 2002. http://www.cdc.gov.tw/uploads/files/201304/78dcc96b-16d3-401b-93a1-14976f022e40.pdf. Accessed 2 July 2013

Chen KT, Chou MY, Ma LS (1987) The primary investigation report of dengue outbreak in southern Taiwan. Taiwan Epidemiol Bull 3:93–95

Chen D, Cane MA, Kaplan A, Zebiak SE, Huang D (2004) Predictability of El Niño over the past 148 years. Nature 428:733–736

Chen SC, Liao CM, Chio CP, Chou HH, You SH, Cheng YH (2010) Lagged temperature effect with mosquito transmission potential explains dengue variability in southern Taiwan: insights from a statistical analysis. Sci Total Environ 408:4069–4075

Chowell G, Sanchez F (2006) Climate-based descriptive models of dengue fever: the 2002 epidemic in Colima, Mexico. J Environ Health 68:40–44

Christophers SR (1960) *Aedes aegypti* (L.) The yellow fever mosquito: its life history, bionomics and structure. Cambridge University Press, London

Dai A, Wigley TML (2000) Global patterns of ENSO-induced precipitation. Geophys Res Lett 27:1283–1286

Dakos V, Scheffer M, van Nes EH, Brovkin V, Petoukhov V, Held H (2008) Slowing down as an early warning signal for abrupt climate change. Proc Natl Acad Sci USA 105:14308–14312

Dakos V, van Nes EH, Donangelo R, Fort H, Scheffer M (2010) Spatial correlation as leading indicator of catastrophic shifts. Theor Ecol 3:163–174

Drake JM, Griffen BD (2010) Early warning signals of extinction in deteriorating environments. Nature 467:456–459

Earnest A, Tan SB, Wilder-Smith A (2012) Meteorological factors and El Niño Southern Oscillation are independently associated with dengue infections. Epidemiol Infect 140:1244–1251

Figueeiredo MA, Rodrigues LC, Barreto ML et al (2010) Allergies and diabetes as risk factors for dengue hemorrhagic fever: results of a case control study. PLoS Negl Trop Dis 4:e699

Focks DA, Barrera R (2007) Dengue transmission dynamics: assessment and implications for control. Report of the Scientific Working Group meeting on Dengue, World Health Organization, Geneva, pp 92–109

Gagnon AS, Bush ABG, Smoyer-Tomic KE (2001) Dengue epidemics and the El Niño Southern Oscillation. Clim Res 19:35–43

Gubler DJ (1998) Dengue and dengue hemorrhagic fever. Clin Microbiol Rev 11:480–496

Gubler DJ, Reiter P, Ebi KL, Yap W, Nasci R, Patz JA (2001) Climate variability and change in the United States: potential impacts on vector- and rodent-borne diseases. Environ Health Perspect 109:223–233

Guttal V, Jayaprakash C (2008) Changing skewness: an early warning signal of regime shifts in ecosystems. Ecol Lett 11:450–460

Hales S, Weinstein P, Woodward A (1996) Dengue fever epidemics in the South Pacific: driven by El Niño southern oscillation? Lancet 348:1664–1665

Hales S, Weinstein P, Souares Y, Woodward A (1999) El Niño and the dynamics of vectorborne disease transmission. Environ Health Perspect 107:99–102

Hales S, de Wet N, Maindonald J, Woodward A (2002) Potential effect of population and climate changes on global distribution of dengue fever: an empirical model. Lancet 360:830–834

Halstead SB (2008) Dengue virus-mosquito interactions. Annu Rev Entomol 53:273–291

Hii YL, Rocklöv J, Wall S, Ng LC, Tang CS, Ng N (2012) Optimal lead time for dengue forecast. PLoS Negl Trop Dis 6:e1848

Hu WB, Clements A, Williams G, Tong SL (2010) Dengue fever and El Niño/Southern Oscillation in Queensland, Australia: a time series predictive model. Occup Environ Med 67:307–311

Joanes DN, Gill CA (1998) Comparing measures of sample skewness and kurtosis. Statistician 47(1):183–189

Johansson MA, Dominid F, Glass GE (2009) Local and global effects of climate on dengue transmission in Puerto Rico. PLoS Negl Trop Dis 3:e382

King CC, Wu YC, Chao DY et al (2000) Major epidemics of dengue in Taiwan in 1981–2000: related to intensive virus activities in Asia. Dengue Bull 24:1–10

Kovats RS, Bouma MJ, Hajat S, Worrall E, Haines A (2003) El Niño and health. Lancet 362:1481–1489

Kyle JL, Harris E (2008) Global spread and persistence of dengue. Annu Rev Microbiol 62:71–92

Lai LW (2011) Influence of environmental conditions on asynchronous outbreaks of dengue diseases and increasing vector population in Kaohsiung, Taiwan. Int J Environ Health Res 21:133–146

Lambrechts L, Paaijmans KP, Fansiri T, Carrington LB, Kramer LD, Thomas MB, Scott TW (2011) Impact of daily temperature fluctuations on dengue virus transmission by *Aedes aegypti*. Proc Natl Acad Sci USA 108:7460–7465

Lei HY, Huang JH, Huang KJ, Chang C (2002) Status of dengue control programme in Taiwan—2001. Dengue Bull 26:14–23

Lenton TM (2011) Early warning of climate tipping points. Nature Clim Change 1(4):201–209

Lin CC, Huang YH, Shu PY, Wu HS, Lin YS, Yeh TM, Liu HS, Liu CC, Lei HY (2010) Characteristic of dengue disease in Taiwan: 2002–2007. Am J Trop Med Hyg 82:731–739

Livina VN, Lenton TM (2007) A modified method for detecting incipient bifurcations in a dynamical system. Geophys Res Lett 34(3):L03712

Mackenzie JS, Gubler DJ, Petersen LR (2004) Emerging flaviviruses: the spread and resurgence of Japanese encephalitis, West Nile and dengue viruses. Nat Med 10:S98–S109

Martinerie J, Adam C, Le Van Quyen M, Baulac M, Clemenceau S, Renault B, Varela FJ (1998) Epileptic seizures can be anticipated by non-linear analysis. Nat Med 4:1173–1176

McMichael AJ, Haines A, Slooff R, Kovats S (1996) Climate changes and human health. World Health Organization, Geneva

McMichael AJ, Woodruff RE, Hales S (2006) Climate change and human health: present and future risk. Lancet 367:859–869

Patz JA, Campbell-Lendrum D, Holloway T, Foley JA (2005) Impact of regional climate change on human health. Nature 438: 310–317

Phillips ML (2008) Dengue reborn widespread resurgence of a resilient vector. Environ Health Perspect 116:A382–A388

Promprou S, Jaroensutasinee M, Jaroensutasinee K (2005) Climatic factors affecting dengue haemorrhagic fever incidence in Southern Thailand. Dengue Bull 29:41–48

Reiter P, Lathrop S, Bunning ML et al (2003) Texas lifestyle limits transmission of dengue virus. Emerg Infect Dis 9:86–89

Scheffer MJ, Bascompte J, Brock WA et al (2009) Early-warning signals for critical transitions. Nature 461:53–59

Scott TW, Amerasinghe PH, Morrison AC, Lorenz LH, Clark GG, Strickman D, Kittayapong P, Edman JD (2000) Longitudinal studies of *Aedes aegypti* (Diptera: Culicidae) in Thailand and Puerto Rico: blood feeding frequency. J Med Entomol 37:89–101

Shepard DS, Suaya JA, Halstead SB, Nathan MB, Gubler DJ, Mahoney RT, Wang DN, Meltzer MI (2004) Cost-effectiveness of a pediatric dengue vaccine. Vaccine 22:1275–1280

Su GLS (2008) Correlation of climatic factors and dengue incidence in Metro Manila, Philippines. Ambio 37:292–294

Takimoto G (2009) Early warning signals of demographic regime shifts in invading populations. Popul Ecol 51:419–426

Thammapalo S, Chongsuvivatwong V, Geater A, Dueravee M (2008) Environmental factors and incidence of dengue fever and dengue haemorrhagic fever in an urban area, Southern Thailand. Epidemiol Infect 136:135–143

Tipayamongkholgul M, Fang CT, Klinchan S, Liu CM, King CC (2009) Effects of the El Niño-Southern Oscillation on dengue epidemics in Thailand. BMC Public Health 9:422

Tsai JJ, Chan KS, Chang JS et al (2009) Effect of serotypes on clinical manifestations of dengue fever in adults. J Microbiol Immunol Infect 42:471–478

Tsai CT, Sung FC, Chen PS, Lin SC (2012) Exploring the spatial and temporal relationships between mosquito population dynamics and dengue outbreaks based on climatic factors. Stoch Environ Res Risk Assess 26:671–680

Watts DM, Burke DS, Harrison BA, Whitmire RE, Nisalak A (1987) Effect of temperature on the vector efficiency of *Aedes aegypti* for dengue 2 virus. Am J Trop Med Hyg 36:143–152

Wilder-Smith A, Gubler DJ (2008) Geographic expansion of dengue: the impact of international travel. Med Clin North Am 92:1377–1390

Wiwanitkit V (2006) An observation on correlation between rainfall and the prevalence of clinical cases of dengue in Thailand. J Vector Borne Dis 43:73–76

Wu PC, Guo HR, Lung SC, Lin CY, Su HJ (2007) Weather as an effective predictor for occurrence of dengue fever in Taiwan. Acta Trop 103:50–57

Yu HL, Yang SJ, Yen HJ, Christakos G (2011) A spatio-temporal climate-based model of early dengue fever warning in the southern Taiwan. Stoch Environ Res Risk Assess 25:485–494