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# MODELING DENGUE VIRUS INFECTION PATIENTS FOR EACH SEVERITY OF DENGUE DISEASE IN THAILAND

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## Abstract

Dengue is an infectious mosquito-borne viral disease. Dengue or dengue-like epidemics ranks highly among new and newly emerging infectious diseases in public health significance and may affect persons of all ages in dengue endemic area. Dengue virus infections



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may lead to dengue fever (DF), dengue haemorrhagic fever (DHF) and may lead to hypovolaemic shock (dengue shock syndrome, DSS) then we separate dengue data by severity of dengue disease, i.e., DF, DHF and DSS. The objective of this study is to find factors which affect the dengue virus infection patients for each severity of dengue disease in Thailand by using multiple regression models. Amongst the models fitted, the best are chosen based on the analysis of variance, F-test and *t*-test. The results of this study show that the factors are time, seasonal factors, and monthly multivariate ENSO index for dengue fever (DF) and dengue haemorrhagic fever (DHF) while the factors for dengue shock syndrome (DSS) are population in each month, seasonal factors, and monthly multivariate ENSO index.

## 1. Introduction

One of the most important public health programs in many tropical countries is the program to control or to eliminate dengue disease. This is due to dengue is regarded as a very dangerous disease that may lead to deaths [17]. Dengue is an infectious mosquito-borne viral disease. It is estimated that 50 million infections occur annually over 100 countries [21]. It is found in many countries throughout the world, and is particularly common in South-East Asia, India, the Caribbean, South and Central America, and Africa. Dengue fever is common and may be increasing in Southeast Asia. According to the World Health Organization, there is an estimated 50 million cases of dengue fever with 500,000 cases of dengue haemorrhagic fever requiring hospitalization each year. Nearly 40% of the world's populations live in an area endemic with dengue [13].

Dengue virus is one of the most difficult arbovirus to isolate. There are four serotypes of the dengue virus: Den-1, Den-2, Den-3, Den-4, and each of the serotype have numerous virus strains. Infection with one dengue serotype may provide lifelong immunity to that serotype, but there is no cross-protective immunity to the other serotypes [3]. Dengue fever (DF) can sometimes develop into a more serious illness called *dengue haemorrhagic fever* (DHF). Each person is unlikely to get this condition if he/she is just visiting areas where the disease is common (i.e., South-East Asia and India). In Thailand, every year, the increasing dengue incidence rate starts in May. It gradually subsides in October or November as shown in Figure 1.

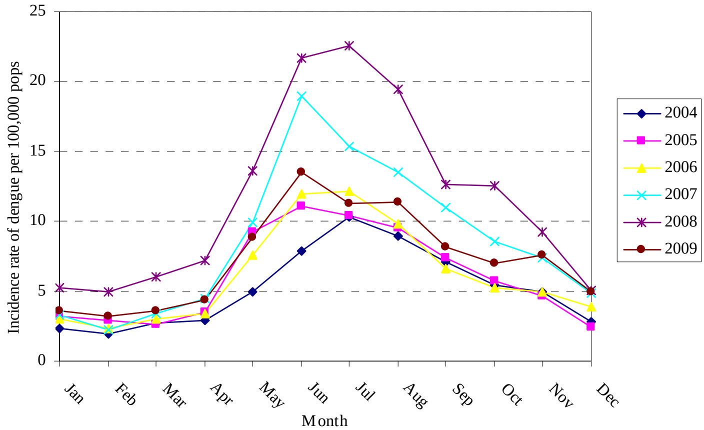


**Figure 1.** Monthly incidence of reported dengue cases per 100,000 populations in Thailand, 2004-2009.

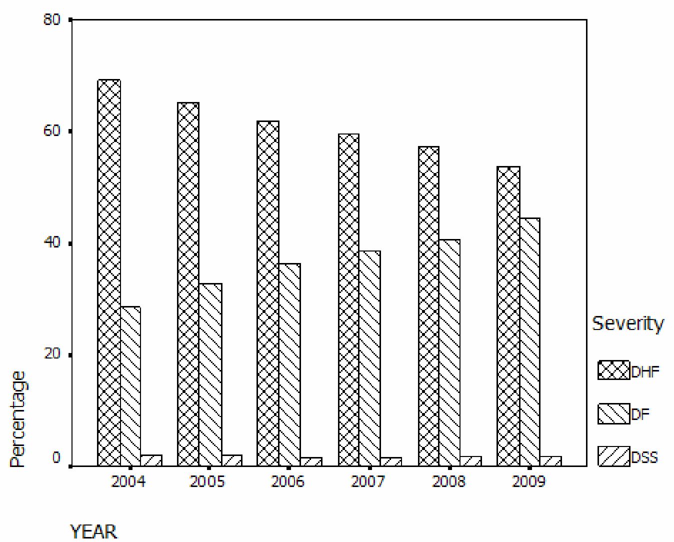


**Figure 2.** Percentage (%) of cases of dengue haemorrhagic fever in Thailand during years 2004-2009.

In most cases, especially in children less than 15 years old, who live in the countries where the dengue fever virus is widespread, and people who are infected more than once with different forms of the virus, are more likely to develop DHF. In most severe cases of DHF, the condition can suddenly worsen and lead to dengue shock syndrome (DSS). The people may develop severe pain in abdomen keep vomiting, feel irritable and the temperature may suddenly drop. DSS can be life threatening without proper medical treatment. If each person has any of these symptoms, he/she must seek an urgent medical attention [13]. The proportion (%) of cases of dengue haemorrhagic fever of Thailand is shown in Figure 2. Dengue virus is transmitted to humans through the bites of infective female *Aedes* mosquitoes. Mosquitoes generally acquire the virus while feeding on the blood of an infected person. After virus incubates for eight to ten days, an infected mosquito is capable, during probing and blood feeding, of transmitting the virus for the rest of its life. Infected female mosquitoes may also transmit the virus to their offspring by transovarial (via the eggs) transmission, but the role of the sustaining transmission of the virus to humans has not yet been defined. Infected humans are the main carriers and multipliers of the virus, serving as a source of the virus for uninfected mosquitoes. The virus circulates in the blood of infected humans between two and seven days, at approximately the same time that they have a fever. *Aedes* mosquitoes may acquire the virus when they feed on an individual during this period. Some studies have shown that monkeys in some parts of the world play a similar role in transmission [24].

Dengue virus is transmitted to the humans through the bite of the infected *Aedes* mosquitoes, principally *Aedes aegypti*, and is therefore considered to be arboviruses (arthropod-borne viruses). Once infected, a mosquito remains infected for life, transmitting the virus to susceptible individuals during probing and feeding. Infected female mosquitoes may also pass the virus to the next generation of mosquitoes by transovarian transmission, but this occurs infrequently and probably does not contribute significantly to human transmission. Human are the main amplifying host of the virus, although studies have shown that monkeys in some parts of the world may become infected and perhaps serve as a source of virus for feeding mosquitoes. The virus circulated in the blood of infected humans at approximately the time that they have fever, and uninfected mosquitoes may acquire the virus if they feed on an individual when he or she is viraemic. The virus then develops in the mosquito for a period of 8-10 days before it can be transmitted to other humans during subsequent probing or feeding. The length of time required for this extrinsic incubation depends in part on environmental conditions, especially ambient temperature [24].

## 2. Dengue Virus Infections

Dengue virus infections may be asymptomatic or may lead to undifferentiated fever, dengue fever (DF) or dengue haemorrhagic fever (DHF) with plasma leakage that may lead to dengue shock syndrome (DSS). Dengue is classified into four grades of severity, where grades III and IV are considered to be DSS. The presence of thrombocytopenia with concurrent haemoconcentration differentiates grade I and II DHF from DF.

### 2.1. Grading severity of dengue disease

The severity of dengue disease is classified into grades as follows.

**Grade I:** Fever accompanied by non-specified constitutional symptom; the only haemorrhagic manifestation is a positive tourniquet test and/or easy bruising.

**Grade II:** Spontaneous bleeding in addition to the manifestations of Grade I patients, usually in the forms of skin or other haemorrhages.

**Grade III:** Circulatory failure manifested by a rapid, weak pulse and narrowing of pulse pressure or hypotension, with the presence of cold, clammy skin and restlessness.

**Grade IV:** Profound shock with undetectable blood pressure or pulse.

Grading the severity of dengue disease at the time of discharge has been found clinically and epidemiologically useful in DHF epidemics in children in the WHO Regions of the Americas, South-East Asia and the Western Pacific, and experience in Cuba, Puerto Rico and Venezuela suggests that grading is also useful for adult cases.

### 2.1.1. Dengue fever (DF)

The clinical features of DF frequently depend on the age of the patient. Infants and young children may have an undifferentiated febrile disease, often with a maculopapular rash. Older children and adults may have either a mild febrile syndrome or the classic incapacitating disease with high fever of abrupt onset, sometimes with 2 peaks (saddle-backed), severe headache, pain behind the eyes, muscle and bone or joint pains, nausea and vomiting, and rash. Skin haemorrhages (petechiae) are not uncommon. Leukopenia is usually seen and thrombocytopenia may be observed. Recovery may be associated with prolonged fatigue and depression, especially in adults. Unusually severe bleeding can cause death in such cases. The case-fatality rate of DF, however, is less than 1%. It is important to differentiate cases of DF with unusual bleeding from case of DHF with increased vascular permeability, the latter being characterized by haemoconcentration.

### 2.1.2. Dengue haemorrhagic fever (DHF)

Typical cases of DHF are characterized by four major clinical manifestations: high fever, haemorrhagic phenomena, and often, hepatomegaly and circulatory failure. Moderate to marked thrombocytopenia with concurrent haemoconcentration is a distinctive clinical laboratory finding of DHF. The major path physiological change that determines the severity of disease in DHF and differentiates it from DF is the leakage of plasma, as manifested by an elevated haematocrit (i.e. haemoconcentration).

Children with DHF commonly present with a sudden rise in temperature accompanied by facial flush and other non-specified constitutional symptoms resembling DF, such as anorexia, vomiting, headache, and muscle or bone and joint pain. Some patients complain of sore throat, and an injected pharynx is frequently evident on examination, but rhinitis and cough are infrequent. Mild conjunctive injection may be observed. Epigastria discomfort, tenderness at the right costal margin, and generalized abdominal pain are common. The temperature is usually high (> 39°C) and remains so for 2-7 days. Occasionally, temperature may be as high as 40-41°C; febrile convulsions may occur, particularly in infants.

The severity of the disease can be modified by early diagnosis and replacement of plasma loss. Thrombocytopenia and haemoconcentration are usually detectable before the subsidence of fever and the onset of shock.

### 2.1.3. Dengue shock syndrome (DSS)

The condition of patients who progress to shock suddenly deteriorates after a fever of 2-7 days' duration. This deterioration occurs at the time of, or shortly after, the fall in temperature-between the third and the seventh day of the disease. There are the typical signs of circulatory failure: the skin becomes cool, blotchy, and congested; circumoral cyanosis is frequently observed; the pulse become rapid. Patients may initially be lethargic, then become restless and rapidly enter a critical stage of shock. Acute abdominal pain is a frequent complaint shortly before the onset of shock.

There are many related researches which involved dengue and methods to identify the risk factors such as Andrick et al. [1], Hales et al. [4], Tiensuwan [18], Kongsomboon et al. [10], Husin et al. [5], Nor Azura et al. [14], Wenbiao et al. [22], Johansson et al. [8], Lu et al. [12], Tipayamongkholgul et al. [19], Lowe et al. [11], Rosa-Freitas et al. [15], Shang et al. [16], and Wan Fairos et al. [21].

Therefore, the purpose of this study is to model dengue virus infection patients for each severity of dengue disease in Thailand in order to identify the factors which affect the dengue patients by using multiple regression models.

## 3. Data Collection

In this study, we collected dengue patients' data in Thailand between January 2004 and December 2009 from the Bureau of Epidemiology, Ministry of Public Health. The dengue data were considered as severity of dengue disease patient, namely, dengue fever (DF), dengue haemorrhagic fever (DHF), and dengue shock syndrome (DSS) patients. The scatter plot of dengue virus infection patients and logarithm of dengue fever virus infection patients in Thailand during years 2004-2009 for each severity of dengue disease is shown in Figures 3-5, respectively.

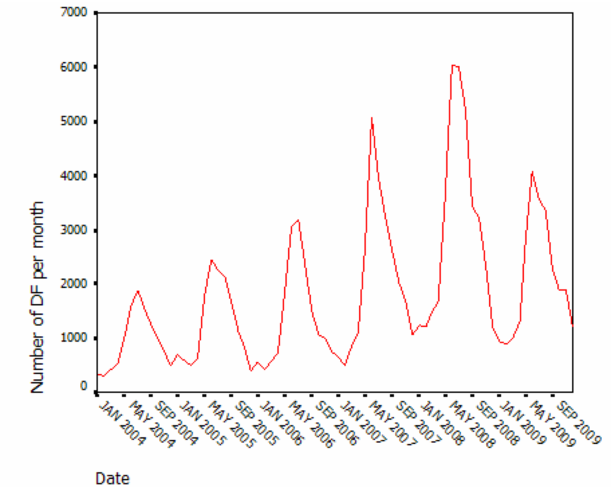


**Figure 3.1.** Dengue fever virus infection patients in Thailand during years 2004-2009.

As shown in Figures 3.1-5.2, it is clearly seasonal with a slightly upward trend and after taking logarithm it indicates that the dengue fever virus infection patient series in Thailand during years 2004-2009 are stationary in variance.

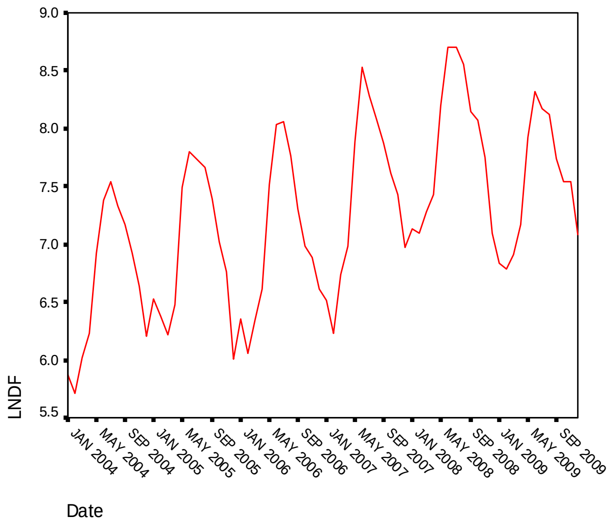


**Figure 3.2.** Logarithm of dengue fever virus infection patients in Thailand during years 2004-2009.

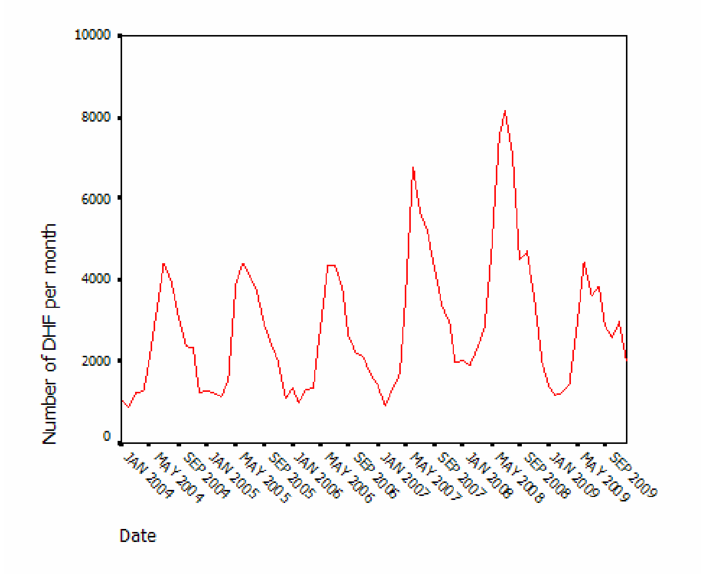


**Figure 4.1.** Dengue haemorrhagic fever virus infection patients in Thailand during years 2004-2009.

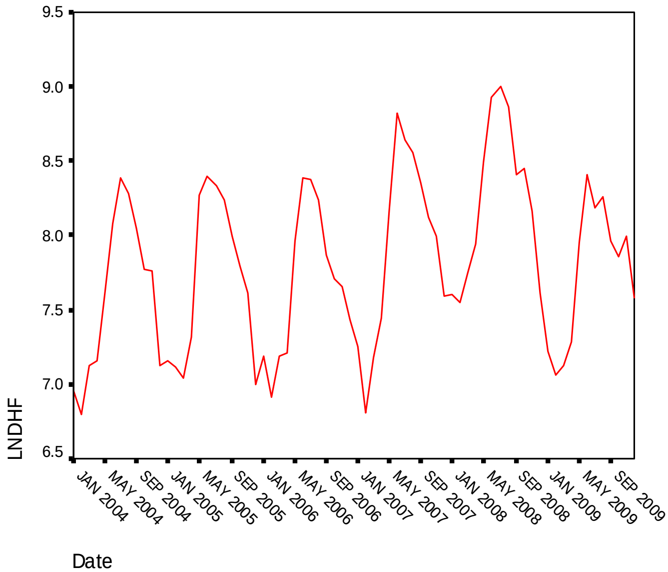


**Figure 4.2.** Logarithm of dengue haemorrhagic fever virus infection patients in Thailand during years 2004-2009.

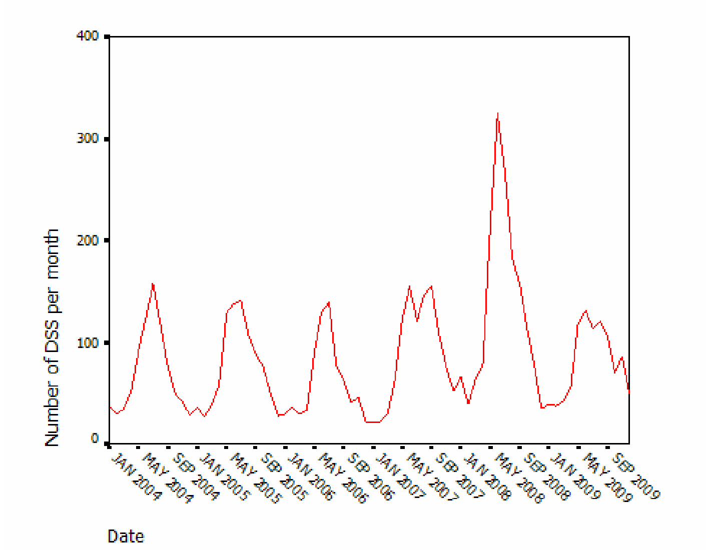


**Figure 5.1.** Dengue shock syndrome fever virus infection patients in Thailand during years 2004-2009.

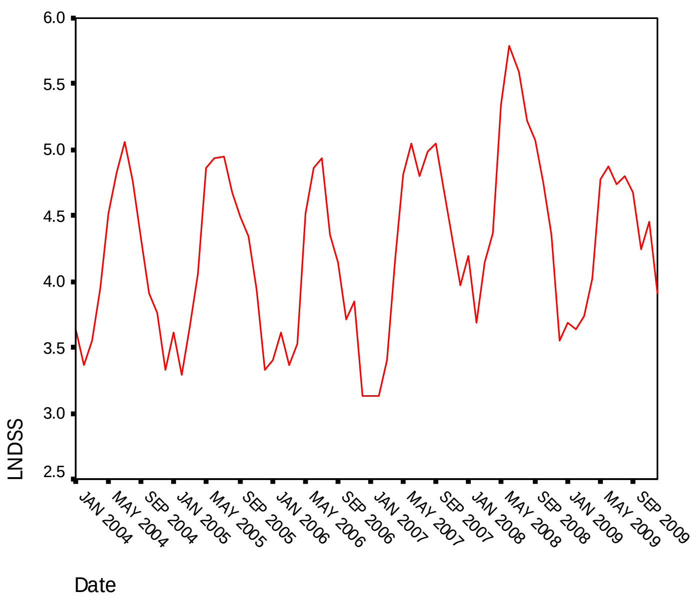


**Figure 5.2.** Logarithm of dengue shock syndrome fever virus infection patients in Thailand during years 2004-2009.

## 4. Method of Analysis

In this study, we consider models for normal distribution and identify the factors which affect the number of dengue virus infection patients for each severity of dengue disease, that is DF, DHF, and DSS by using standard normal multiple regression and obtain the best model by using the analysis of variance, i.e., F-test and *t*-test [2].

A normal regression model was used to find factors associated with the number of dengue virus infection patients for each severity of dengue disease. The number of dengue virus infection patients is the dependent variable. Explanatory variables are given as time, time$^2$, populations in each month, seasonal factor, monthly multivariate ENSO index and monthly anomalies of the sea level pressure index. We used a backward selection method to select variables in the model because of the small number of variables under study. The second order interactions were also investigated for every pair of explanatory variables. A justification for the choice of variables retained in the backward selection procedure is that the probability of significant parameter is less than 0.05. Otherwise, the variable is not included in the model. The data was analyzed by using the statistical package SPSS for Windows Version 18.

The analysis of variance and *t* test [2] were used to obtain the best model for the dependent variable (number of dengue virus infection patients for each severity of dengue disease). According to Figures 3-5 the estimated seasonal factor for each severity of dengue disease is shown in Table 1. The estimated coefficients, estimated standard errors, *t*- and *p*-values of the best model for each severity of dengue disease are shown in Tables 2-4. The standardized residual plot of the best model indicated that the assumption on identically independence distributed of normal distribution is adequate.

**Table 1.** Seasonal factor for each severity of dengue disease

| Period | Monthly DF | Monthly DHF | Monthly DSS |
|---|---|---|---|
| January | 43.2 | 51.7 | 44.6 |
| February | 37.2 | 42.8 | 37.8 |
| March | 42.9 | 48.5 | 46.7 |
| April | 55.1 | 57.9 | 68.6 |
| May | 130.6 | 116.7 | 150.8 |
| June | 203.5 | 180.1 | 190.2 |
| July | 193.9 | 183.0 | 204.9 |
| August | 164.1 | 161.2 | 145.7 |
| September | 121.0 | 118.4 | 115.9 |
| October | 93.4 | 99.6 | 88.1 |
| November | 71.0 | 87.3 | 69.1 |
| December | 44.0 | 53.0 | 37.6 |

**Table 2.** Estimated coefficients, standard errors and *t*- and *p*-values of the best model of ln(DF)

| Model | Estimated coeff. | Estimated SE | *t*-value | *p*-value |
|---|---|---|---|---|
| Constant | 5.617 | 0.066 | 85.114 | 0.000 |
| Month | 0.016 | 0.001 | 13.034 | 0.000 |
| Seasonal factors | 1.036 | 0.045 | 23.116 | 0.000 |
| Monthly multivariate ENSO index | –0.156 | 0.038 | –4.093 | 0.000 |
| $R^2 = 91.9\%$; $\hat{\sigma}^2 = 0.046$ | | | | |

**Table 3.** Estimated coefficients, standard errors and *t*- and *p*-values of the best model of ln(DHF)

| Model | Estimated coeff. | Estimated SE | *t*-value | *p*-value |
|---|---|---|---|---|
| Constant | 6.586 | 0.071 | 92.154 | 0.000 |
| Month | 0.006 | 0.001 | 4.334 | 0.000 |
| Seasonal factors | 1.029 | 0.053 | 19.230 | 0.000 |
| Monthly multivariate ENSO index | –0.147 | 0.039 | –3.790 | 0.000 |
| $R^2 = 85.9\%$; $\hat{\sigma}^2 = 0.047$ | | | | |

**Table 4.** Estimated coefficients, standard errors, *t*- and *p*-values of the best model of ln(DSS)

| Model | Estimated coeff. | Estimated SE | *t*-value | *p*-value |
|---|---|---|---|---|
| Constant | –12.354 | 3.728 | –3.313 | 0.001 |
| Population in each month | 2.454E-7 | 0.000 | 4.180 | 0.000 |
| Seasonal factors | 1.028 | 0.056 | 18.287 | 0.000 |
| Monthly multivariate ENSO index | –0.180 | 0.047 | –3.853 | 0.000 |
| $R^2 = 84.0\%$; $\hat{\sigma}^2 = 0.071$ | | | | |

Moreover, the fitted and observed dengue virus infection patients for each severity of dengue disease in Thailand during years 2004-2009 are shown in Figures 6-8, respectively.

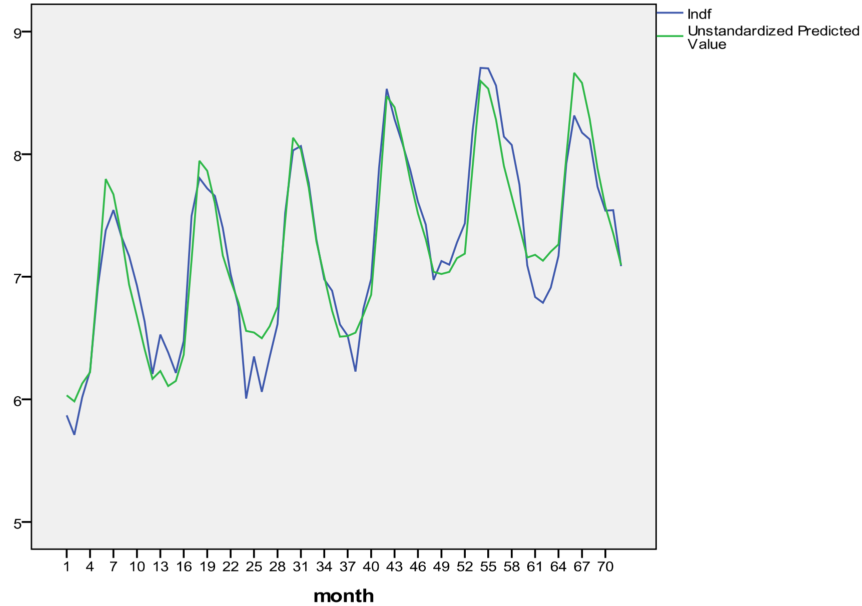


**Figure 6.** Fitted ln(DF) and observed ln(DF) of the best model.

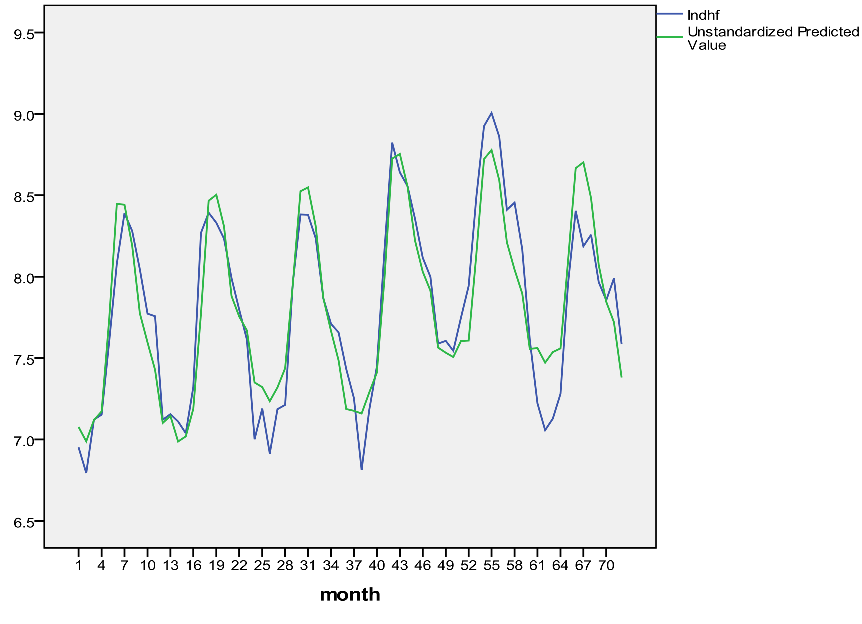


**Figure 7.** Fitted ln(DHF) and observed ln(DHF) of the best model.

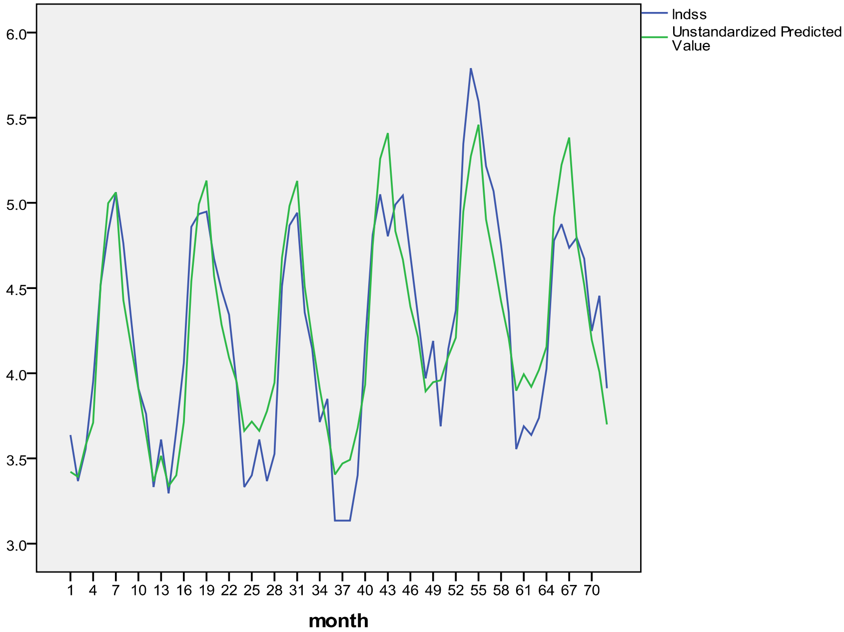


**Figure 8.** Fitted ln(DSS) and observed ln(DSS) of the best model.

## 5. Results and Discussion

We use the data of dengue patients between January 2004 and December 2009 from the Ministry of the Public Health, there were 343,715 patients that consist of 130,598 DF patients, 206,924 DHF patients and 6,193 DSS patients. We found that in Thailand, every year, the seasonal factors increasing starts in May. It gradually decreases in October or November as indicated in Table 1.

According to severity of dengue disease the results of modeling are classified into 3 models as follows: dengue fever (DF), dengue haemorrhagic fever (DHF), and dengue shock syndrome (DSS). The final section shows a discussion of the results.

### Dengue virus infection patients modeling

By using the estimated coefficients in Tables 2-3 the fitted model for each severity of dengue disease are written below.

**Dengue fever (DF)**

$$\ln(DF) = 5.617 + 0.016 \times \text{time} + 1.036 \times \text{seasonal factors}$$
$$- 0.156 \times \text{monthly multivariate ENSO index}$$

**Dengue haemorrhagic fever (DHF)**

$$\ln(DHF) = 6.586 + 0.006 \times \text{time} + 1.029 \times \text{seasonal factors}$$
$$- 0.147 \times \text{monthly multivariate ENSO index}$$

**Dengue shock syndrome (DSS)**

$$\ln(DSS) = -12.354 + 2.454\text{E-}7 \times \text{population} + 1.028 \times \text{seasonal factors}$$
$$- 0.180 \times \text{monthly multivariate ENSO index}$$

From the best model, factors which affect the dengue virus infection patients for each severity of dengue disease in Thailand are time, seasonal factors, and monthly multivariate ENSO index for dengue fever (DF) and dengue haemorrhagic fever (DHF) while the factors affect dengue shock syndrome(DSS) are population in each month, seasonal factors, and monthly multivariate ENSO index. There are no interaction effects between factors in the best model.

The main reason that seasonal factor is the most important factor for the dengue virus infection patients for each severity of dengue disease since most DF, DHF and DSS patients were found in the rainy season, while in the summer season, there was the smallest number of dengue cases. The highest number of DF, DHF and DSS cases found in the rainy season because rain water is contained in various containers that increase mosquitoes. Temperature and humidity in the rainy season are also the effects of the mosquitoes egg developed into larvae more than other seasons.

The monthly multivariate ENSO index is also the most important factors in the best model for each severity of dengue disease. The number dengue virus infection patients for each severity of dengue disease will decrease if the monthly multivariate ENSO index is increased.

The population has an effect on only DSS but not on DF and DHF. There were about 27.2 percent of DF patients were recovered, while the patients who alive with dengue were 20.2 percent. For DHF patients who alive with dengue and recovered were about 29.2 and 22.4 percent of DHF patients, respectively. Moreover, we found that the number of recovered DSS patients and the alive of DSS patients were almost equal about 25%.

Occurrence of dengue disease is the highest during the rainy season because dengue-carrying mosquitoes breed during these times when humidity is high [6]. Bangkok and central Thailand were the regions where had the highest number of DF and DHF patients because the populations of these areas are very dense and convenient transportation. If it is an area that is welded to the other provinces, it may spread the disease to nearly provinces. Northeast Thailand was the region where had the highest number of DSS patients because the occupation of the most people in Northeast Thailand is agriculturist.

Moreover, other factors such as race, marital status, age, region, zone and season in each severity of dengue disease are different. The best way to prevent the spread of the disease is to eliminate mosquito breeding places by covering all water containers, throwing away trash that collect rainwater, and cleaning roof gutters and canals regularly. The risk of getting dengue is highest during the day because mosquitoes bite during daytime. They are most active during early morning (from 4a.m. to 11a.m.) and late afternoon (from 4p.m. to 6p.m.). Persons with dengue disease should rest and drink plenty of fluids. They should consult a doctor immediately for prompt treatment [7]. Dengue is treated by replacing lost fluids. Some patients need transfusions to control bleeding.

Anyone who is bitten by an infected mosquito can get dengue disease. Risk factors for dengue disease are age and immune status of the patients, as well as the type of infecting virus. Persons who were previously infected with one or more types of dengue virus are thought to be at greater risk for developing dengue haemorrhagic fever if they are infected again.

Thailand has claimed a major success in developing the world's first vaccine against dengue, and hopes to mass produce the vaccine within 10 years [9].

Prevention centers on avoiding mosquito bites when traveling to areas where dengue occurs. Eliminating mosquito breeding sites in these areas is another key prevention measure.

Avoid mosquito bites when traveling in tropical areas: Use mosquito repellents on skin and clothing. When staying outdoors during times that mosquitoes are biting wear long-sleeved shirts and long pants tucked into socks. Avoid heavily populated residential areas. When indoors, stay in air-conditioned or screened areas. Use bed-nets if sleeping areas are not screened or air-conditioned.

Although the $R^2$ of the fitted models are not closed to 100% it might be other factors need to include in the model but the method has used under the study is not so difficult or need more advance knowledge to perform. Any researcher can obtain the fitted model.

Moreover, further study should be applying other statistical methods such as univariate- or multivariate Box-Jengins models which require the advance knowledge to analyze this data and comparing the results. Poisson regression or negative binomial models can apply for modeling.

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