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建立以氣候資訊為基礎的台灣登革流行預測模式：

1998-2007 年登革流行病學和氣象學因子之時序分析

Establishment of a Better Prediction System for Dengue Epidemics in Taiwan: Temporal Analyses of Epidemiological and Meteorological Factors of Dengue during 1998-2007

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摘要

受登革病毒感染的旅客經常成為散播病毒至其他地區的重要途徑，甚而引發他國的流行；然而這些感染的旅客入境後和當地氣候、病媒以及本地疫情之間的互動關係並不清楚。由於境外移入病例與本地登革疫情關係的議題長期受到忽略，本研究即在探究臺灣地區的境外移入登革病例和氣候因子，對於本地疫情發生之影響，進而可讓基層與中央衛生人員將危險層級資訊馬上應用於疾病防控策略。

我們使用羅吉斯（logistic）和普瓦松（Poisson）迴歸模式分析 1998 至 2007 年間臺灣南部地區經實驗室診斷證實的登革確定病例，以區辨在氣候因子的作用下，境外移入和本地登革病例的時序相關性。結果發現本地登革疫情的發生與境外移入病例數（2 至 14 週前）、高溫（6 至 14 週前）及低濕度（6 至 20 週前）之間，具有延遲的相關性。此外，境外移入病例數和本地登革病例數僅在流行被引發的「初期」階段，才有明顯數量上的相關性；一旦流行持續發生，此種關係即不復見。另外，根據單變項分析的結論，挑選出的重要氣候因子所建立的羅吉斯迴歸模式，可以進一步建立登革危險性指標的預警數值。經初步運算，此法優於僅以前期登革危險性指標(dengue risk index, DRI)值預測本期 DRI 值的效果，在加入氣候因子後，模式預測值與觀察值的相關係數(Spearman correlation)可達 0.71(屏東地區)、0.84(高雄地區)以及 0.86(台南地區)；至於泰國地區也有 0.66-0.77 的水準。由此可知此法不但適用於台灣登革疫情層級之預警，也適用於泰國海岸五省的疫情預測。

這些發現顯示，惟有氣象條件適宜時，境外移入登革病例才有可能引發本地的疫情。據此，經由境外移入病例的快速實驗診斷、早期發現以及管理，可以遏止其後大規模登革/登革出血熱流行的發生。因此整合氣象資訊的早期警示監測系統，將是登革疫情尚未成為地方性流行的地區用以成功防治疫情的無價利器。

關鍵字：登革熱/登革出血熱、本土流行、境外移入病例、氣象、迴歸模式、登革危險性指標

Abstract

Travelers who acquire dengue infection are often routes for virus transmission to other regions. Nevertheless, the interplay between infected travelers, climate, vectors, and indigenous dengue incidence remains unclear. The role of foreign-origin cases on local dengue epidemics has thus been largely neglected by research. This study investigated the effect of both imported dengue and local meteorological factors on the occurrence of indigenous dengue in Taiwan.

Using logistic and Poisson regression models, we analyzed bi-weekly, laboratory-confirmed dengue cases at their onset dates of illness from 1998 to 2007 to identify correlations between indigenous dengue and imported dengue cases (in the context of local meteorological factors) across different time lags. Our results revealed that the occurrence of indigenous dengue was significantly correlated with temporally-lagged cases of imported dengue (2-14 weeks), higher temperatures (6-14 weeks), and lower relative humidity (6-20 weeks). In addition, imported and indigenous dengue cases had a significant quantitative relationship in the onset of local epidemics. However, this relationship became less significant once indigenous epidemics progressed past the initial stage. Polytomous Logistic regression model with relevant meteorological variables stepwise selected were able to fitting the value of Dengue Risk Index (DRI) in both Taiwan and Thailand. The Spearman correlation between observed DRI and model-expected DRI ranged from 0.71 to 0.86 in Taiwan and from 0.66 to 0.77 in Thailand, respectively.

These findings imply that imported dengue cases are able to initiate indigenous epidemics when appropriate weather conditions are present. Early detection and case management of imported cases through rapid diagnosis may avert large-scale epidemics of dengue/dengue hemorrhagic fever. The potential application of DRI with meteorological modeling in both Taiwan and Thailand demonstrated that its feasibility to be extended to other countries for the current important issue on global warming and dengue. The deployment of an early-warning surveillance system, with the capacity to integrate meteorological data, will be an invaluable tool for successful prevention and control of dengue, particularly in non-endemic countries.

Keywords: dengue, meteorology, climate, weather, regression model, Dengue Risk Index

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Chapter 1 Introduction

1.1 The impact of climate on dengue epidemics

Dengue/dengue hemorrhagic fever is the world's most widely spread mosquito-borne arboviral disease and threatens more than two thirds of the world's population. Cases are mainly distributed in tropical and subtropical areas, between 23.5^{o}N and 23.5^{o}S, in accordance with vector habitats for *Aedes aegypti* and *Ae. albopictus*. Climate is believed to have complex and long-lasting effects on the epidemics of infectious diseases, especially vector-borne diseases [1-4]. The meteorological factors interact with human and mosquito vector, and affect the occurrence and distribution of diseases ecologically [5-8] through both infectious agents and arthropod vectors biologically [9,10].

The possible role of international travel in cross-country and cross-continent transmission dengue has been identified an increasing public concern in recent years [11-13]. More and more infectious travellers carry viruses back to home countries, and disperse the virus within the network established by indigenous populations of both mosquito vectors and human hosts. Thousands of international travelers infected dengue viruses in endemic areas, where a disease occurs continuously and with predictable regularity in a specific area or population (http://www.cdc.gov/ncidod/dvbid/dengue/index.htm), have been speculated as an important pathway in transmitting the disease into non-endemic areas [14-17]. Potasman et al. have discovered that Israeli travellers were at higher risk for acquiring dengue infection when they arrived in tropical countries in summer [18]. Seasonality of imported dengue is therefore supposed to have potentially complex and long-lasting effects on the epidemics of dengue [13]. Nonetheless, some of the previous studies even underestimate or neglected the effects that imported cases may have on the occurrence of epidemics [19,20]. The interaction between seasonality and imported dengue is reasonably to play an important role in the occurrence of indigenous cases, and thus worthy of detailed investigation.

1.2 Unsolved questions

Up to now, the effects of regional weather may have on vector-borne infectious diseases are not well-understood. The most frequently studied meteorological factors have been temperatures and rainfall [1,21-23]. However, many other meteorological factors have been mostly neglected. The time lag between those meteorological factors and the incidence of a studied disease has generally be overlooked or underestimated in investigating their real correlations. How to use the best model to consider all important meteorological factors with time lags and unique epidemiological characteristics of dengue in Taiwan becomes very important.

Chapter 2 Literature review

2.1 Global status of dengue

Dengue fever is caused by dengue viruses (four serotypes), classified as *flaviviridae*. Both the incidence and epidemic areas have been increasing in the past four decades. About 50% of population in the world is under the threat of dengue infection and 100 million cases occur annually [24]. Its potential severer complications, including dengue hemorrhagic fever (DHF) and dengue shock syndromes (DSS), result in the leading cause of death in children in endemic areas [25,26]. Historically, after the first official case report of dengue in the 18th century, the major epidemics occurred mainly in Asia, especially in South East Asia, such as Thailand, the Philippines, and Indonesia. Nevertheless, dengue epidemics have also been frequent in the Pacific islands, South Asia, Australia, Africa, Latin America, etc. Even high latitude areas are also involved through frequent and instant international transportation [27,28].

2.2 Dengue in Taiwan

As early in 1870s, there was reported dengue-like disease. Sporadic cases occurred mainly in Kaohsiung area every two or three years. The disease had not been reoported after 1940s. Dengue reappeared in Pingtung area (Liuchiu islets) in 1981 and Kaohsiung area in

1987 with thousands of cases. Hereafter, there are epidemics every year in southern Taiwan. After 1990, Taichung (1995) and Taipei (1996, 2007) have been also involved in indigenous dengue.

2.2.1 Surveillance of dengue in Taiwan

Surveillance of dengue in Taiwan is made up of three parts: passive reporting of dengue, including dengue fever (DF) and dengue hemorrhagic fever (DHF) within 24 hour, active and semi-active surveillance. In passive surveillance, dengue-like illness reports by health care workers to local health authorities account for most confirmed dengue cases. Active surveillance, including volunteer reporting and fever screenings at international airports (identifying fever cases by infrared thermal scanner, which has been routinely operated by the government since 2003) [29,30]. In semi-active surveillance, fever cases are investigated in residential areas, schools, and work places with epidemiological linkage, and specimens are taken once confirmed dengue cases are identified. These active and semi-active components, serve to complement and reinforce in support of comprehensive virus detection. Among active strategies, fever screening detects imported dengue cases efficiently [30]. All febrile patients identified through fever screening are required to submit blood samples for testing. In addition, public health professionals at local health authorities monitor suspected cases for the development of dengue-like symptoms/signs until dengue virus infection is excluded [31]. These strategies identify and manage potential dengue cases before they enter into the community. In other words, Taiwan's dengue surveillance involves serologically detected mild and asymptomatic dengue cases that are quite different from many dengue-endemic countries where most of severe DHF cases are reported with less involving mild dengue cases. Under these circumstances, the true relationship between meteorological factors and dengue can be appropriately under investigation.

2.2.2 Case definition of dengue

The current definitions for dengue, including DF, DHF and dengue shock syndrome (DSS) in Taiwan have been applied since the 1980s. Cases of "probable DF" are patients with body temperatures $\geq 38^{o}C$ and two or more of the following clinical manifestations: headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations and leucopenia. Cases of "probable DHF" and DSS are further identified based on criteria established by the World Health Organization [32]. Identified probable dengue cases must provide blood specimens for laboratory confirmation tests. These laboratory tests include molecular identification of dengue virus by reverse-transcriptase polymerase chain reaction (RT-PCR) [33], single or paired serum samples testing for dengue-specific IgM seropositives, 4-fold dengue-specific IgG serotiter rises (with the exclusion of Japanese encephalitis virus infection) [32], or virus isolation [34,35].

2.2.3 Definition of imported dengue cases

Epidemiological questions such as travel history, incubation period, and first day of illness were evaluated to identify the possible origin of dengue infection. "Imported dengue cases into Taiwan" were defined as laboratory-confirmed dengue cases with travel history to endemic countries within 14 days before the date of onset of dengue (based on Taiwan-CDC's definition) [31].

2.2.4 Serotype of dengue viruses in major epidemics

According to the reports of Taiwan-CDC, the major epidemics areas located in southern Taiwan: TN, KH and PT [31]. Information on the predominant serotype of isolated dengue viruses (Figure 1C) showed that the dominant serotypes/genotypes of epidemic DENV varied by year and area [30]. However, in 2002, a DENV-2 epidemic attacked all these three areas. During our study period, KH had the most frequent occurrence of dengue epidemics, with epidemics of DENV-2 in 1998 and 2001-2003; DENV-1 in 2004; DENV-3 in 2006, and DENV-1 in 2007. TN had four major epidemics, including DENV-3 in 1998 [36], DENV-4 in 2000, DENV-2 in 2002, and DENV-1 in 2007. PT had two major epidemics, including DENV-2 in 2001-2003 and

DENV-1/DENV-4 in 2004. Interestingly, we found that local dengue epidemics, with geographical variations in these three areas, only had higher numbers of indigenous cases during certain years.

2.3 The impact of imported cases

2.3.1 International transmission of dengue

Dengue outbreaks initiated by international tourists, immigrants, and foreign workers have been reported in numerous developed areas and countries [11-13]. Not only tropical/subtropical areas, but distant areas/countries are also under the threat of dengue through international tourists, immigrants, foreign workers, and militaries [16,27]. Developed areas and countries have reported outbreaks in the recent decade, including Hawaii [37] and Texas [38] in the United States, France[17], and Germany [15]. Nevertheless, the potential impact from the complicated interaction among infected travellers, climate, vectors and incidence is unclear [13,15].

2.3.2 Correlation between season and imported dengue cases

Historically, the link between imported cases and indigenous cases has been established through phylogenetical analysis and viral sequence comparisons [29,30].

However, these retrospective studies are not capable of providing timely, relevant information about transmission dynamics, nor do they provide quantitative insight for disease control strategies in a broader context. For example, epidemiological data has indicated that imported dengue cases enter Taiwan almost every month from other countries (Figure 1B) but have not always resulted in local dengue epidemics [18,30]. This suggests that the timing of imported dengue's entrance may have considerable effect on domestic dengue epidemics [13,16]. However, the role of these foreign-origin cases in local dengue epidemics has not yet been quantitatively assessed [20].

2.4 Meteorological effects

Climate has been identified to be correlated with disease incidence and thus may be usable to predict the occurrence of infectious diseases, especially for those vector-borne ones which are sensitive to seasonality [4,13,39,40]. Higher temperature is believed to increase the occurrence of dengue because of it shortens the time of virus replication in mosquito vectors (known as extrinsic incubation period, EIP) [10]. Warmer condition may also reduce the size of adult mosquito with higher metabolism rates, and thus require more blood meal through higher biting rate [41]. Rainfall related factors are also considered positively correlated with the incidence of dengue by increasing the breeding sites of mosquito vectors [1,21,39]. Rainy days have been reported significantly associated with DHF incidence in Thailand [42]. Extremely heavy rains was thought to flush away mosquito eggs, larvae and pupae from the breeding sites [42]. Nevertheless, a recent study with more precise experiments concluded that the larva and pupa of *Aedes aegypti* populations, comparing with *Culex pipiens,* were slightly affected by excessive rain [43]. They found that the fourth instars of *Ae. aegypti* were not affected by flushing when exposed for longer rain intervals (30 versus 60 min) or at a colder water temperature (24 versus 16°C). This difference was most dramatic during the pupal stage. Higher relative humidity has also been reported correlated with higher mosquito density and higher vector capacity [44,45] (e.g. "the daffy rate at which future inoculations arise from a currently infective case, provided that all female adults (the original text: flies) biting that case become infected" [46]), and thus used for the projection of global dengue [2].

2.5 Modeling for dengue incidence

In order to control the disease, recent studies attempt to predict dengue incidence with regression models. ARIMA (Autoregressive Integrated Moving Average) has been popular in time series fitted models designed to simulate or predict the number or incidence of dengue with meteorological information [5,19,20,47,48]. ARIMA models are based on linear regression, assuming that dengue incidence is under normal distribution. Although some previous studies fit the incidence pretty well, the disease data is actually count in its nature and thus need more reasonable assumptions.

2.6 Potential usage of dengue risk index (DRI)

2.6.1 A need for an understandable index

A globally understandable index for epidemics or risk of dengue is needed. Currently, most countries in the world have individual or international surveillance systems for dengue with a focus mainly on the total number of cases (e.g. DengueNet of World Health Organization). If we are able to integrate their information about dengue epidemics with an indexing system, each country or area may have its specific value within certain period. This index will be able to alert people before they enter an endemic area of dengue, as well as governments once they have travelers from high risky countries. One example of international-accepted indexing system is the ultraviolet index (UVI), which transforms the daily maximum UVB flux into a digital value, named as UVI [49], and then assigned it into one of five interpretable ordinal categories: low, moderate, high, very high and extreme. Another commonly used indexing system is the Pollutant standard index (PSI), which helps one to be alert on the air pollution condition where he lives or he will visit.

Although the importance of imported cases to local dengue epidemics has been reported worldwide [12,27], unfortunately, for the travelers, there has been no advice from a system to quantify the risk of their destinations. Human movements are identified to have impact on spreading of dengue rather than solely mosquito dispersing [35,50]. The relevance of different spatial distances are from household, neighborhood, regional to international spreading [51]. Most strategies for dengue control are limited within a country or an area, such as insecticide spraying and case notification, however, the management and prevention for global transmission is lacked.

2.6.2 Categorized number of dengue cases

Previous studies on prediction models for dengue mainly focused on calculating the number of dengue cases with regression models mostly [5,20,47]. However, this method is not appropriate especially for those non-endemic areas of dengue because of the over-dispersion (super high variance) among the numbers of indigenous dengue in different seasons. On the other hand, it is not necessary for the public to realize the exact case number if there is an epidemic. Instead, categorization of the case number of dengue into an accessible risk index may not only enhance the efficiency of disease prediction, but also become more practical for disease control and prevention.

In this study, we propose a Dengue Risk Index (DRI) by establishing polytomous (multi-level) Logistic regression models based on the information about local epidemiological data. We applied this concept to calculate area-specific DRI with real data, and compared the expected values with observed ones in Taiwan and Thailand, two countries with different status of dengue epidemics. In addition, a preliminary forecasting method was also developed to illustrate how to implement DRI on dengue predicting.

Chapter 3 Objectives and Specific Aims

3.1 Objectives and specific aims

The study used data of all imported and indigenous dengue cases nationwide that had been confirmed by the Taiwan-CDC) [31,52] to investigate the relationship between imported and indigenous dengue, and all concurrent meteorological characteristics with potential for facilitating disease transmission.

The specific aims of this study were:

1) To investigate the relationship between imported and indigenous dengue, and all concurrent meteorological characteristics with potential for facilitating disease transmission.
2) To clarify the relationship between imported dengue, local weather, and domestic epidemics of dengue, and to further identify the role of imported cases (in different phases) during a dengue epidemic in non-endemic areas such as Taiwan.

To explore the potential usage of categorized case number, named as Dengue Risk Index, in describing and analyzing the epidemiology of indigenous dengue outbreaks, and to further establish a predicting system with succinct meteorological regression model.

3.2 Hypotheses

3.2.1 Specific meteorological variables correlated with more indigenous dengue cases

3.2.2 Imported dengue cases positively correlated with more indigenous dengue cases

3.2.3 Dengue risk index is able to reflect the number of confirmed/reported dengue cases

3.2.4 Previous dengue risk index correlate with current dengue risk index, thus is able to predict

3.2.5 Specific meteorological variables selected in a regression model are able to fit the distribution of dengue risk index

Chapter 4 Materials and methods

4.1 Study areas

Confirmed indigenous dengue cases in three epidemic areas in Southern Taiwan [Tainan (TN), Kaohsiung (KH), and Pingtung (PT)] were investigated. All three areas had identified both *Aedes aegypti* and *Ae. albopictus* mosquitoes as vectors for transmitting dengue virus. KH, including both metropolitan Kaohsiung and Kaohsiung County (total area is 2,946.27 km^2, and total population was 2,770,050 in year 2008), had served as the location for the majority of Taiwan's dengue epidemics involving all four serotypes of dengue viruses. Smaller scale epidemics of dengue also occurred in both TN and PT, located adjacent to Kaohsiung. For this study, TN included Tainan City and County (total area is 2,191.65 km^2, and total population was 1,873,678 in year 2008), while PT referred to Pingtung City and County (total area is 2,775.60 km^2, and total population was 884,067 in year 2008). The subtropical climate of southern Taiwan presents an annual hot and rainy summer season lasting from June to August and daily mean temperatures ranging from 18^o to 32^oC year round.

4.2 Epidemiological data

Information on these confirmed cases of dengue fever (DF) and dengue hemorrhagic fever (DHF) were obtained from Taiwan-CDC from 1998 to 2007 through dengue surveillance in Taiwan. Date of onset of dengue illness, age, gender, clinical manifestations, reporting hospital, and laboratory results were all thoroughly documented for each dengue case.

4.3 Meteorological data

We systematically collected daily weather data for Taiwan that was publicly available through the 26 branch stations of the Central Weather Bureau (http://www.cwb.gov.tw/). The meteorological variables analyzed in this study were selected after comprehensive evaluation of all available data with biological relevance to vectors or cases of dengue, including daily mean temperature, daily maximum temperature, daily minimum temperature, daily mean relative humidity, daily mean wind speed, daily accumulative rainfall, daily accumulative rainy hours, daily sunshine accumulation hours, daily mean sunshine rate (from sunrise to sunset), and daily sunshine total flux. Unlike weather stations in Tainan and Kaohsiung, Pingtung County's station is located a far distance from Pingtung City, where the majority of Pingtung's dengue cases occurred. We therefore used weather data collected by the Environment Protecting Agency (EPA) at their station in Pingtung City. This EPA weather station was only able to provide data regarding daily mean temperature, daily maximum temperature, daily minimum temperature, daily mean wind speed, and daily accumulative rainfall. We then substituted Kaohsiung's data for Pingtung's meteorological variables not provided by the EPA because of

Pingtung City's close proximity to Kaohsiung City.

4.4 Thailand's data

Thailand has been an important origin country of dengue viruses that result in local epidemics [30]. Datasets were available for related analyses through international cooperation. Considering the similar meteorological and demographical situation of dengue to Taiwan, five coastal provinces in Thailand were selected to compare with the model fitting in Taiwan. The five provinces are (a) Phetchaburi, (b) Prachuap Khirikhan, (c) Chumphon, (d) Surat Thani and (e) Nakhon Sitammarat. Since there were only reported dengue cases available in Thailand's data, we replaced confirmed dengue by reported dengue in Thai's models. Both meteorological and epidemiological data were kindly offered by Dr. Mathuros Tipayamongkholgul in Mahido University, Thailand.

4.5 Statistical analyses

All laboratory-confirmed daily dengue cases, according to the date of onset of dengue illness, were summed into total case numbers in bi-weekly intervals for data analysis. The mean value of each meteorological variable was also calculated for each biweekly interval. Abbreviations of all variables analyzed are listed in the Table. As the effects of imported dengue and meteorological factors on indigenous dengue logically had a time lag, we thus tested different time lags for each variable from lag 1 up to lag 12 (lag 1 representing two weeks, lag 2 representing four weeks, and so on)

4.5.1 Logistic and Poisson regression models

Logistic regression was used to analyze the correlation between the occurrence/increase of indigenous dengue and the number of imported cases, as well as the correlation between the occurrence/increase of indigenous dengue and each meteorological variable across various time lags (from 2 weeks to 24 weeks). Poisson regression was used to analyze the correlation between the number of indigenous dengue cases and the number of imported cases, as well as the correlation between the number of indigenous dengue cases and quantitative data of each meteorological variable across time lags from 2 weeks to 24 weeks. Regression with the negative binomial model [53] was used for over-dispersed data. All models were adjusted by area (two dummy variables, area_KH and area_TN), popd (area-specific population density), and sine24 plus cosine24 (the oscillatory *sine* and *cosine* functions were used to model seasonal variations of dengue cases [54]).

4.5.2 Three phases in epidemics outbreak

Because the quantitative relationship between indigenous and imported dengue cases may exist only at the onset of local dengue epidemics, we further divided all bi-week intervals into three categories for further analysis: 1) **Period of "low intensity transmission"**: From March to May during our study period, 94.44% (170/180) of bi-week intervals during these three months had no indigenous dengue cases in these studied areas. 2) **Period of "early phase of outbreaks"**: Those bi-week intervals presenting <10 indigenous dengue cases for months excluding March to May. 3) **Period of "late phase of outbreaks"**: Those bi-week intervals presenting ≧10 indigenous dengue cases. Further information on these regression models are listed in the Appendix 1.

4.5.3 The contents of regression models

1. Modeling the temporal correlation between "Occurrence" of indigenous dengue and variables: Occurrence (y/n) ~ sin24 + cos24 + two dummy variables for areas+ population density + tested lagged variable, link = logistic, family = binomial
2. Modeling the temporal correlation between "Increase" of indigenous dengue and variables: Increase (y/n) ~ sin24 + cos24 + two dummy variables for areas+ population density + tested lagged variable, link = logistic, family = binomial
3. Modeling the temporal correlation between the number of indigenous dengue and variables: Case (count) ~ sin24 + cos24 + two dummy variables for areas+ population density + tested lagged variable, link = log-linear, family = negative binomial

4. Modeling the temporal correlation between the number of indigenous and imported dengue in Period of "low intensity transmission" (Those bi-week intervals were from March to May):

   Case (count) in Period of "low intensity transmission"~ sin24 + cos24 + two dummy variables for areas+ population density + tested lagged variable, link = log-linear, family = Poisson

5. Modeling the temporal correlation between the number of indigenous and imported dengue in Period of "early phase of known outbreaks" (Those bi-week intervals presenting <10 indigenous dengue cases for months excluded March to May):

   Case (count) in Period of "early phase of known outbreaks"~ sin24 + cos24 + two dummy variables for areas+ population density + tested lagged variable, link = log-linear, family = Poisson

6. Modeling the temporal correlation between the number of indigenous and imported dengue in Period of "late phase of known outbreaks" (Those bi-week intervals presenting ≧ 10 indigenous dengue cases):

   Case (count) in Period of "late phase of known outbreaks"~ sin24 + cos24 + two dummy variables for areas+ population density + tested lagged variable, link = log-linear, family = negative binomial

4.5.4 The definition of Dengue Risk Index (DRI)

Five categories (Table 2) were distinguished and identified by a digit number of 0, 1, 2, 3 and 4 respectively, representing different levels of indigenous dengue condition based on the number of indigenous cases confirmed during a time interval, e.g. one month or two weeks. The cut-off points of categories are 0, 10, 100 and 1000, which are not only mathematically meaningful, but also epidemiologically. For most non-endemic countries of dengue, there is usually zero indigenous cases, thus “0” is supposed to be a major group for case number (color green). When there are cases no more than 10, it may just because of sporadic diseases initiated by imported cases (color yellow). Furthermore, if case number gets to between 10 and 99, it may represent a limited, local epidemic is happening (color orange). An epidemic is obviously spreading if cases are over 100 (color red). The situation of dengue is out of control when the number indigenous cases is higher than 1,000 (color purple).

4.5.5 Meteorological regression model

Statistical significant variable in univariate analyses were recruited into regression model selection. Relevant variables selected by stepwise procedure were used to fit observed and expected DRI, but also conduct out-of-fit to verify the prediction with different datasets. In Taiwan’s part, these models were applied to calculate the expected

DRI for each bi-week interval during 1998 to 2007. Furthermore, out-of-fit of fitted models were performed with data of year 2008 to predict the values of DRI. Similarly, Thailand's data from 1996 to 2004 were used to build up regression models, and year 2005 to predict DRI.

4.5.6 Comparison of different DRI forecasting methods

In order to validate the meteorological regression models in the use of predicting DRI, we performed two other strategies for comparison by applying both Taiwan's and Thailand's data from 1998 to 2005. As for forecasting, two classical approaches are usually concerned. First is "continuous method", which means predicting according to what just happened. It is to move DRI curve with a certain lag forward as the prediction. The second one, "historic method", is predicting with the mean value of the past years. For example, if we want to predict monthly DRI in 2001, the mean DRI of each month from 1991 to 2000 may be conducted to predict.

In order to testify the consistence between observed and expected values, Gamma, Kendall's Tau-b, Stuart's Tau-c and Spearman's rank correlation on ordinal data were conducted. All formulas are adapted from User's Manual of SAS and listed in Appendix 2.

Two-tailed $p < 0.05$ was regarded as statistically significant. The statistical analysis was conducted using S-PLUS Enterprise Developer Version 8.0.4 (TIBCO Software Inc., Palo Alto, CA, USA) and SAS 9.1.3 Service Pack 4 (SAS Institute Inc., Cary, NC, USA).

Chapter 5 Results

5.1 Logistic regression models for the occurrence and increase of indigenous dengue cases: Univariate analyses

Figure 3 displays estimates of regression coefficients of independent variables (Xs) in the logistical regression model for the "occurrence" of indigenous dengue cases. We found that the variables of the number of imported cases (imported, $p = 0.0023$~0.0315) and daily maximum/mean/minimum temperatures (tmax/tmean/tmin, $p = 0.0002$~0.0495) were positively correlated. On the contrary, relative humidity (rh) was negatively correlated with indigenous case occurrences ($p < 0.0001$ ~ $p = 0.0433$). These findings indicate that an increase in imported cases, in conjunction with warmer and drier weather, is favorable for the occurrence of indigenous dengue. Among other meteorological variables, one sunshine related variable and wind speed did not exhibit consistently significant relationships with indigenous dengue (data not shown). However, Figure 4 reveals that, the influence of both imported cases and weather conditions on the "increase" of indigenous dengue was less significant. In addition, when binary outcomes were replaced with indigenous case counts (Figure 5), the quantitative relationships between imported and indigenous dengue cases became insignificant.

5.2 Impact of imported dengue on indigenous dengue at three epidemic phases

In Figure 6, we observed variation in the impact of imported dengue at different epidemic phases (please see definitions in Methods). Using Poisson models, we found that the imported dengue cases were significantly correlated with indigenous dengue with lag 4 (i.e. 8 weeks) only in **periods of "low intensity transmission"** (Figure 6A). However, this relationship was more statistically significant in the **"early phase of outbreaks"** (Figure 6B). Imported dengue had their greatest impact on epidemics during this phase. When local epidemics entered a p**eriod of "late phase of outbreaks"**, these correlations disappeared (Figure 6C), suggesting that imported cases were unlikely to have influence on indigenous cases during this period. These findings may indicate that imported dengue cases initiate local dengue cases almost exclusively during the onset of an epidemic.

5.3 Poisson regression model fitted with meteorological variables of dengue cases

We attempted to fit the numbers of dengue cases with Poisson regression models, but it did not show satisfactory results because the large variances of case numbers led to over-dispersion.

5.3.1 Square root of case number

As shown in Figure 7A, although the square roots of case number replaced the case numbers to lower the variance, the fitted case numbers are still out of expectation. The same situation was also observed in using cubic root of case numbers.

5.3.2 Principal component analysis

To reduce the number of independent variables, we then compiled different time lags of the same variable, i.e. factor of relative humidity (RH) may represent original rh lag 1~8 with different weighted or adjusted process. Nevertheless, the fitting result for the numbers of dengue cases was still poor (Figure 7B). In addition, the different lag of a same variable is not independent one another, so the application of PCA is inappropriate.

5.3.3 Zero-inflated Poisson

In order to overcome the problem that zero dengue cases occurred over half of time intervals, we used zero-inflated Poisson regression models to fit the numbers of dengue cases. Unfortunately, the variation among numbers of dengue cases were too large to fit Poisson distribution and the model fitting thus failed.

5.4 The distribution of monthly DRI

5.4.1 DRI in Taiwan and Thailand.

Figure 8A and 8B demonstrates monthly DRI from January 1998 to December

2005 in Taiwan and Thailand, respectively. (Taking the year of 1998 as an example, the Taiwan's health authority could be aware of the earlier peaking of DRI in Thailand. On the contrary, if tourists from Thailand planned to visit Taiwan in 2002, they would have better to be notified about the trend in increasing DRI in those months before August.

The temporal distributions of DRI in Taiwan and Thailand were very different. As shown in Table 3A, the percentages of bi-weekly DRI (levels of 0, 1, 2, 3) in Taiwan during 1998-2008 were 69.19% (548/792), 16.92% (134/792), 10.98% (87/792) and 2.90% (23/792), respectively. The majority was level 0 (no confirmed indigenous dengue), and most (58.18%, 64/110) of higher DRI (including level 2 and level 3) appeared in autumn (September to November). On the other hand, the distribution of monthly DRI in Thailand, listed in Table 3B was 1.33% (8/600), 12.67% (76/600), 66.50% (399/600), 18.83% (113/600) and 0.67% (4/600) from 1996 to 2005. Level 2 was the most frequent level of DRI, and higher DRIs were usually observed in summer (June to August). More frequent, earlier and higher DRI in Thailand than in Taiwan actually reflect different endemicity of dengue in the two countries. In other words, Thailand's DRIs were earlier and higher than Taiwan's.

5.5 Correlation between monthly reported and confirmed DRI in Taiwan

The Pearson correlation coefficient between the number of confirmed and reported dengue cases was 0.9833 ($p<0.0001$). Meanwhile, this Pearson correlation coefficient between these numbers of confirmed dengue cases and DRI was 0.5770 ($p<0.0001$). On the other hand, the Spearman correlation coefficient between these numbers of confirmed dengue cases and DRIs was 0.9925 ($p<0.0001$), and such a coefficient between current DRI and previous DRI was 0.7196 ($p<0.0001$). This analysis means that DRI is able to represent the tendency of dengue incidence, as well as to be predicted by the DRI value of the previous month.

5.6 Comparison with different time unit of DRI

Daily levels of DRIs and the numbers of confirmed dengue cases were significant correlated ($R^2=0.6780$, $p<0.0001$), as well as biweekly DRIs and biweekly case numbers ($R^2=0.9958$, $p<0.0001$), and monthly DRIs and monthly case numbers ($R^2=0.9925$, $p<0.0001$).

5.7 Predicting model of DRI

5.7.1 Meteorological models

5.7.1.1 Model fitting (1998-2007) and prediction (2008) in three areas in Taiwan

Table 4 shows area-specific regression models for indigenous DRI established with local meteorological data during 1998 to 2007 in Taiwan. Selected weather variables are temperatures and relative humidity with different time lag in different areas. The DRI of previous bi-week explained most of correlation in models.

We examined the consistency comparison of observed and expected values of DRI by area in Table 5A, and observed high concordance. The correlation diagnoses in Table 5B support this finding. However, the harmony relationship disappeared in area TN in 2008, the year after the ever largest epidemic of dengue in 2007. Figure 8 compares the two values with plotting curves, and the values of year 2008 after dash line are out-of-fit. Most of time two curves go together, including most level zero and infrequent level 3 in KH (2002, 2006) and TN (2007).

5.7.1.2 Model fitting (1996-2004) and prediction (2005) in five coastal provinces in Thailand

Similar results were found in Thailand. In Table 6, most models include relative humidity and temperatures in different time lags. The simplest model is area b, province Prachuap Khirikhan, contains only daily mean temperature at lag 1 (tmean1). The concordance between observed and expected values of DRI in Table 7 is satisfying through areas during 1996 to 2004, while the predictability for DRI in year 2005 (Table 7B) is not stable in area a (province Phetchaburi) and e (province Nakhon

Sitammarat). The consistency between observed and expected category values is varied among different provinces. Figure 9 compares the two values with plotting curves, and the values of year 2008 after the red dash line are out-of-fit. The two curves match most of time (Spearman correlation=0.66~0.77 in Table 7).

5.7.2 Comparison with different methods

In Table 7B and Table 5B, all fitted and predicted DRI were compared with the correlation between current DRI and previous DRI (e.g. fitting with only previous DRI and without meteorological variables). The results show that although the predictability of DRI1 is good, the values fitted with regression models with meteorological variables are better than the values of only previous DRI.

Chapter 6 Discussion

This study examined all laboratory-confirmed dengue cases detected through a combination of active, semi-active, and passive surveillance, and found that imported dengue are able to serve as an initial facilitator, or spark, for domestic epidemics. Nevertheless, imported dengue cases do not have a noteworthy effect from March to May, during the low transmission period of dengue in Taiwan. When these sparks meet suitable weather conditions, the tinder, local dengue epidemics result. Eventually, this relationship does not persist once biweekly indigenous case numbers rise over ten, indicating that a local epidemic has occurred. Our findings thus provide evidence that a significant quantitative relationship between Taiwan's imported and indigenous dengue case numbers exists solely at the onset of an epidemic and in the context of appropriate meteorological conditions. In addition, we also used dengue risk index to describe the different endemicity of dengue in Taiwan and Thailand. Although the DRI values in previous time intervals are able to fit current DRIs, we found logistic regression models with meteorological variables improve the correlation between observed and expected DRIs. The following discussion will focus mostly on the two major parts of the results – the role of imported cases and meteorological factors and the dengue risk index modeling.

6.1 The uniqueness of dengue analyses in Taiwan

To the best of our knowledge, this is the first study to simultaneously identify the relationship between indigenous and imported dengue cases in the context of meteorological factors. Our findings provide a highly accurate epidemiological portrait of dengue in Taiwan because of the following components of the research: First, a better surveillance system was instituted to actively rather than passively detect dengue cases. This system was also laboratory-based to minimize confounding infection and manifestations [29,33,55,56]. Second, we avoided a potential bias as a result of delays in dengue notification by analyzing all confirmed dengue cases in accordance to their onset dates of illness rather than their reporting dates. Third, all the dengue cases we analyzed are laboratory-confirmed plus the fact that fever surveillance at airport to pick up mild cases and semi-active serological surveillance involving even asymptomatically infected cases. All together makes our data source is closer to wide spectrum of dengue infection, quite different from only severe dengue hemorrhagic cases are required to be reported in many South East Asian countries where dengue has been endemic and hyper-endemic.

6.2 The combined effect of imported dengue and meteorological factors

Because the numbers of imported dengue cases that initiate indigenous cases have been increasing in non-endemic areas such as Taiwan [15,16,29,30] (further supported by the high nucleotide identities of dengue viruses isolated from travelers with travel history to endemic countries [29,30,33,36,57]), this study ventures to provide epidemiological evidence of the combined impact of both imported dengue and weather conditions on local outbreaks.

Climate-factors have provided helpful clues for monitoring dengue's transmission in affected areas [1,4,10,58]. Higher temperature has the effect of shortening the time intervals of extrinsic incubation in the mosquito life cycle [10,59] and is positively correlated with more occurrences of indigenous dengue in this study. This is consistent with previous findings that demonstrate the suitability of warm or hot weather for the survivorship of adult mosquitoes and, thus, dengue transmission [45,58]. In addition, although increased rainfall has been shown to increase the number and quality of mosquito breeding sites (as well as the density of resting sites) [1], lower rainfall and relative humidity (RH) were significantly related to indigenous dengue in this study.

The correlation between lower RH and indigenous dengue with time lags was also observed in previous studies in Thailand [60,61]. We explain this phenomenon as follows. Drier conditions may facilitate dengue transmission through the increase of water storage behavior, which result in an increase of breeding sites for *Aedes* mosquitoes, particularly in areas without reliable water supplies [62-64]. Although piped water supply is available in 90% of Taiwan (http://www.water.gov.tw/eng/08statistics/ sta_a_main.asp?bull_ id=4341), water storage for gardening or agricultural use is popular during water restriction period in the dry season, October to April, in southern Taiwan. In fact, a previous field survey identified water buckets as the most common breeding sites of *Ae. aegypti* in southern Taiwan [65]. Entomologically, lower RH (50% vs. 90%) aids higher flight speed of female adult *Ae. aegypti* at temperatures higher than 21 degrees of Celsius [66] thus facilitating dengue transmission. This may explain why both RH and rainfall showed a negative correlation with the number of indigenous dengue (Figure 4) and, that while higher temperatures occurred during July to September in the summer of Taiwan, the number of indigenous dengue cases usually peak in October-November.

On the other hand, although the correlation between drier conditions and increased transmission is unlikely to be caused by higher temperatures, we acknowledge that the effects of meteorological factors have a complex relationship. Unlike the consistent negative correlation across lags 3-8 (rain) and lags 4-10 (rainhr) in Figure 4, the positive correlation of "rain" and "rainhr" in Figure 3 occurred only in lag 9, and was therefore most likely a random statistical anomaly rather than a conclusive finding. We believe that weather-based mechanisms that support the proliferation of indigenous dengue therefore need further region-specific investigation and more international collaboration.

6.3 The effect of vector control on epidemics of dengue

We consider that vector control efforts on dengue cases do not affect outbreak initiation, but rather the size and magnitude of an outbreak. A dengue notification delay of over one month allows for two transmission cycles, and increases the potential for a large outbreak [67]. Vector control operations in Taiwan are unlikely to influence imported cases to initiate local dengue epidemics because they are implemented after case notification [31]. By the time indigenous dengue cases increase, the relationship with imported cases disappear (Figure 5C). Hence, the focus of this study was to verify the correlation between imported dengue and the onset of local dengue epidemics under appropriate weather conditions.

6.4 The increasing severity of dengue/DHF epidemics in Taiwan

Under suitable weather conditions, dengue viruses introduced via travelers are likely to result in further domestic spread and subsequent occurrence of epidemics. In addition, the introduction of more virulent genotypes of dengue viruses has been documented as a potential factor for driving new epidemics [68-70]. For example, Thai strains belonging to the

1980-1994 clade within the genotype I of dengue virus serotype 1 (DENV-1) were replaced by a 1990-2002 clade [30]. Additionally, an old clade in genotype I of DENV-3 during 1976-1978 was also replaced by a new 1991-2002 clade in genotype II [29,30]. Furthermore, cosmopolitan genotypes of DENV-2, the causing agent of Taiwan's largest-scale epidemic of dengue/DHF in last thirty years, had been gradually and effectively replacing Asian genotype 2 in the Philippines since 1998 and entered Taiwan in 2001 [71]. This cosmopolitan genotype of DENV-2 is different from the Asian 1 and Asian 2 genotypes of Taiwan's DENV-2 isolates from 1981 to 1998 and the American/Asian genotype of Taiwan's isolates in 2005, when the majority of dengue cases were dengue fever [72]. In other words, the more virulent genotypes/strains of the same serotype that have emerged during later years have resulted in more severe and/or larger-scale epidemics of dengue/DHF in many Asian countries [68,70].

Based on phylogenetic analyses of dengue viruses isolated from imported cases [30] at the micro-level, we find that local dengue epidemics in Taiwan typically originate in South East Asia. It is therefore imperative to establish a stable surveillance system to detect the spread of different genotypes of DENV. Currently, Taiwan's comprehensive dengue surveillance system is evolving and, hopefully, it may continuously monitor the possible evolution of DENV in SE Asian countries through international collaboration. We believe that global warming may have further impact on the incidence of imported dengue cases and future dengue/DHF epidemics [73]. Advanced research integrating virus displacement and meteorology will be necessary to provide a fuller understanding of both the macro and micro changes contributing to the increasing severity of dengue/DHF epidemics.

6.5 Better interpretation with logistic and Poisson regression models

In order to construct the best possible regression models to reflect meteorological conditions, we built alternative statistical models to demonstrate the role of imported cases in the onset of dengue epidemics. Previous modeling studies using ARIMA (Autoregressive Integrated Moving Average) found that the number of imported dengue cases was not associated with the incidence of local dengue [19,20]. ARIMA examined a linear relationship between case numbers of imported dengue cases and incidence of indigenous dengue cases over several time lags. However, the quantitative relationship between imported and indigenous dengue was likely limited to the onset (i.e. early phase) of outbreaks, and was therefore not subject to linear modeling. We believe these conclusions by logistic and Poisson regression models are not only demonstrable in countries with distinct seasonality, but also applicable in non-endemic areas of dengue. However, meteorological conditions may need to be modified for countries in higher altitudes.

6.6 Application of DRI to dengue control

This study performed a new categorical system, Dengue Risk Index, to quantify the risk of local epidemics of dengue with both Taiwan and Thailand's data. The risk of indigenous dengue is able to be forecasted with previous case number and weather, such as weather forecasting, as an early warning signal. Using real-time meteorological and epidemiological information, public health officials are able to apply this DRI system and then easily communicate with its prediction results to the public and international travelers. The timeliness is better than currently used surveillance systems of dengue focused on human cases reporting or entomological survey for earlier prevention and control of dengue before an epidemic starts.

For practical concerns, it is supposed to be more convenient to apply DRI in routine surveillance. Since the calculation of DRI is to sum up total case numbers, once case are confirmed, DRI is able to be announced immediately. Every month or two weeks, each country or region may have area-specific real-time monthly or bi-weekly DRI. Accompanying with weather forecasting information, region-specific DRI can be projected. In addition to evaluate traveling risk, the most important usage of predicting DRI is for governmental disease prevention and control. Moreover, international collaboration on dengue control will be feasible through sharing newest nationwide DRI data from open-channel internet system.

6.7 The predictability of newly developed DRI models

Comparing with case number prediction in a variety of mathematical models for dengue epidemics, polytomous (ordinal) logistic category models have much less variance in distributed numbers. Therefore, it is much less fluctuated but more informative. The cumulative-odds model in polytomous logistic regression is often considered most appropriate in dealing with categorized data [74]. It is thus straightforward to interpret the effect of independent variables with odds ratio by regression models.

The correlations of local weather variables with DRI in Taiwan were similar to in Thailand, although their statuses of dengue endemicity were different. Temperatures and relative humidity are the two statistically significant weather variables in regression models after stepwise variable selecting process. Higher temperatures, including daily mean/minimum/maximum temperature, and lower relative humidity were observed related with higher DRI. However, when more than one lags of the same weather variable were selected, the coefficient became puzzling. These regression models are not able to afford comprehensive details, but offer a simple and direct method to detect possible occurrence of local dengue epidemics.

The non-endemicity of Taiwan's dengue status was observed in DRI exploration. The annual local epidemics of dengue, caused by different serotypes and/or genotypes of dengue viruses, have been mostly initiated by imported cases in the past three decades [30]. Therefore, mean DRI in most months within one year is zero. Even the epidemics start, high values of DRI seldom appear and usually vanish in winter. On the contrary, mean DRI in Thailand is two and number of cases peak before summer.

6.8 Limitations

This study had notable limitations. First of all, meteorology alone does not initiate an epidemic. Herd immunity also plays a decisive role in the spread of disease. Once a new or more virulent genotype/strain of dengue virus is introduced, public health officials should alert the public and implement prevention efforts regardless of meteorological conditions. Second, local entomological data from Taiwan's entomology surveillance was not included. Non-government scholars do not have access to such data prior to 2002. Furthermore, the data was divided by village or "Li" – the basic administration unit in Taiwan, and was not systematically collected with a standardized process. Therefore, we did not use entomological data because of its lack of consistency and inability to adequately represent the locations covered in our study. Lastly, although socioeconomic status may influence vector habitat [75], it was assumed to be relatively stable during the studied ten years.

6.9 Future direction

As an increase in viremic international travelers has led to global increasing DHF case numbers to surge in recent two to three decades [24], efficient measures have to be instituted to prevent imported dengue cases from igniting local dengue/DHF epidemics. Additionally, it has been previously found that DHF cases with higher viral load [76] appeared when the number of dengue fever cases increased rapidly, particularly in areas with higher dengue clusters [77]. Advanced investigation and integration of immunological, virological, meteorological, and entomological findings with prevention/control strategies will support a more comprehensive understanding of the mechanisms that initiate dengue epidemics, and will help guide realistic public health interventions in the era of rapid globalization and climate change [78].

The established DRI method from this dissertation research using ordinal logistic regression incorporating with Taiwan's data first and then extended to Thailand's data imply that DRI is a feasible approach from the initial concept of prediction with different warning color flags to implementation for travelers crossing different countries. For public health practical application, it is necessary to investigate the feasibility by using more data obtained from different regions, such as other countries in the South East Asia, Caribbean and South America, and to testify the reliability of meteorology-based DRI on epidemics prediction across different geographical areas and climate zones. Using data of case number on WHO's website and the same log scale of dengue cases for different countries, the overall picture of where is global endemicity of dengue with higher risk levels, better than case number alone, is easily understandable to general public and local/regional public health officials. Future efforts in combining with local weather information into regression models, the possible impact of climate change on increasing DRI is able to be quantified and supported with probability calculation. In other words, this study and further investigation efforts will enlighten decision makers by providing an evidence-based projection of how many people will be under the risk of dengue in the future.

Chapter 7 Recommendations

All these findings suggest that the entrance of imported cases, in conjunction with suitable meteorological conditions, may have the potential to precipitate severe epidemics involving more DHF cases. Careful monitoring and clinical management of imported dengue cases, along with relevant meteorological information, are able to provide earlier warning signals for emerging indigenous dengue epidemics than current surveillance systems [4,52]. For those high risk seasons, the recommendations include: (1) to have both rigorous fever screening at airports and public health efforts for case management once it is a laboratory-confirmed dengue cases that is more efficient to catch the cases and then minimize further possible local transmission chains after the entrance of imported cases; (2) to use the DRI serving as a forecasting system, to alert the public and the government for disease prevention and control. These early alerts allow for the proper implementation of targeted public health interventions and valuable buffer time for preventing subsequent large-scale epidemics of dengue/DHF locally and in affected countries.

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Table 1: Abbreviations of variables

Abbreviation	Explanation	Unit
Independent variables		
imported	number of imported dengue cases in the area	cases
rain	daily accumulative rainfall	mm
rainhr	daily accumulative rainy hours	hours
rh	daily mean relative humidity	%
sunhr	daily sunshine accumulation hour	hours
sunrate	daily mean sunshine rate (from sunrise to sunset)	%
tmax	daily maximum temperature	^oC
tmean	daily mean temperature	^oC
tmin	daily minimum temperature	^oC
area_TN, area_KH	dummy variables: for cases from Tainan (TN) area, area_TN=1 and area_KH=0; for cases from Kaohsiung (KH) area, area_TN=0 and area_KH=1; cases from Pingtung (PT) area, area_TN=0 and area_KH=0)	none
popd	area-specific population density	population/km^2
sin24	Oscillation function sin (2πt/T), T (period) = 12 months	none
cos24	Oscillation function cos (2πt/T), T (period) = 12 months	none
Dependent variables		
Occurrence (Figure 2)	Occurrence= 1 when any new indigenous confirmed dengue cases were present in the studied bi-week	none

	intervals, else Occurrence=0.	
Increase (Figure 3)	Increase=1 when relative risk= [(number of indigenous dengue cases in the studied bi-week interval+0.5)/ (number of indigenous cases in the prior interval+0.5)] was larger than 1.2#, else Increase=0.	none
Case (Figure 4)	the number of indigenous dengue per bi-week in an area	cases/bi-week

#: The threshold of 1.2 was chosen for optimizing the apportionment ratio, in order to increase statistical efficiency. Use of alternative threshold, such as 1.5 or 2.0, decreased statistical efficiency for the analysis. Because that the number of indigenous cases per area during a bi-week in low transmission season is mostly zero, we calculate the ratio by adding 0.5 to both the denominator and numerator.

Table 2: The definitions of risk category for dengue epidemics

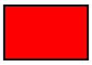
Risk category	**Category color**	**Number of indigenous cases**	**Epidemiological meaning**	**Actions should be taken**
0		0	Non case	Keep alert on meteorology and imported cases
1		1-9	Sporadic cases	Start investigation on reported cases
2		10-99	Initiation of an epidemic	Campaign of cleanup breeding sites; self-isolation of suspected cases
3		100-999	Peaking of an epidemic	Insecticide use and severe case management
4		1000-	Super-spreading of epidemic	Severe case management

Table 3: The monthly frequency of dengue risk category (DRI) in Taiwan and Thailand

A. **Taiwan: NKP areas during 1998-2008, biweekly DRI**

month	Frequency of category											
	TN				KH				PT			
	0	1	2	3	0	1	2	3	0	1	2	3
Jan	16	6	0	0	10	9	3	0	16	5	1	0
Feb	22	0	0	0	16	6	0	0	21	1	0	0
Mar	21	1	0	0	18	4	0	0	22	0	0	0
Apr	21	1	0	0	20	2	0	0	22	0	0	0
May	22	0	0	0	19	3	0	0	22	0	0	0
Jun	19	2	1	0	14	6	1	1	22	0	0	0
Jul	17	3	2	0	9	6	5	2	16	6	0	0
Aug	12	6	3	1	8	6	6	2	14	6	2	0
Sep	15	3	3	1	5	9	6	2	16	2	4	0
Oct	10	6	4	2	4	6	8	4	15	3	4	0
Nov	10	5	5	2	4	3	11	4	14	4	4	0
Dec	12	5	4	1	6	7	8	1	18	2	2	0
Total	**197**	**38**	**22**	**7**	**133**	**67**	**48**	**16**	**218**	**29**	**17**	**0**

Note:

1. No record of DRI=4

2. TN: Tainan area, including Tainan City and County; KH: Kaohsiung area, including Kaohsiung City and County; PT: Pingtung area, including Pingtung City and County.

B. Thailand: coastal provinces during 1996-2005, monthly DRI

month	Frequency of category																			
	a				b				c				d				e			
	0	**1**	**2**	**3**	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**	**1**	**2**	**3**	**4**
Jan	2	3	5	0	1	2	7	0	0	5	5	0	0	2	5	3	1	7	2	0
Feb	1	2	7	0	1	2	7	0	1	3	6	0	0	2	7	1	2	7	1	0
Mar	0	2	8	0	1	2	7	0	0	1	9	0	0	2	7	1	2	8	0	0
Apr	0	2	7	1	0	3	5	2	0	3	6	1	0	1	8	1	4	3	3	0
May	0	0	8	2	0	1	6	3	0	1	6	3	0	1	5	4	1	5	4	0
Jun	0	0	8	2	0	0	7	3	0	1	6	3	0	0	5	5	2	3	5	0
Jul	0	0	7	3	0	0	7	3	0	0	7	3	0	0	6	4	0	4	4	2
Aug	0	1	7	2	0	0	7	3	0	0	9	1	0	0	6	4	0	4	5	1
Sep	0	0	8	2	0	1	8	1	0	0	9	1	0	0	7	3	2	3	4	1
Oct	0	1	8	1	0	1	8	1	0	0	9	1	0	0	7	3	3	2	5	0
Nov	0	1	9	0	0	0	10	0	0	4	6	0	0	1	7	2	1	4	5	0
Dec	0	3	7	0	0	1	9	0	1	2	7	0	0	0	10	0	1	7	2	0
Total	**3**	**15**	**89**	**13**	**3**	**13**	**88**	**16**	**2**	**20**	**85**	**13**	0	**9**	**80**	**31**	**19**	**57**	**40**	**4**

Note:

1. Five coastal provinces are (a) Phetchaburi, (b) Prachuap Khirikhan, (c) Chumphon, (d) Surat Thani and (e) Nakhon Sitammarat.

2. No record of DRI=4 in provinces a-d, and no record of DRI=0 in province e

Table 4: Area-specific polytomous logistic regression models based on local meteorology for predicting dengue risk index (DRI) in Taiwan from 1998 to 2007

area	variables recruited	β	SE	p	OR
TN	rh3	-0.0920	0.0457	0.0442	0.912(0.834-0.998)
	tmin4	0.2885	0.0754	0.0001	1.334(1.151-1.547)
	DRI1	2.6614	0.3083	<0.0001	14.317(7.824-26.197)
	popd	0.0105	0.0308	0.7331	1.011(0.951-1.073)
KH	rh8	-0.0838	0.0384	0.0293	0.920(0.853-0.992)
	tmean3	0.2967	0.0602	<0.0001	1.345(1.196-1.514)
	DRI1	3.3144	0.3113	<0.0001	27.506(14.943-50.631)
	popd	-0.0064	0.0229	0.7790	0.994(0.950-1.039)
PT	tmax6	0.8228	0.1808	<0.0001	2.277(1.598-3.245)
	tmax7	-0.4172	0.1462	0.0043	0.659(0.495-0.878)
	DRI1	3.2207	0.4518	<0.0001	25.045(10.331-60.717)
	popd	0.0123	0.0991	0.9016	1.012(0.834-1.229)

Note:

1. rh: relative humidity; tmax/mean/min: daily maximum/mean/minimum temperature
2. DRI1: value of DRI in the previous time interval; popd: population density
3. TN: Tainan area, including Tainan City and County; KH: Kaohsiung area, including Kaohsiung City and County; PT: Pingtung area, including Pingtung City and County.

Table 5: The consistence of DRI between observed and expected values for dengue epidemics in Taiwan from 1998 to 2008

A. Distribution of frequencies

Observed		**Predicted**											
		TN				**KH**				**PT**			
		0	**1**	**2**	**3**	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**
1998-2007	**0**	*171	6	1	0	*111	9	0	0	*178	7	0	0
	1	16	*9	4	0	19	*30	9	0	13	*10	1	0
	2	0	7	*14	1	1	10	*25	2	0	2	*12	0
	3	0	0	2	*5	0	0	2	*14	0	0	0	0
2008	**0**	*11	4	0	0	*10	0	0	0	*23	0	0	0
	1	6	*2	1	0	2	*0	2	0	1	0	0	0
	2	0	0	0	0	0	2	*8	0	0	0	0	0
	3	0	0	0	0	0	0	0	0	0	0	0	0

Note:

1. *: concordant pairs
2. TN: Tainan area, including Tainan City and County; KH: Kaohsiung area, including Kaohsiung City and County; PT: Pingtung area, including Pingtung City and County.

B. Diagnoses of the predictability of risk category for dengue epidemics in Taiwan

Area		1998-2007 (Fit)		2008 (Out-of-fit)	
		Model	**DRI1 only**	**Model**	**DRI1 only**
TN	**Gamma**	0.9620±0.0144	0.9455±0.0177	0.2131±0.4213	0.1667±0.3977
	Spearman	0.8570±0.0291	0.7539±0.0479	0.1018±0.2104	0.0861±0.2100
	N	236	239	24	24
KH	**Gamma**	0.9552±0.0133	0.9398±0.0163	0.9444±0.0499	0.9333±0.0505
	Spearman	0.8380±0.0278	0.8131±0.0229	0.8680±0.0563	0.8500±0.0641
	N	232	239	24	24
PT	**Gamma**	0.9623±0.0183	0.9183±0.0299	NA(C=23, D=1)	-1.00±0.00 (C=22, D=2)
	Spearman	0.7061±0.0654	0.6316±0.0659	NA	-0.0435±0.0307
	N	223	239	24	24

Note:

1. DRI1: value of DRI in the previous time interval
2. C: concordant pairs, D: discordant pairs
3. TN: Tainan area, including Tainan City and County; KH: Kaohsiung area, including Kaohsiung City and County; PT: Pingtung area, including Pingtung City and County.

Table 6: The logistic regression model based on meteorology for predicting risk category of dengue epidemics, Thailand, 1996-2004

area	variables recruited	β	SE	p	OR
a	rh5	-0.2015	0.1051	0.0552	0.818(0.665-1.004)
	tmin2	-0.6259	0.1964	0.0014	0.535(0.364-0.786)
	tmin7	-0.3821	0.1549	0.0136	0.682(0.504-0.924)
	tmean1	0.7759	0.2340	0.0009	2.173(1.373-3.437)
	DRI1	4.9065	1.0692	<0.0001	135.170(16.625->999.99)
	popd	1.1618	0.8280	0.1605	3.196(0.631-16.194)
b	tmean1	0.5577	0.1460	0.0001	1.747(1.312-2.325)
	DRI1	3.0966	0.5348	<0.0001	22.122(7.755-63.101)
	popd	0.4555	0.2383	0.0560	1.577(0.988-2.516)
c	rh3	-0.3132	0.0998	0.0017	0.731(0.601-0.889)
	rh4	0.2803	0.1071	0.0089	1.324(1.073-1.633)
	tmax2	0.5459	0.1681	0.0012	1.726(1.242-2.400)
	DRI1	3.0583	0.6373	<0.0001	21.291(6.106-74.240)
	popd	0.3274	0.1642	0.0462	1.387(1.006-1.914)
d	tmin1	0.5476	0.2534	0.0307	1.729(1.052-2.841)
	tmean1	0.3838	0.2005	0.0556	1.468(0.991-2.175)
	DRI1	3.4051	0.6008	<0.0001	30.117(9.277-97.772)
	popd	0.1795	0.1397	0.1988	1.197(0.910-1.574)
e	tmin8	0.5421	0.2348	0.0210	1.720(1.085-2.724)
	tmax2	0.4179	0.1132	0.0002	1.519(1.217-1.896)
	DRI1	2.9168	0.4440	<0.0001	18.482(7.741-44.125)
	popd	0.2022	0.3153	0.5213	1.224(0.660-2.271)

Note: Five coastal provinces are (a) Phetchaburi, (b) Prachuap Khirikhan, (c) Chumphon, (d) Surat Thani and (e) Nakhon Sitammarat.

Table 7: The consistency comparison of observed and predicted category values from Thailand models

A. Distribution of frequency

Obs.		**Predicted**																								
		a					**b**					**c**					**d**					**e**				
		0	**1**	**2**	**3**	**4**	**0**	**1**	**2**	**3**	**4**	**0**	**1**	**2**	**3**	**4**	**0**	**1**	**2**	**3**	**4**	**0**	**1**	**2**	**3**	**4**
1996-2004	**0**	0	1	0	0	0	2	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	1	8	3	0	0	0	8	5	0	0	1	4	9	0	0	0	5	4	0	0	0	9	7	0	0
	2	0	2	77	1	0	0	2	71	3	0	0	3	72	0	0	0	2	68	5	0	0	3	41	6	0
	3	0	0	3	5	0	0	0	6	10	0	0	0	5	8	0	0	0	7	16	0	0	0	7	24	0
	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	1
2005	**0**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	1	0	0	1	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0
	2	0	2	4	0	0	0	0	12	0	0	0	0	9	1	0	0	0	3	1	0	0	0	2	0	0
	3	0	0	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	7	0	0	0	7	2	0
	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0

Note:

1. *: concordant pairs.
2. Five coastal provinces are (a) Phetchaburi, (b) Prachuap Khirikhan, (c) Chumphon, (d) Surat Thani and (e) Nakhon Sitammarat.

B. Diagnoses of the predictability of risk category for dengue epidemics in Thailand

Province		1996-2004 (Fit)		2005 (Out-of-fit)	
		Model	DRI1 only	Model	DRI1 only
a	Gamma	0.9845±0.0105	0.9534±0.0251	0.6667±0.3043	0.9231±0.1127
	Spearman	0.7718±0.0735	0.6915±0.0776	0.2883±0.1725	0.6538±0.1952
	N	101	107	12	12
b	Gamma	0.9683±0.0179	0.9405±0.0268	1.00±0.00	1.00±0.00
	Spearman	0.7237±0.0670	0.6767±0.0683	NA(C=12)	NA(C=12)
	N	107	107	12	12
c	Gamma	0.9565±0.0276	0.8987±0.0426	1.00±0.00	1.00±0.00
	Spearman	0.6617±0.0785	0.6363±0.0736	0.5477±0.2588	0.6742±0.2611
	N	104	107	12	12
d	Gamma	0.9506±0.0260	0.9426±0.0271	0.9091±0.1366	0.5000±0.4841
	Spearman	0.6827±0.0709	0.6741±0.0688	0.6250±0.2398	0.2500±0.2915
	N	107	107	12	12
e	Gamma	0.9448±0.0239	0.9204±0.0282	1.00±0.00	0.00±0.2357
	Spearman	0.7499±0.0510	0.7336±0.0484	0.4771±0.1780	-0.00±0.0601
	N	100	107	12	12

Note:

1. DRI1: value of DRI in the previous time interval

2. C: concordant pairs

3. Five coastal provinces are (a) Phetchaburi, (b) Prachuap Khirikhan, (c) Chumphon, (d) Surat Thani and (e) Nakhon Sitammarat.

Figure 1: The rationale of local climate and imported effects on indigenous dengue epidemics

The area within red line demonstrates the local correlation among climate, mosquito density and epidemics of dengue. Imported dengue cases also involve local mosquito vector and human population in initiating indigenous epidemics.

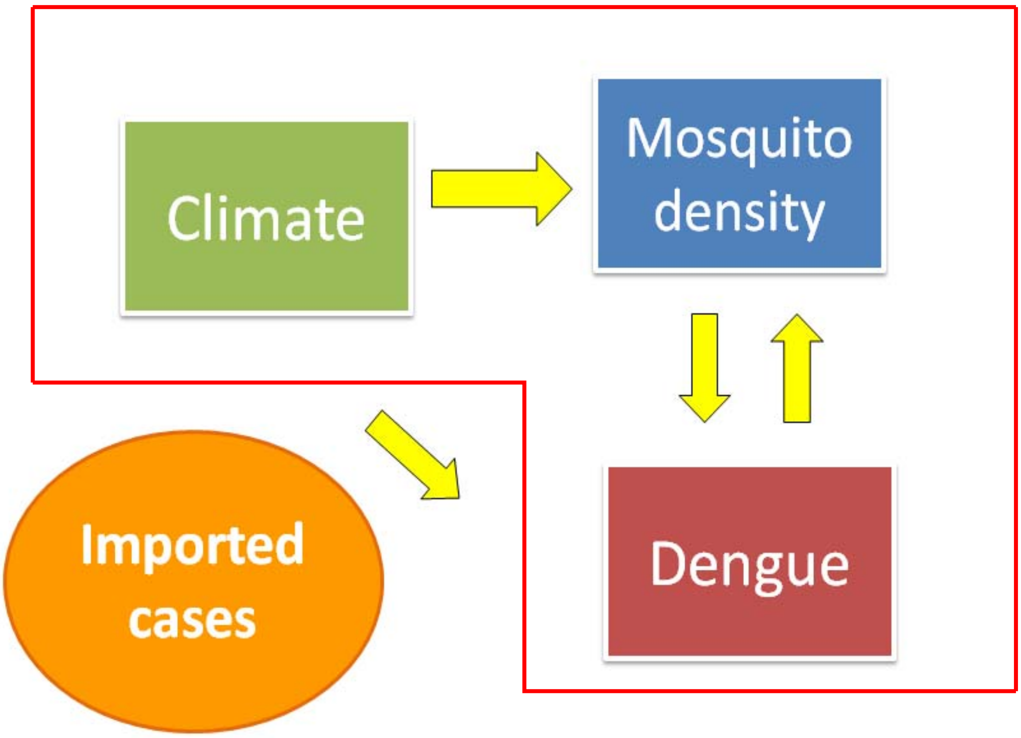
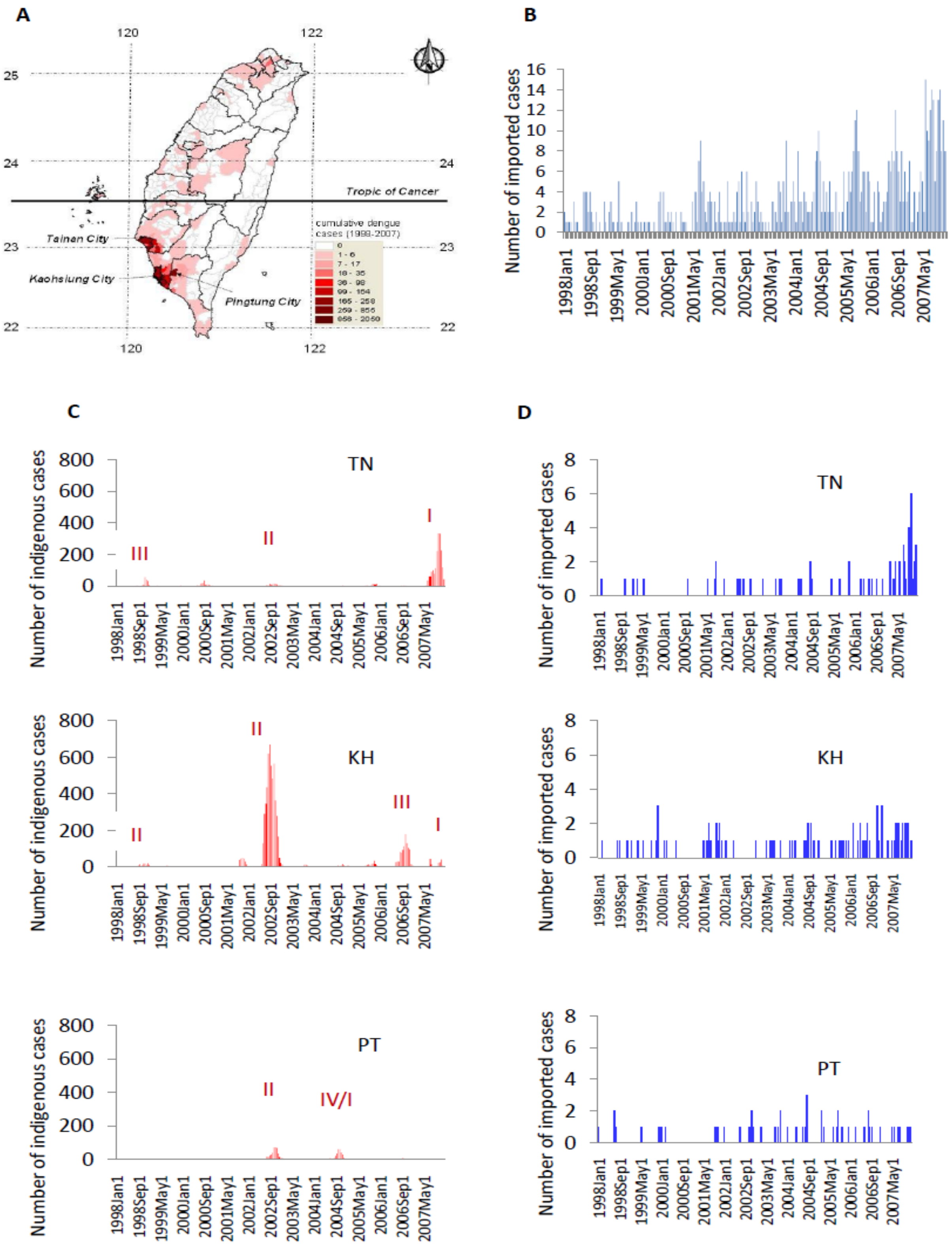


Figure 2: Numbers of laboratory-confirmed dengue (including dengue and dengue hemorrhagic fever) cases in Taiwan, 1998-2007.



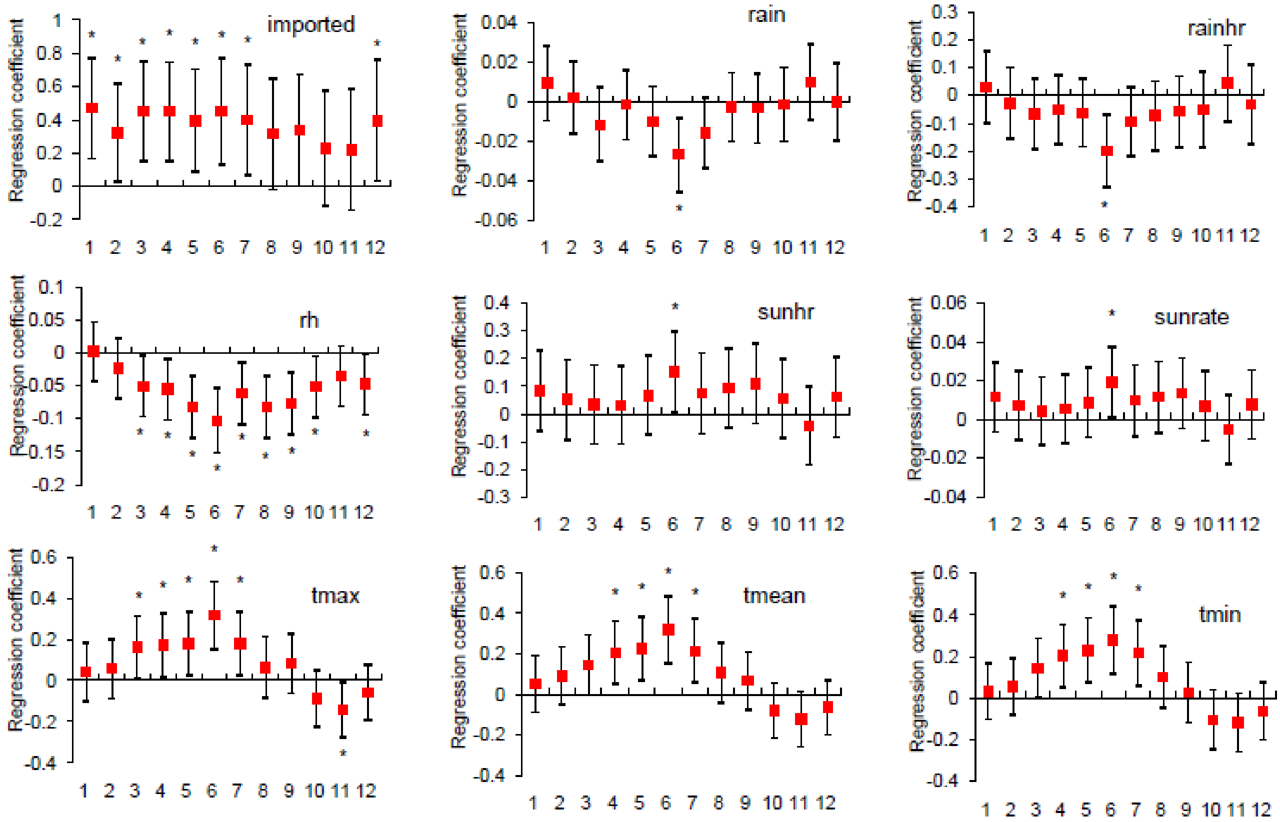
A. **Spatial distributions of cumulative indigenous dengue cases.**

B. **Biweekly number of imported dengue cases.**

C. **Biweekly number of indigenous dengue cases in the studied areas.** TN: Tainan area, including Tainan City and County; KH: Kaohsiung area, including Kaohsiung City and County; PT: Pingtung area, including Pingtung City and County. The Roman numbers denote predominant serotypes of dengue virus isolated during major epidemics in that area [31].

D. **Biweekly number of imported dengue cases in the studied areas.**

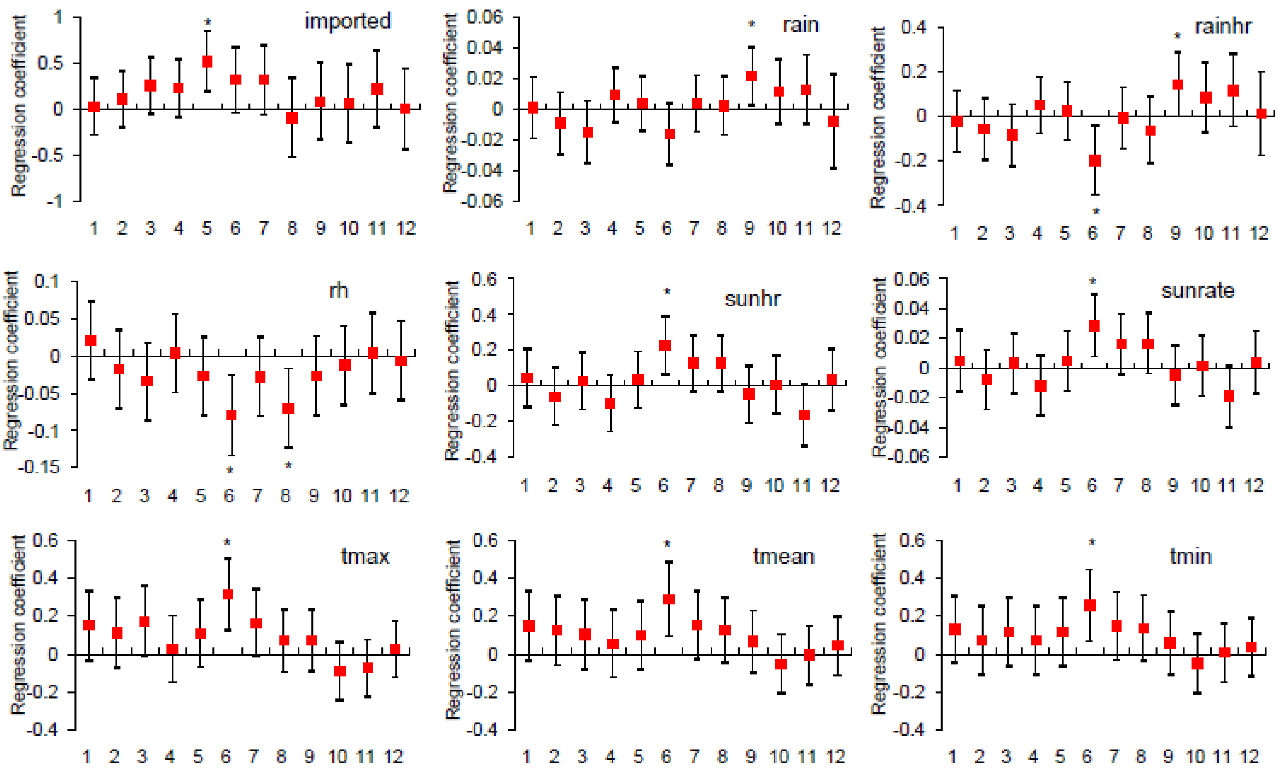
Figure 3: Correlation between bi-weekly "occurrence" of indigenous dengue cases and 1) the number of imported cases as well as 2)meteorological variables across time lags from 1 to 12 bi-weeks.



Note:

1. Each vertical line segment corresponds to a 95% confidence interval of the regression coefficient and the red solid squares indicate the value of each coefficient estimate. (*: $p<0.05$)
2. The X-axis displays different time lags: 1 for two weeks lag, 2 for four weeks lag, and so on.
3. Abbreviations: see Table.

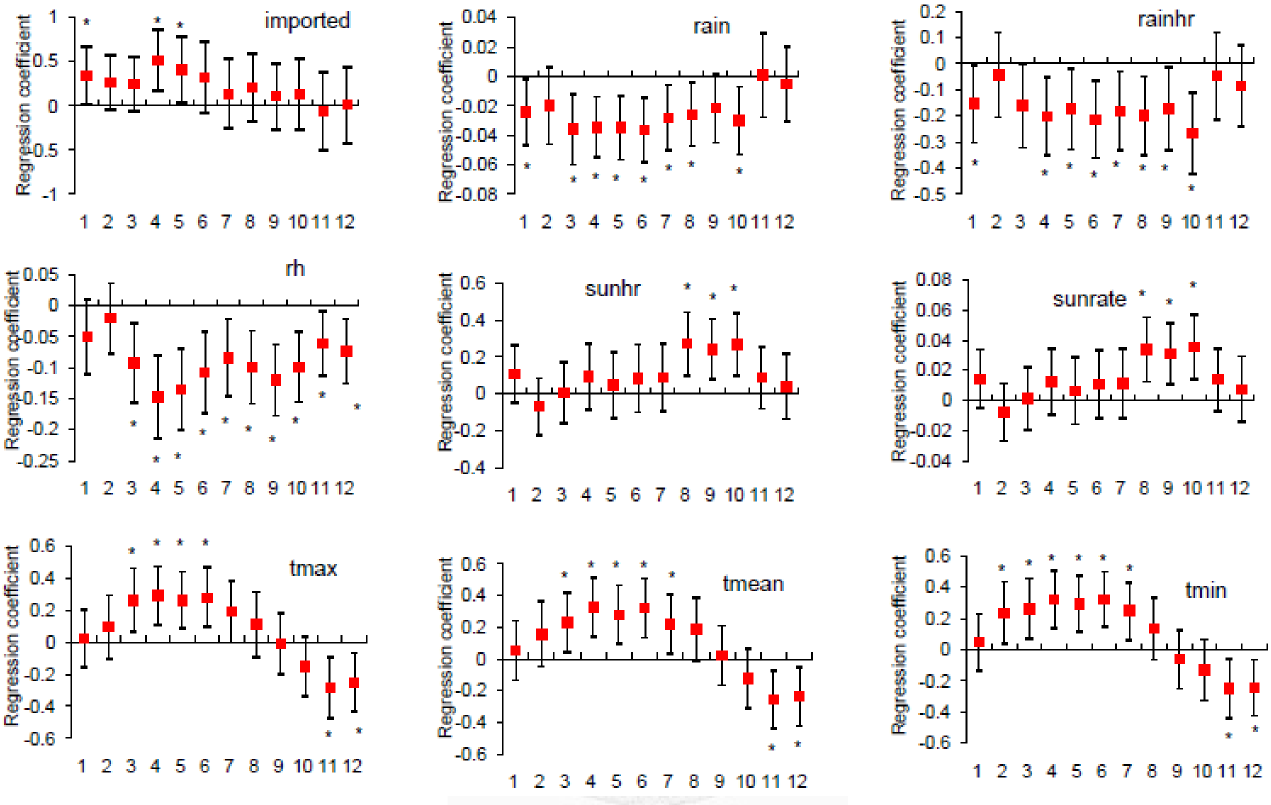
Figure 4: Correlation between bi-weekly "increase" of indigenous dengue cases and 1) the number of imported cases as well as 2)meteorological variables across time lags from 1 to 12 bi-weeks.



Note:

1. Each vertical line segment corresponds to a 95% confidence interval of the regression coefficient and the red solid squares indicate the value of each coefficient estimate. (*: $p<0.05$)
2. The X-axis displays different time lags: 1 for two weeks lag, 2 for four weeks lag, and so on.
3. Abbreviations: see Table.

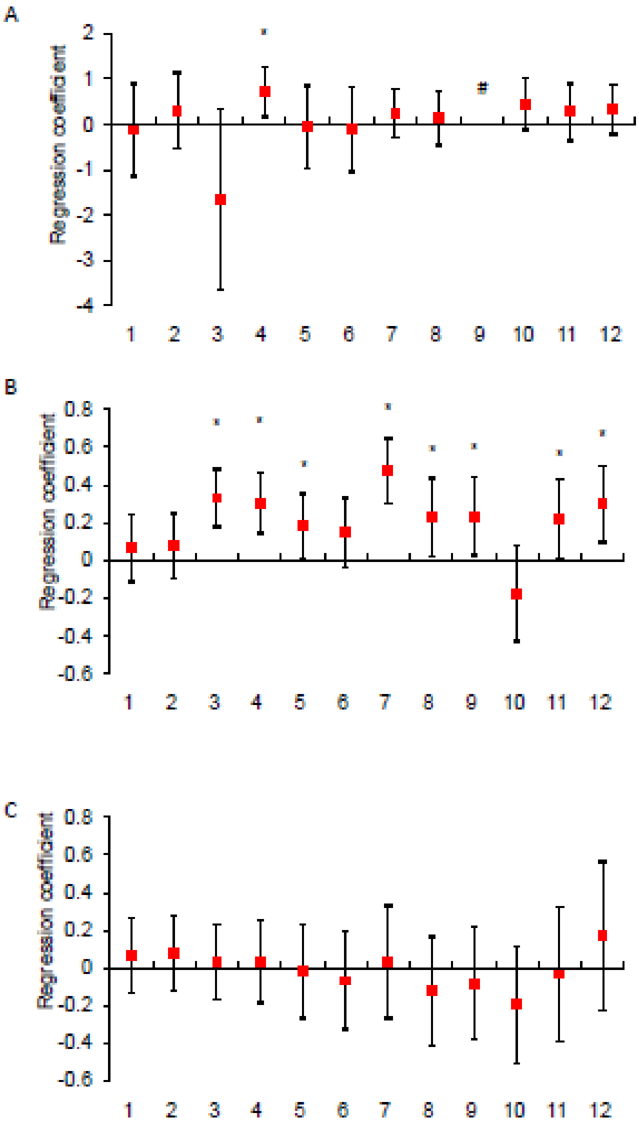
Figure 5: Correlation between bi-weekly number of indigenous dengue cases and 1) the number of imported cases as well as 2)meteorological variables across time lags from 1 to 12 bi-weeks.



Note:

1. Each vertical line segment corresponds to a 95% confidence interval of the regression coefficient and the red solid squares indicate the value of each coefficient estimate. (*: $p<0.05$)
2. The X-axis displays different time lags: 1 for two weeks lag, 2 for four weeks lag, and so on.
3. Abbreviations: see Table.

Figure 6: Correlation between bi-weekly number of indigenous dengue cases and the number of imported cases over time lags from 1 to 12 bi-weeks.



A. **Period of "low intensity transmission"**: Those bi-week intervals were from March to May. #: 95% Confidence interval=[-419930, 419876.8]

B. **Period of "early phase of outbreaks"**: Those bi-week intervals presenting <10 indigenous dengue cases for months excluding March to May.

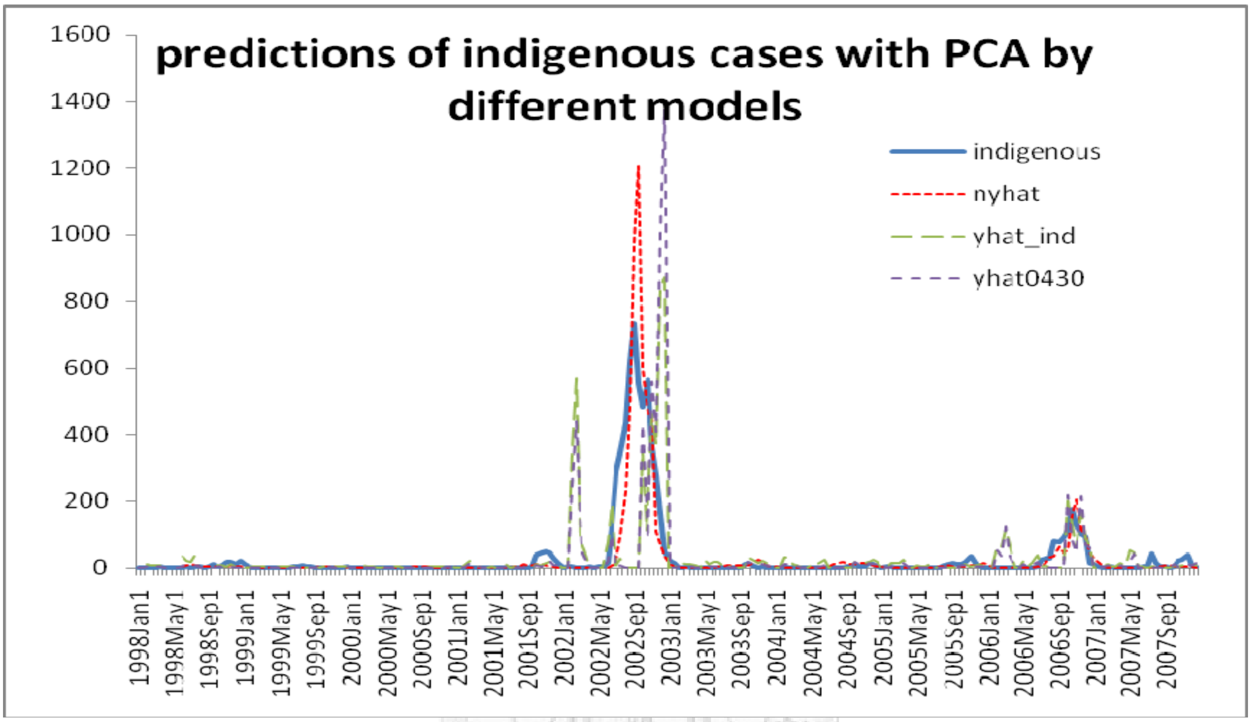
C. **Period of "late phase of outbreaks"**: Those bi-week intervals presenting ≧10 indigenous dengue cases.

Note:

1. Each vertical line segment corresponds to a 95% confidence interval of the regression coefficient and the red solid squares indicate the value of each coefficient estimate. (*: $p<0.05$)
2. The X-axis displays different time lags: 1 for two weeks lag, 2 for four weeks lag, and so on.

Figure 7: Fitting the number of dengue cases with meteorological regression models

A. Principal component analysis (PCA)



B. Square/cubic root of case number

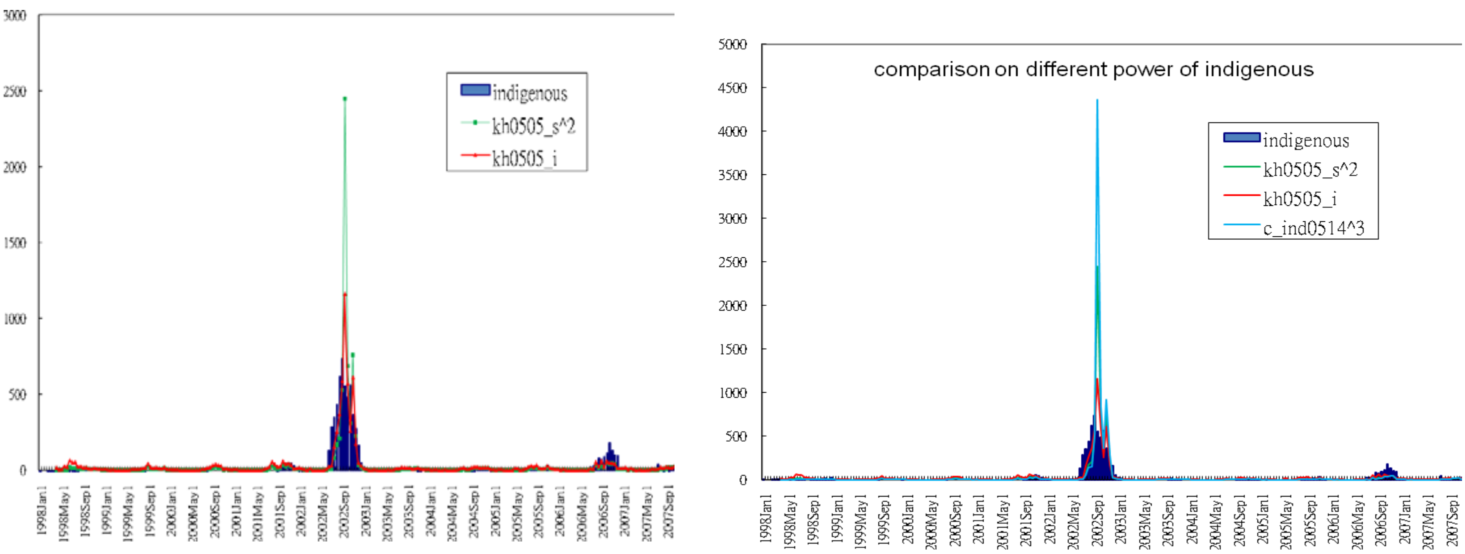
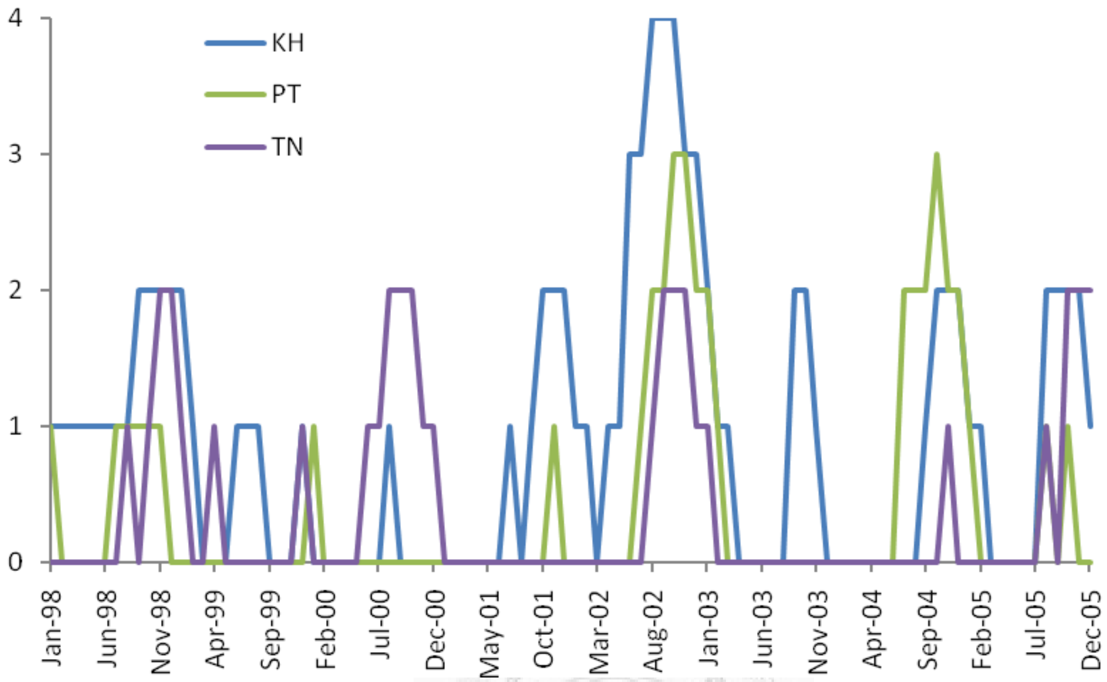
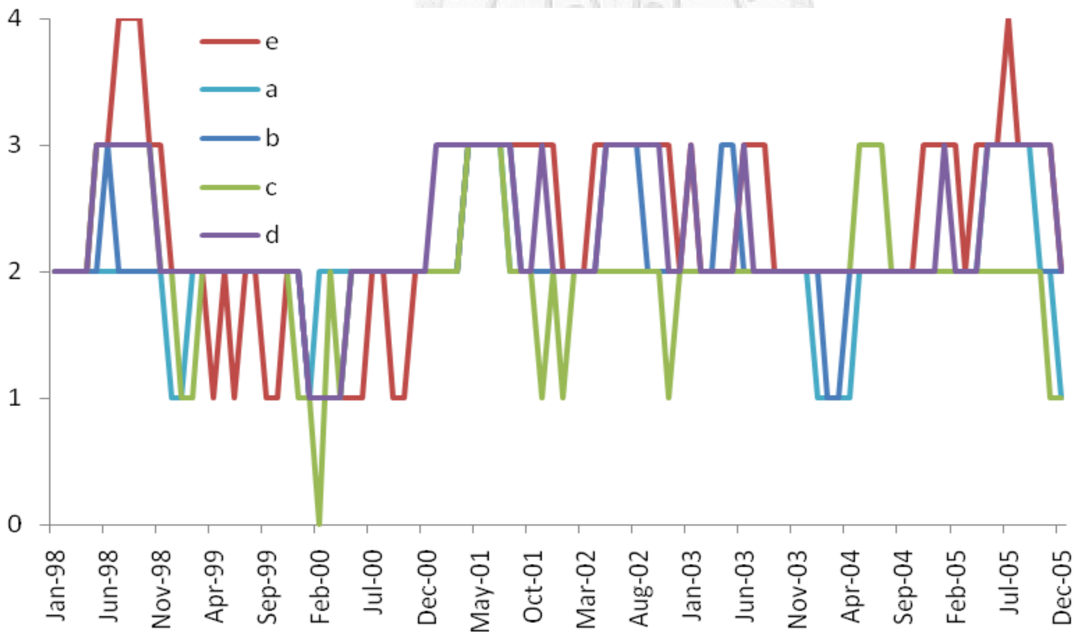


Figure 8: Distribution of monthly Dengue Risk Index in Taiwan and Thailand, 1998-2005





Note:

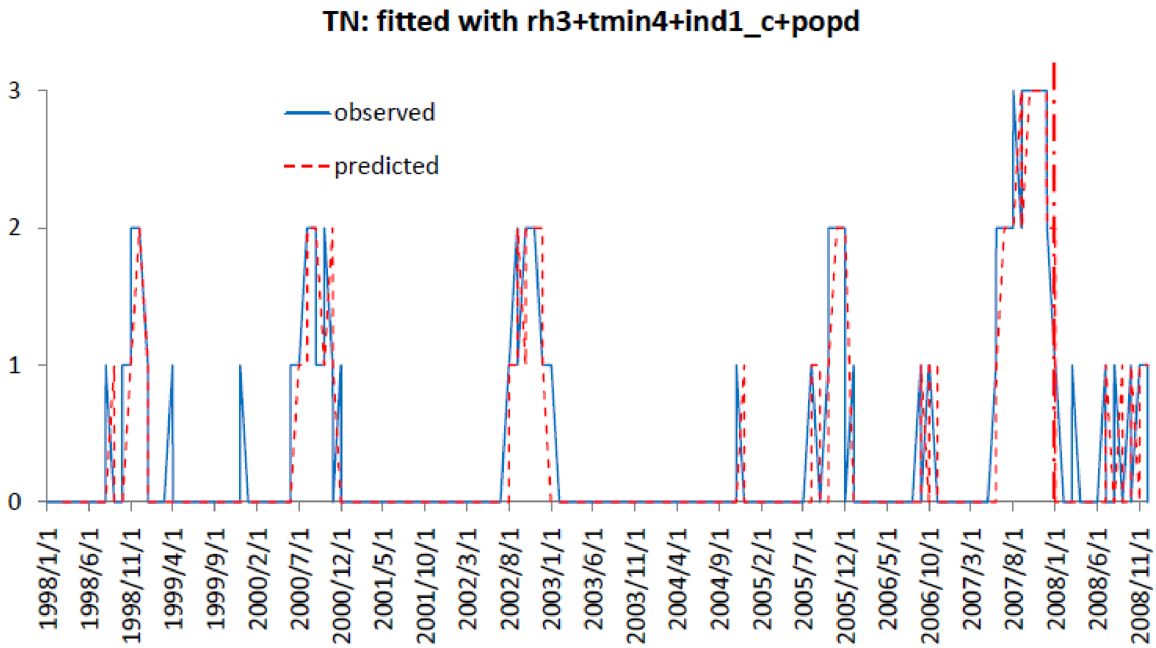
1. Taiwan:

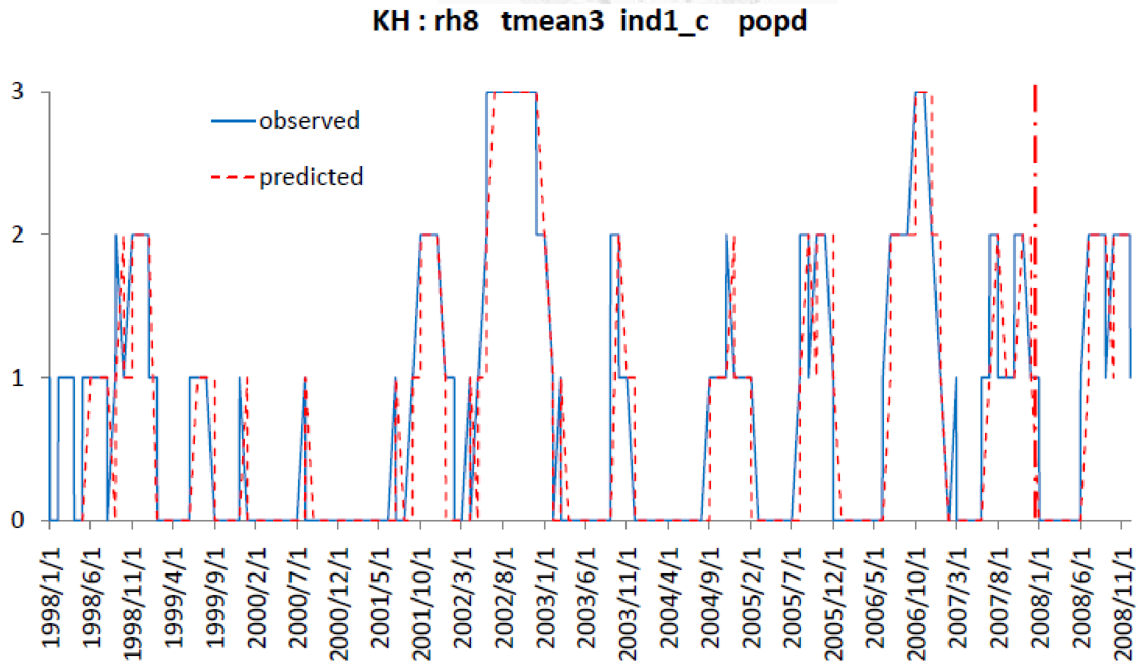
   TN: Tainan area, including Tainan City and County; KH: Kaohsiung area, including Kaohsiung City and County; PT: Pingtung area, including Pingtung City and County.

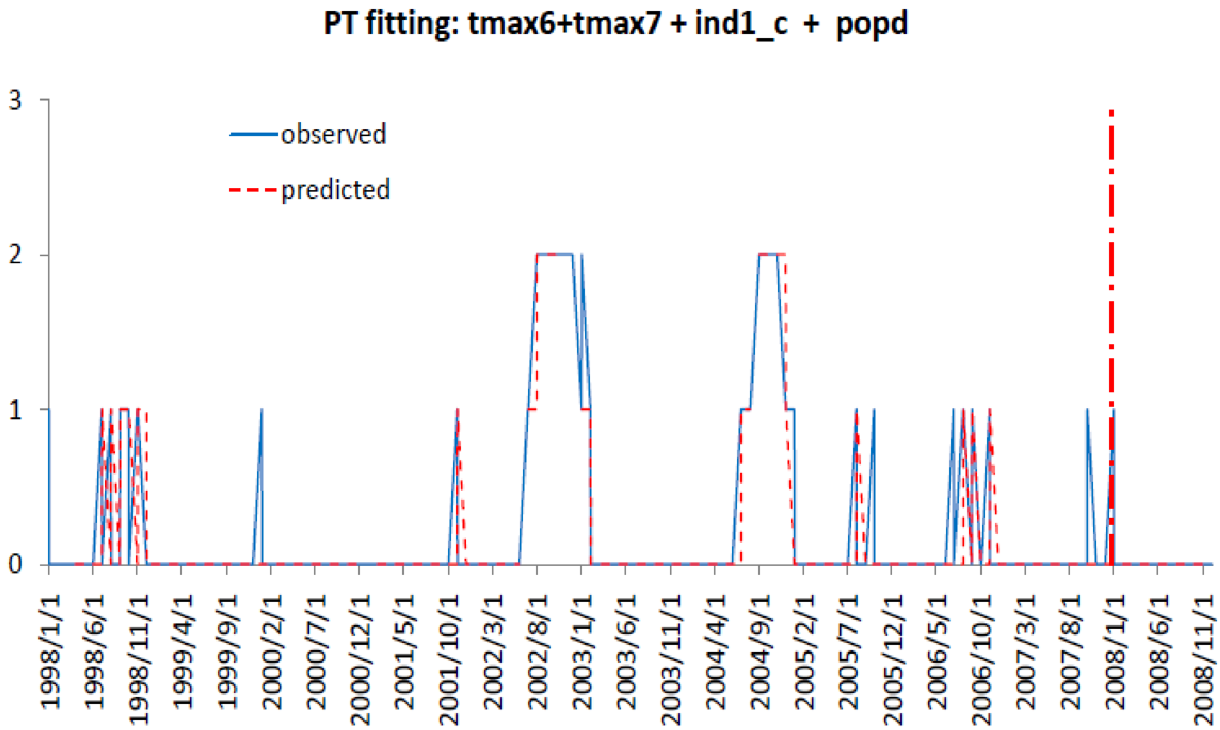
2. Thailand:

   five coastal provinces are (a) Phetchaburi, (b) Prachuap Khirikhan, (c) Chumphon, (d) Surat Thani and (e) Nakhon Sitammarat.

Figure 9: Fitting (1998-2007) and predicting (2008, after red dash line) DRI in Taiwan with meteorological regression model



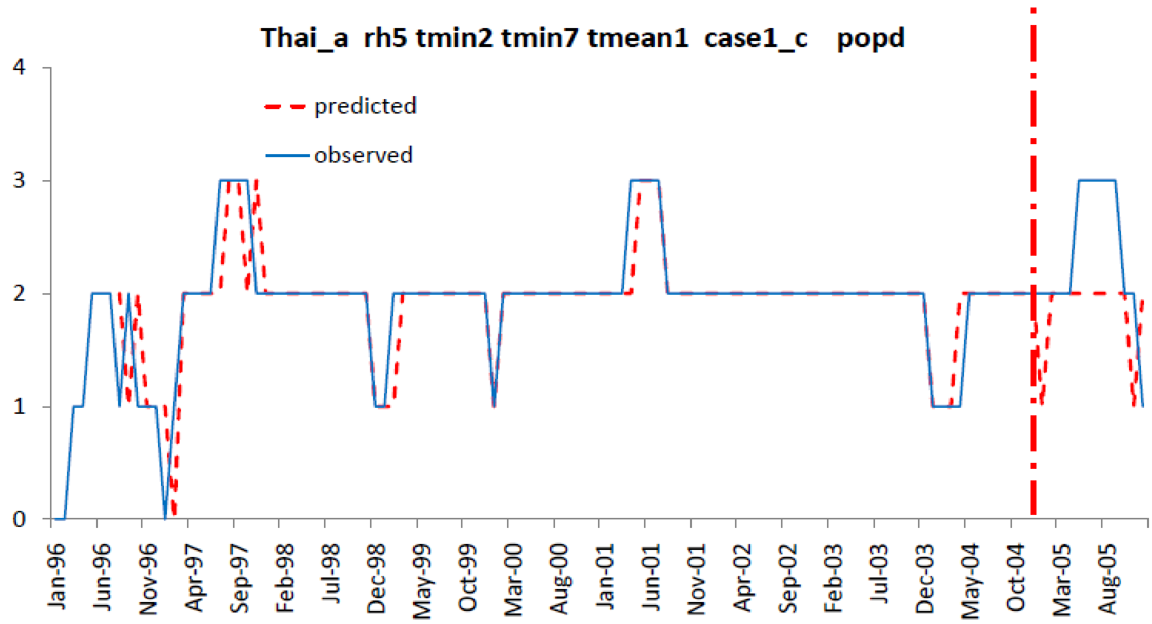


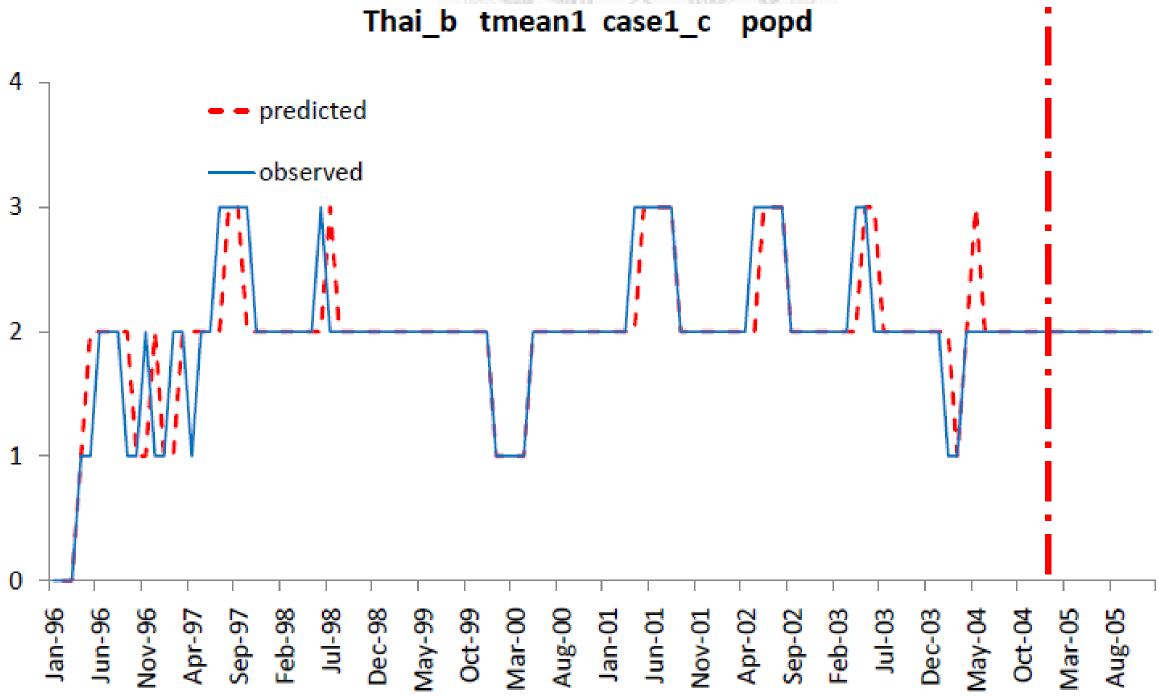


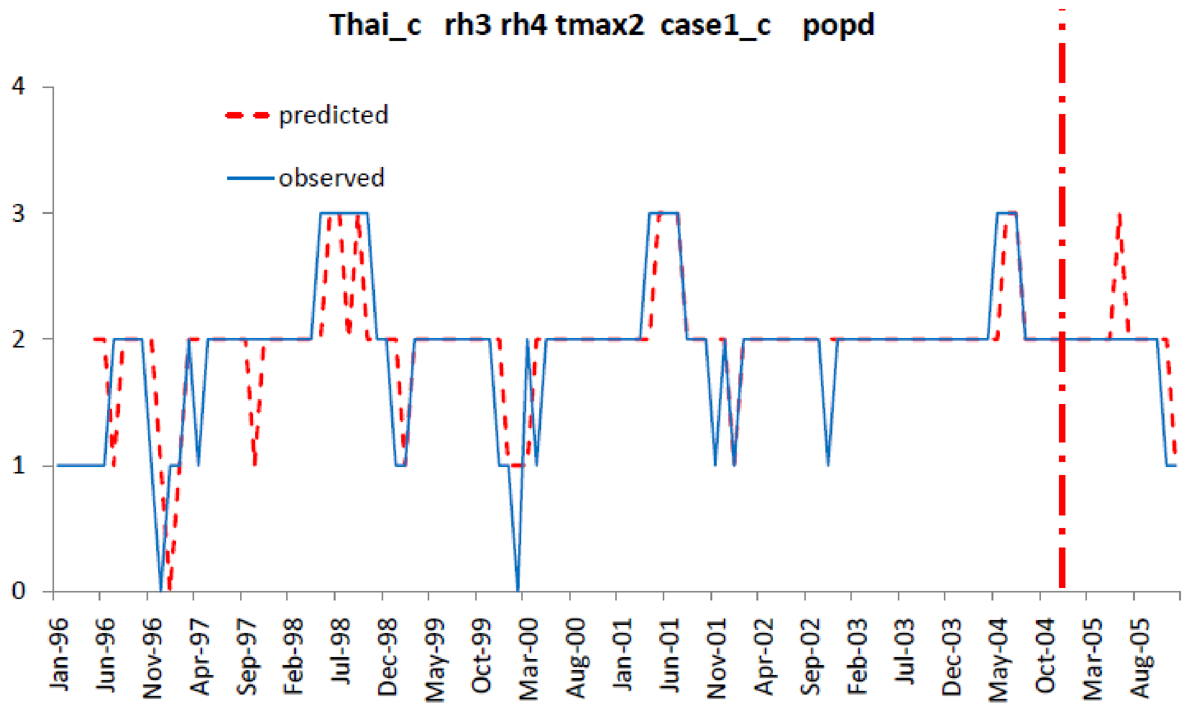
Note:

TN: Tainan area, including Tainan City and County; KH: Kaohsiung area, including Kaohsiung City and County; PT: Pingtung area, including Pingtung City and County.

Figure 10: Fitting (1996-2004) and predicting (2005, after red dash line) DRI in Thailand with meteorological regression model







Thai_c rh3 rh4 tmax2 case1_c popd
predicted
observed
Jan-96
Jun-96
Nov-96
Apr-97
Sep-97
Feb-98
Jul-98
Dec-98
May-99
Oct-99
Mar-00
Aug-00
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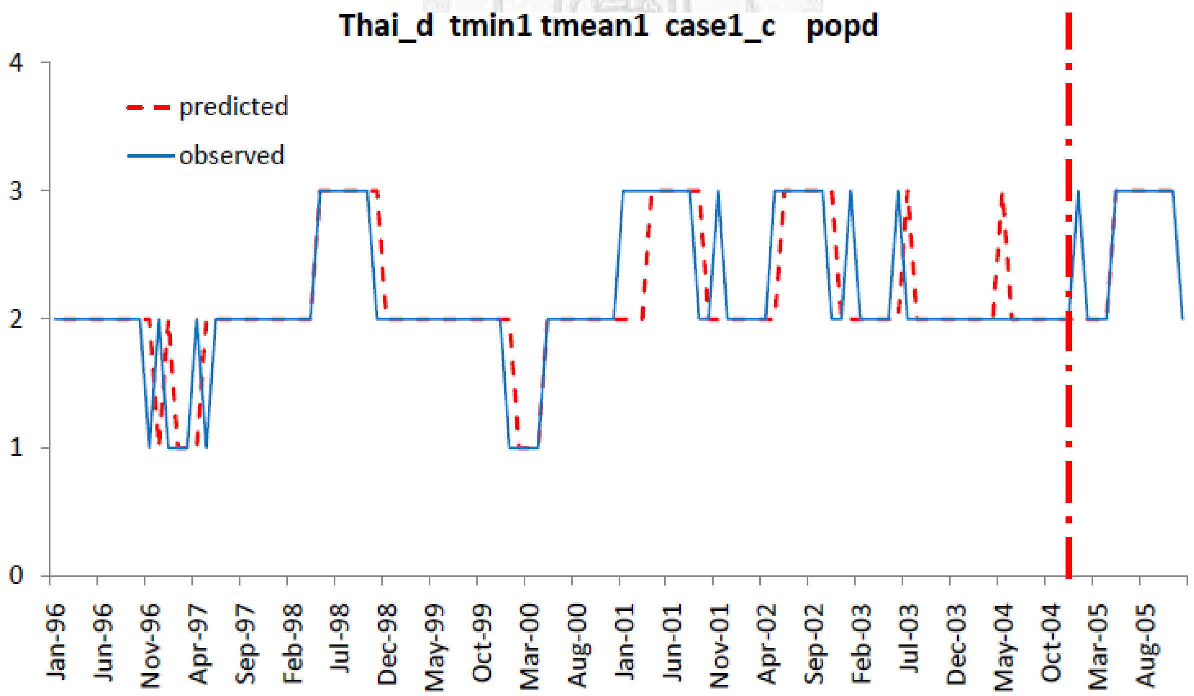
Oct-04
Mar-05
Aug-05



Thai_d tmin1 tmean1 case1_c popd
predicted
observed
Jan-96
Jun-96
Nov-96
Apr-97
Sep-97
Feb-98
Jul-98
Dec-98
May-99
Oct-99
Mar-00
Aug-00
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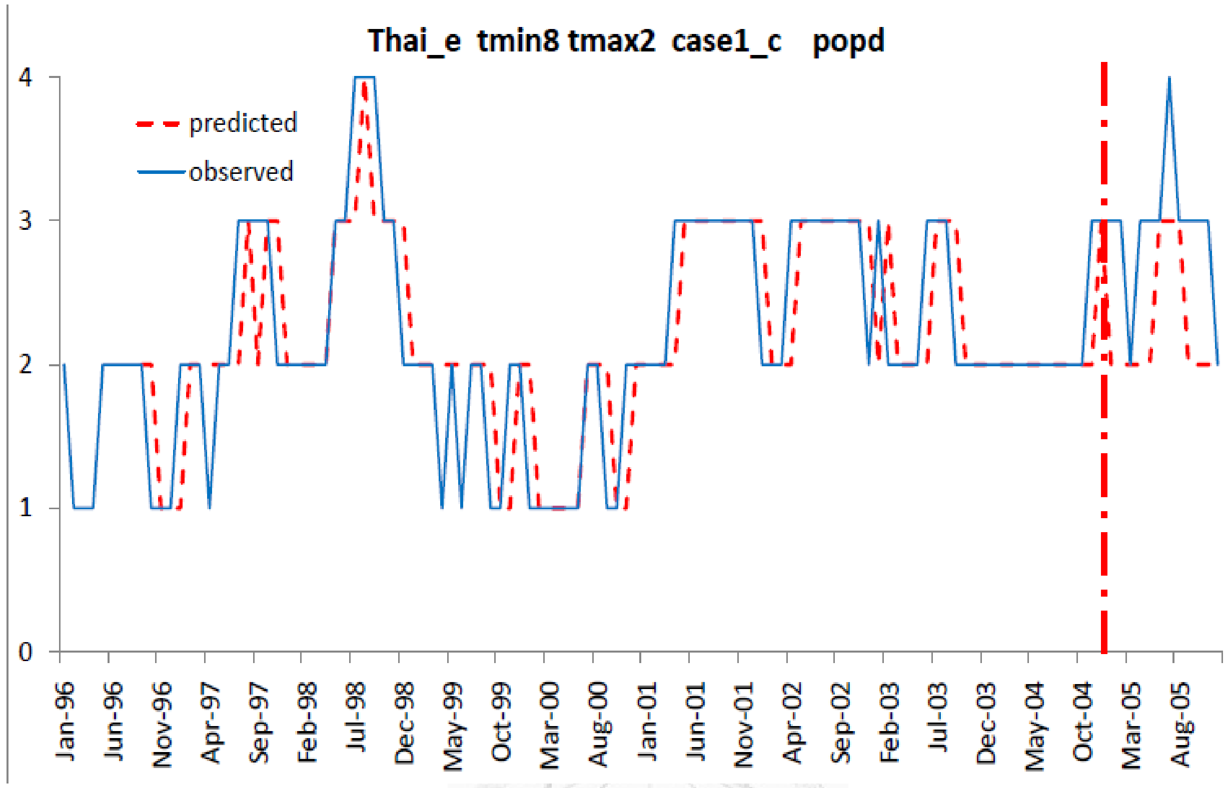
Aug-05



Note:

Five coastal provinces are (a) Phetchaburi, (b) Prachuap Khirikhan, (c) Chumphon, (d) Surat Thani and (e) Nakhon Sitammarat.

Appendix: Diagnostic tests for consistence between expected and observed DRI

(adapted from User's manual of SAS)

1. Gamma=(P-Q)/(P+Q) $P=\Sigma\Sigma n_{ij}A_{ij}$ (twice the number of concordance)

   $Q=\Sigma\Sigma n_{ij}D_{ij}$ (twice the number of discordance)

   $A_{ij}=\Sigma\Sigma n_{kl}(k>i,\ l>j)+\Sigma\Sigma n_{kl}(k<i,\ l<j)$

   $D_{ij}=\Sigma\Sigma n_{kl}(k>i,\ l<j)+\Sigma\Sigma n_{kl}(k<i,\ l>j)$

2. The Spearman correlation coefficient (ρ_s) is computed by using rank scores. This measure is appropriate only when both variables lie on an ordinal scale. The range of the Spearman correlation is $-1\leq\rho_s\leq1$.

Autobiography

Ms. Chuin-Shee Shang has been interested in ecology of infectious diseases since her first medical entomology class in sophomore. Shang received her Master degree of science with the thesis titled “Establishment of a Dengue Virus Surveillance System in Mosquitoes by Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR)”.

In recent years, Chuin-Shee has involved in several study projects, including (1) “The surveillance and control of dengue and mosquito vectors in Taiwan” (DOH-96-DC-1101, 2007-present), (2) “The impact analysis of climate change on public health and infectious diseases in Taiwan” (NSC94-2621-Z-002-010, 2005-present), (3) “The evaluation of health effect of vegetarian food on high blood cholesterol patients” (in Taiwan Adventist Hospital, 1999-2000), and (4) “Modification of RT-PCR system on surveillance of dengue virus in Taiwan”(including human and mosquito systems, 1998-1999).

All the above research findings have been presented in several international conferences in Hong Kong, Tahiti, Singapore, USA (annual meeting of the American Society of Tropical Medicine and Hygiene) and Beijing.

Chuin-Shee has teaching experiences at National Taiwan University involving liberal education classes on the course of “Scientific Attitude and Social Responsibility of Infectious Diseases”. She guiding younger students and has worked voluntarily as a counselor in church’s teenager group for seven years and a coordinator in the re-establishment conducted by local churches after the 921 earthquake in central Taiwan in year 1999.