The seasonal reproduction number of dengue fever: Impacts of climate to transmission

Sittisede Polwiang

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Sittisede Polwiang

Department of Mathematics, Faculty of Science, Silpakorn University, Thailand

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Keywords: Dengue, Infectious disease, Mathematical Model, Reproduction Number

INTRODUCTION

Dengue fever and Dengue hemorrhagic fever are the most frequent mosquito-borne viral disease in human and become a major international public health concern in recent decades. Over 50 millions people living in tropical and subtropical urban areas from Latin America to South East Asia are infected with dengue virus annually. The dengue fever is caused by one of four distinct serotypes of dengue virus (DENV), DENV1-4 (World Health Organization, 2014). Recovery from infection by one of serotypes provides lifelong immunity against that serotype but confers only temporary immune against the other serotypes for approximately 2 years (Montoya et al., 2013). For dengue virus, the infection is transmitted through an intermediate vector, the infected mosquitoes. The primary vector of DENV is *Aedes aegypti* and secondary is *Aedes albopictus*. Aedes mosquitoes are found throughout tropical and subtropical areas and have adapt to cohabiting with humans in both urban and rural environment. *Aedes aegypti* bites primarily during the day and most active for approximately two hours after sunrise and several hours before sunset, but it can bite at night in well lit areas. Only females bite to obtain blood in order to gain energy for eggs laying (Centers for Disease Control and Prevention, 2014).
Thailand locates in tropical regions, with relatively high temperature (22-29^{o}C) and humidity all year-round. These conditions are ideal location for Aedes mosquito to establish. Dengue is local endemic in Chiang Mai, Thailand, throughout the year with the highest peak of endemic from June to August (Campbell et al., 2013). The counter dengue programs provided by public health services that consisted of educating people how to remove breeding sites of mosquitoes inside and outside residential areas, preventing from mosquito biting, mosquitoes population control during high dengue season. Statistically data suggested that the programs still unable to stop the disease. The number of dengue fever incidences

is increasing. According to Vector borne disease bureau of Thailand (2014), the largest outbreak in the last decade was reported in 2013 with 11,432 cases compare to 664 in 2006 and 2,733 on average for the last decade and these number were hospitalized data only. All four dengue serotypes have been detected, with DENV2 dominating in country (Anantapreecha et al., 2005). Major dengue outbreak has occurred irregularly every 3-4 years. Several studies suggest that entomological parameters are temperature sensitive as dengue fever normally occurs in tropical regions (Liu-Helmersson et al., 2014). The high temperatures increase the life span of the mosquito and shorten the extrinsic incubation period of the dengue virus and would increase the infected mosquitoes (Wu et al., 2009). The rainfall provides places for eggs and larva development (Chompoosri et al., 2012). Global warming will certainly affects the abundance and distribution of dengue vectors (Khasnis, 2005). Exploring the relationships between climate and dengue transmission is important task.

In recent decades, mathematical models were used as a tool for infectious epidemiology study. Most of the models developed try to incorporate several factors of the disease to predict the possible magnitude of outbreaks. The basic reproduction number, R_0, is defined as the number of infected people generated by a single infectious person in an entirely susceptible population. Typically, if $R_0 > 1$ an epidemic occurs while $R_0 < 1$ no outbreak and larger value of R_0 means the harder to control the epidemic (Heffernan et al., 2005). Estimations of the reproduction number of dengue have varied widely which suggests highly heterogeneous levels of population immunity, vector density coupled with weather conditions, and differences in the intensity of dengue control efforts. These control interventions target vector breeding sites, killing adult mosquitoes, and reducing the contact between adult mosquitoes and hosts.

The objectives of this study were i) to improve knowledge of the relationships between climate sensitive variables and dengue transmission dynamics, ii) to identify optimal conditions for a dengue epidemic potential, and iii) to develop a model dengue transmission that can be included in an early warning system.

THEORY AND METHODS

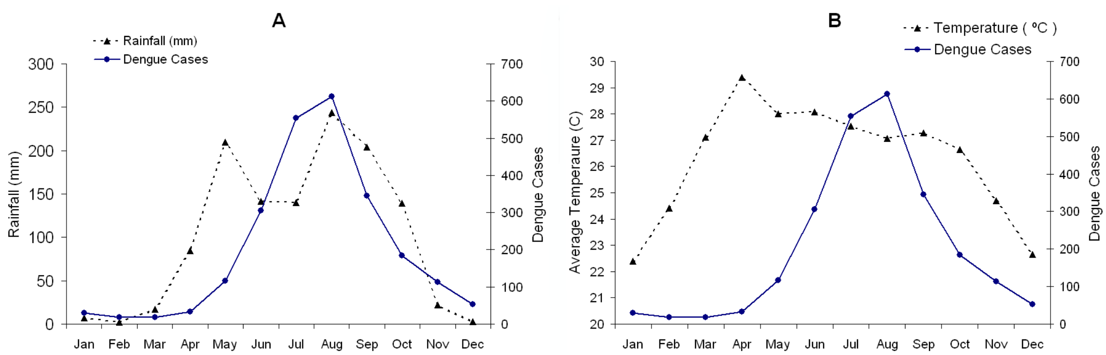

Figure 1. The dengue incidences record and weather data.
The average monthly dengue incidences from 2004-2013 of Chiang Mai, Thailand is complete line. The broken lines are (A) average monthly rainfall and (B) average temperature during the same period.

The Dengue Situation in Chiang Mai

Chiang Mai is the largest province in the northern of Thailand in term of population. Its climate is significant different for each season. Dengue fever is one of major public health concern in the province. Epidemiological and meteorological data were analyzed from 2004 to 2013 in Chiang Mai. Fig. 1 shows the average monthly dengue incidences of Chiang Mai from 2004-2013 with (A) the average monthly rainfall during the same period and (B) the average monthly temperature (Meteorological Department of Thailand, 2014). Average dengue incidences are ranged from 18 in February to 612 in August (Vector-Borne Diseases Bureau, Department of Disease Control, 2014). It is obviously seen in the figure that dengue incidences and amount of rainfall are well associated. The association between dengue epidemics and rainfall could be explained by increases in adult survival, breeding sites for eggs and feeding activity of the mosquito. Humidity increases ovipostion rate and extend life span of adult mosquito (Canyon et al., 1999). However, the available data of relationship between humidity and dengue transmission parameters are still insufficient to generate mathematical equation.

Temperature Dependent Parameters

There are several parameters of transmission of dengue transmission and mosquito life cycle that temperature sensitive (T). Our approach is based on scientific literature on dengue transmission with climate sensitive and vector parameters. Several researches have shown such relationship and can be described by mathematical equations (Liu-Helmersson et al., 2014).

Vector-Host Transmission Parameters

Transmission processes involve in infected mosquitoes bit humans then after virus incubation period and humans become infectious and able to transmit the virus to mosquitoes. The daily biting rate, extrinsic incubation period and probability of infection from human to mosquito or mosquito to human are temperature sensitive and can be illustrated as follow

The Daily Biting Rate (b) of female *Aedes aegypti* increased linearly with temperature for 21^{o}C< T <32^{o}C as described by Scott et al. (2000) as following:

$$b = 0.0943 + 0.0043T$$

The probability of infection from human to mosquito per bite (b_m) can be described as:

$$b_m = -0.9037 + 0.0729T$$

for the temperature range 12.4^{o}C< T <26.1^{o}C and equal to 1 for 26.1^{o}C< T <32.5^{o}C (Lambrechts et al., 2011).

The probability of transmission of virus from infected mosquito to human per bite (b_h) is linear relation and increases for for 12.4^{o}C< T <28^{o}C and decreases sharply when T >28^{o}C and equal to zero T >32.5^{o}C (Lambrechts et al., 2011) as following equation:

$$b_h = 0.001044T(T - 12.286)\sqrt{32.461 - T}$$

Extrinsic Incubation Period (c) was demonstrated by Focks et al. (1995) as a decreasing relationship to temperature by using an enzyme kinetics model for 12^{o}C< T <35^{o}C.

$$c = -0.1393 + 0.008T$$

The Mosquito's Life Cycle Parameters

Temperature also impact on entomological parameters regarding the mosquito's life cycle. Depending on temperature and availability of food, *Aedes aegypti* can complete larval development between 4-7 days. The sensitivity of temperature can be described as follow.

Mortality Rate of Mosquito (μ_m) of *Aedes aegypti* was explored by Yang et al. (2009). by using the enzyme experiment (Yang et al., 2009). The results showed that the mortality rate ranged form 0.027 to 0.092 per day as 10.54^{o}C< T <33.4^{o}C.

$$\mu_m = 0.8692 - 0.159T + 0.01116T^2 - 3.408 \times 10^{-4}T^3 + 3.809 \times 10^{-6}T^4$$

Oviposition Rate (a) Yang et al. (2009) showed that the oviposition rate increases with temperature. The value was nearly zero at a temperature of 15^{o}C and presented with large value at T >30^{o}C.

$$a = -15.837 + 1.2897T - 0.0163T^2$$

Pre-adult mosquito maturation rate (s) from which the hatched pupae matured into adult mosquitoes (Yang et al., 2009).

$$s = 0.9089 - 0.2464T + 0.0248T^2 - 0.0012T^3 + 3 \times 10^{-5}T^4 - 2 \times 10^{-7}T^5$$

The Impacts of Rainfall to *Aedes aegypti* Population

Mogi et al. (1988) examined the hatch rate and amount of egg in the containers in Chiang Mai and reported that the peak of population was approximately 1 month after the start of rain season from June until the end of September. Eggs population remain low in dry season but increase exponentially during the first half of the rain season and then decrease sharply in second half of the rain season. Although the rainy season still continues, the population of aquatic stage mosquito is actually decreasing as food supply in containers decline and competitions among larval increase. The amount of rainfall is associated with the mosquito population by increasing breeding sites or egg carrying capacity. An equation of the population dynamics of *Aedes aegypti* is created. Egg carrying capacity indicates the maximum population of aquatic mosquito (egg, larva, pupae) such that resources are sufficient and equation is as follow:

$$K(t) = (K_m + (1 - K_m)\sin^2(\frac{\pi t}{365} + \phi))K_E \tag{1}$$

where $K(t)$ is egg carrying capacity related to the amount of available food and space for egg and then larvae will be able to develop. K_m is fraction of minimum egg carrying capacity in the area, K_E is constant egg carrying capacity. ϕ is adjust year cycle.

THE MODEL

The mosquito population is divided into 5 categories, infected aquatic stage, I_E , susceptible aquatic stage, S_E, susceptible adult mosquito, S_M, latent adult mosquito, L_M, and infectious adult mosquito, I_M. Note that, the mosquito life span is too short to recover from dengue virus. The life of mosquito consists of four stages: eggs, larvae, pupae and adult stage. The first three live in the water and the last one stays in the air. In this study, we included the first three stages as aquatic stage and the last one as adult stage. The lifespan of each stage depends on several factors, for example, temperature, food supply and places for eggs hatching. The human population is classified into susceptible, S_H, infectious, I_H, and recovered individuals, R_H. Flows from the susceptible to infected classes of both populations depend on the biting rate of the mosquitoes, the transmission probabilities, as well as the number of infectious and susceptible of each species. The constant parameters description are shown in Table 1. The model is described as following;

Human Compartment

The total of human population, N_H, is $S_H + I_H + R_H$. The equations for human compartment are following:

$$\frac{dS_H}{dt} = \lambda_h N_H - \frac{bb_m I_M S_H}{N_H} - \mu_h S_H \tag{2a}$$

$$\frac{dI_H}{dt} = \frac{bb_m I_M S_H}{N_h} - (\mu_h + r)I_H \tag{2b}$$

$$\frac{dR_H}{dt} = (1 - \mu_d)rI_H - \mu_h R_H \tag{2c}$$

$$\frac{dC_H}{dt} = \frac{bb_m I_M S_H}{N_h} \tag{2d}$$

where C_H is cumulative number of infection to track the total number of infection in human during given period.

Adult Mosquito Compartment

The total population of adult mosquito, $N_M = S_M + L_M + I - M$. The equations are as follow:

$$\frac{dS_M}{dt} = sS_E - \frac{bb_h S_M I_H}{N_H} - \mu_m S_M \tag{3a}$$

$$\frac{dL_M}{dt} = \frac{bb_h S_M I_H}{N_H} - (\mu_m + c)L_M \tag{3b}$$

$$\frac{dI_M}{dt} = cL_M + sI_E - \mu_m I_M \tag{3c}$$

Aquatic stage Mosquito Compartment

DENV can transfer from infected mosquito to eggs. The process called vertical transmission (Adams,

Table 1. The description of constant parameters of the Dengue transmission model

Parameters	Meaning	Values
λ_h	Birth rate of human	0.00004 day^{-1}
μ_h	Mortality rate of human	0.00003 day^{-1}
r	Recovery rate of human	0.143 day^{-1}
γ	Infection rate in mosquito's egg	0.46
μ_e	Mortality rate of aquatic stage mosquito	0.143 day^{-1}
μ_d	Death due to dengue	0.001

2010). In this part, we divided aquatic stage into susceptible and infectious population groups. Total population for aquatic mosquito (egg, larva and pupae), N_E, is $S_E + I_E$. The population of aquatic stage can be described as follow:

$$\frac{dS_E}{dt} = a\left(1 - \frac{S_E + I_E}{K}\right)(S_M + L_M + (1-\gamma)I_M) - (s + \mu_e)S_E \tag{4a}$$

$$\frac{dI_E}{dt} = a\left(1 - \frac{S_E + I_E}{K}\right)\gamma I_M - (s + \mu_e)I_E \tag{4b}$$

The parameter γ represents the proportion of infected eggs laid by infected female mosquitoes.

The Seasonal Reproduction Number

The Seasonal reproductive number, R_S, is another form of basic reproduction number as the climate factors are included and the value alternated for around the year. can be calculated by using van den Driessche and Watmough method (van den Driessche, 2002) for calculating basic reproduction number. The seasonal reproductive number is as follow:

$$R_S = \frac{\alpha}{2} + \sqrt{\frac{\alpha^2}{4} + \beta} \tag{5}$$

where

$$\alpha = a\left(1 - \frac{N_E}{K_E}\right)\frac{sr}{(s + \mu_e)\mu_m}$$

$$\beta = \frac{b^2 b_h b_m mc}{\mu_m(\mu_m + c)(\mu_h + r)}$$

where m is ratio between adult mosquito and human population. If R_S less than 1 the disease stop and R_S greater 1 the model is the disease become outbreak (Massad et al., 2011). All calculations in this study were carried out by Matlab with ODE45 function for solving non linear equations.

RESULTS

The Effects of Climate to Population of Mosquito

Fig. 2 simulated the population of aquatic stage and adult of mosquito using aquatic and adult Mosquito Compartment in the model with parameter varies as temperature and rainfall. K_E was above zero because several containers are rainfall independent. To demonstrate the population of mosquito under rainfall and temperature influence, we set $K_E = 100,000$ as an example number and $K_m = 0.18$ was chosen from ratio between eggs hatch rate in dry and rain season in Chiang Mai (183:1023) (Mogi et al., 1988). The temperature used in this simulation was average monthly temperature of Chiang Mai and the duration was 1 year ($t = 1$ is January, 1^{st}). The simulations showed that the highest population for adult mosquito was 424,000 occurred at the end of July ($t = 209$), one month after the peak of aquatic stage at the end of June ($t = 180$). During November to February, the population of mosquito was low because this period is cold and dry season. The exponential increasing of population start from April to the peak in the middle

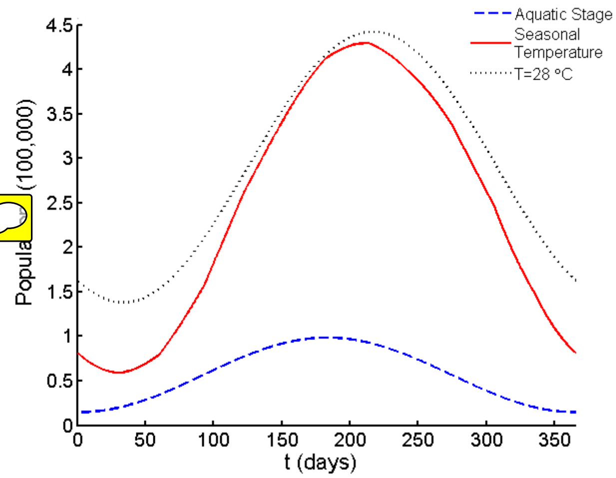

Figure 2. The population of aquatic stage and adult mosquito as function time (days) with period of one year.
The seasonal temperature (line) and constant temperature (28°C, broken line) in the model simulations were illustrated for comparison. The temperature has no significant effects on aquatic stage mosquito

of the year before it declines and the cycle repeat in the following year. Constant temperature (28°C) also illustrated to show the impact of rainfall alone to mosquito population. The trajectories of adult population with constant and variable temperature were similar configuration with constant temperature (28°C) was slightly higher (the highest was 445,000).

The Effects of Climate to Dengue Transmission

The optimal temperature for R_S was calculated by using constant ratio between human and mosquito. Fig. 3A illustrated the R_S as a function of temperature (18°C$< T <$32°C) with constant value of $m = 2,4,6,8$. R_S was increasing from nearly unity as temperature was rising. The highest value of R_S occurred at 28.7°C, equal to 4.2, 6.1, 7.1 and 8.4 for $m = 2,4,6,8$ respectively, then rapidly reducing. The value of R_S calculated in this section were similar to several studies (Nishiura, 2006). Fig. 3B simulated the value of R_S as a function of time for period of one year. For simplicity, we assumed that the maximum of egg carrying capacity was equal to population of human ($K_E = N = 100,000$ and $K_m = 0.18$). The temperatures were the monthly average of Chiang Mai. The value of R_S reached the peak ($3.05, t = 181$) in June and below one during January and December, the lowest was ($0.62, t = 1$).
Fig. 3C illustrated the cumulative number of infection as temperature is constant from 22-32°C and constant number of mosquito population $m = 1$ and Fig. 3D as population of mosquito varies according to time ($K_E = N = 100,000$ and $K_m = 0.18$). The initial value was $(S_H, I_H, R_H, S_M, E_M, I_M, S_E, I_E) = (10000, 10000, 0, 100, 100000, 0, 0, 0)$ and running duration was 365 days. Without intervention, all humans was infected for all cases with different rate. These numbers were not reflect the real number of infection in real situation but were used to determined the potential and severity of the infectious. At temperature equal to 28°C, the cumulative infection number reached total population at $t = 93$ faster than others. The potential of dengue transmission at 28°C is greater than the others.

Sensitive Analysis of Parameters

As no effective vaccine and specific treatment exist, vector control represents the only method to control dengue outbreaks. The most effective reducing R_S control measures were determined, providing important guidance for public health initiatives. The sensitivity of R_S was shown mathematically through partial derivative, dR_S/dx, to each parameter assuming that other parameters are constant: biting rate, the amount of adult mosquito and mortality rate of mosquito were the parameter to investigate because the choice of these parameters was related to general dengue infection control campaigns. The biting rate could be reduced by avoid contact between humans and mosquitoes, using bed nets or repellents substances. The amount of adult mosquito can be reduced by destroying the breeding sites or application of larvicides. Finally, the mosquito's mortality rate can be increased by using killer chemical substances spraying in the

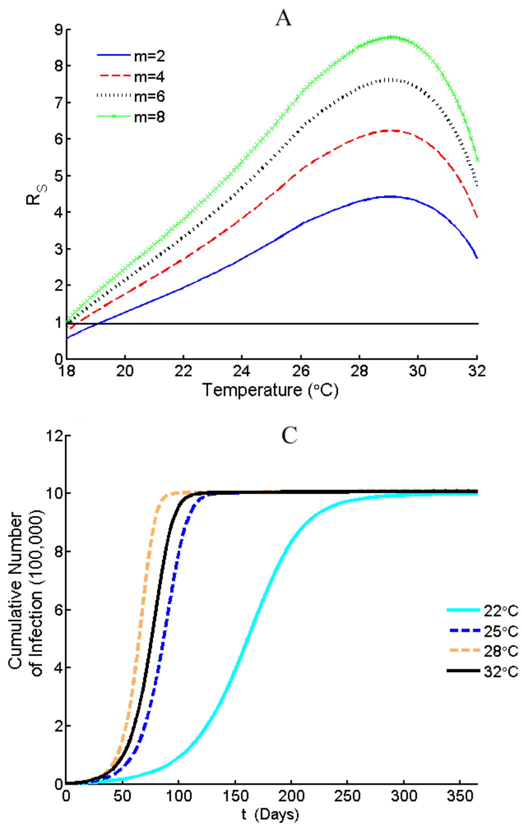

Figure 3. The seasonal reproduction number and cumulative number of human infection (A) R_S as function of temperature with constant ratio between human and mosquito population $m = 2, 4, 6, 8$. (B) R_S as function of time in month with average monthly temperature and mosquito population variation incorporated. The horizontal line indicate R_S =1. The cumulative number of infections with constant temperature as a function of time. (C) with constant $K_E = 100,000$ and (D) with variation of K_E.

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residential area. The partial derivative of R_S was as following

$$\frac{\partial R_S}{\partial b} = \frac{2bb_hb_mmc}{\mu_m(\mu_m+c)(\mu_h+r)}\left(\frac{1}{\sqrt{\alpha^2+4\beta}}\right) \tag{6a}$$

$$\frac{\partial R_S}{\partial \mu_m} = -a\left(1-\frac{N_E}{K_E}\right)\frac{sr}{(s+\mu_e)\mu_m^2} - \frac{b^2b_hb_mmc(2\mu_m+c)}{\mu_m^2(\mu_m+c)^2(\mu_h+r)}\left(\frac{1}{\sqrt{\alpha^2+4\beta}}\right) \tag{6b}$$

$$\frac{\partial R_S}{\partial m} = \frac{b^2b_hb_mc}{\mu_m(\mu_m+c)(\mu_h+r)}\left(\frac{1}{\sqrt{\alpha^2+4\beta}}\right) \tag{6c}$$

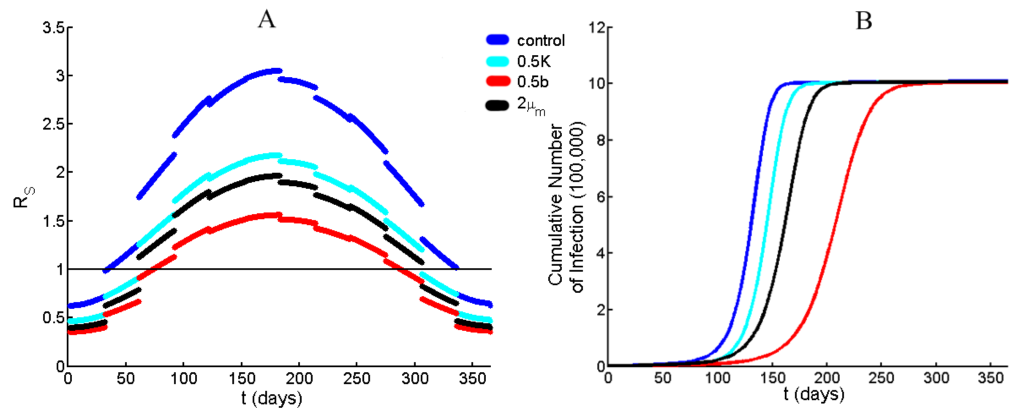

Figure 4. Sensitive analysis on dengue transmission
R_s as function of time in month with average monthly temperature. The parameters were renewing to illustrate the sensitivity. The egg carrying capacity and biting rate were reduced to half of original and mortality rate was doubled. The horizontal line indicate R_S=1.

It was clear that parameter from Eq. 6a-6c that b and m affect R_S positively, and μ_m negatively. In other words, if b and m increased, R_S increased as well. However, if μ_m increased, R_S decreased as negative signs in partial differential equation. Fig. 4A illustrated the numerical calculation of sensitive analysis with using parameter from previous paper. R_S was reduced when the breeding sites or egg carrying capacity ($K*_E = 0.5K_E$) changing provides $R_S = 2.18$, double the mortality rate of adult mosquito ($\mu*_m = 2\mu_u$) reduced R_S to 1.97 and the magnitude of relative change of R_S was the largest when half the biting rate ($b* = 0.5b$) reduced the highest R_S to 1.56. It was clear that the biting rate was the most influential factor to dengue transmission potential.
Fig. 4B simulated the cumulative number of infection as parameters were changing value as Fig. 4A and temperature was average monthly temperature and mosquito population was varied with time (Eq. 1). Reducing biting rate showed the slowest rate of cumulative number of infection. In other words, the biting rate is the most influence parameter to dengue transmission potential.

DISCUSSION

Climate Factors

Mathematical models are very useful tools to understand infectious disease and assist the planning and controlling strategies. In this study, we incorporated six temperature-dependent and one seasonal parameters of dengue transmission model and considered the potential outbreak of the dengue infection. The study showed the severity and persistence of the disease with seasonal fluctuation. The mosquito population dynamics were difficult to evaluate and most of previous studies set this population to a constant value. Climate factors, such as rainfall and temperature, will shorten or extend the life cycle of mosquito. The ratio between mosquito and human population ranges from 0.3 to 20 folds (Chen, 2012). In this study, the mosquito population dynamics were set to be a function that corresponds to

rainfall season and life cycle of mosquito largely depend on temperature. After the start of rain season, the egg populations increased exponentially toward peak abundance in the mid rainy season. The peak density tended to be higher in the rural area than in urban area. This peak was followed by exponential decline despite continuing rains and high temperatures. The seasonal pattern foreshadowed by 1 month the epidemic pattern of dengue infection (Mogi et al., 1988). It is believed that the population burst tended to consume all the food supply accumulated in the containers during the dry season, so later generations were subjected to more severe competition through food exploitation.
The effect of temperature is distinct in different stages of mosquito's life-cycle. The high temperature increases the oviposition rate, pre-adult mosquito maturation rate and extrinsic incubation period. Also the virus transmission probability human-mosquito and mosquito-human and mortality rate of mosquito are temperature dependence. The seasonal reproduction number is 0.62-3.05 for the average monthly temperature in Chiang Mai and the shape of relationship between R_S and temperature is bell curve. January and December have R_S lower than 1, which indicates that dengue outbreak may not occur. Our simulations suggest that the greatest potential of dengue transmission occurs at temperature equal to 28.7^{o}C which is close to average temperature in Chiang Mai from March to October (27-29^{o}C). The result of simulation was agreed with dengue incident report from Vector-Borne Diseases Bureau, Department of Disease Control (2014) and similar to previous model studies (Descloux et al., 2012)(Liu-Helmersson et al., 2014).

Sensitive analysis and control plan

The sensitive analyses (Fig. 4A) have shown that reducing or avoiding contact with mosquito is the most effective way to prevent dengue fever. It is very difficult to eliminate mosquito because it adapts to the environment and becomes resistance to natural and human control measure. Using chemical substance to kill mosquito was proof to be ineffective against dengue for long term strategy. Mosquitoes can rapidly resistance to chemical substance. Spraying may not cover all mosquito resting places, and the population then rebounds within few weeks. Insufficient reduction of vector mosquito may increase long-term dengue incidence (Thammapalo et al., 2014). Aedes mosquito can lay eggs in various types of containers. Removing all breeding sites is intensive works, costly and time consuming. Moreover, some containers may overlook, hidden or out of reach. There is no specific treatment and effective vaccine is still unavailable for Dengue fever. The vector control is only possible way to eradicate the disease. An eco-friendly dengue vector control programs was successfully implemented in urban and peri-urban settings in Thailand, through intersectional collaboration and practical action at household level, with a significant reduction in vector densities (Kittayapong et al., 2010). The best and most economical method is avoiding bitten by mosquito. Bed net and mosquito wire screen are the most common tools to prevent from contacting with mosquito. Some herbs such as *Citrus hystri*, *Cymbopogon nardus*, and *Pelargonium citrosum* have ability to repel mosquito from residential area. Sensitive analysis indicates that not all parameters affect basic reproductive number the same way. Sustainable process of encouraging community to reduce mosquito breeding sites such as outdoor solid waste disposal, such as frequent emptying and cleaning by scrubbing of water-storage vessels; sheltering stored tires from rainfall; flower vases and desert room coolers, is the most effective method to reduce dengue infection (Suwannapong et al., 2014). Both mathematical and practical studies have showed the same agreement.

Limitation

There are few limitations in this study. *Aedes aegypti* live in urban areas which are warmer than environmental temperature due to human activities and places for mosquito to avoid extreme ambient temperature. Also many rainfall independent containers are in the area. The population of mosquito may be under estimated. Another important dengue vector, *Aedes albopictus*, coexists with human in many parts of Thailand and can survive under cold weather. However, the parameters in this study were based on *Aedes aegypti* only. Humidity was excluded from this study due to insufficient data and it is believed to significant affected the mosquito behavior.

CONCLUSION

The number of mosquitoes varies according to seasonal variations. During favorable periods when the size of the mosquito population increases, the potential of dengue infection in human also increases. The potential of dengue transmission requires the following four factors: 1) number of susceptible humans, 2) number of mosquito, 3) virus potential induction, and 4) climate.
Temperature plays significant role in dengue transmission and influenced the dynamic modeling of vector-host interaction. Rainfall provides breeding sites for mosquito to hatch and develop to adult stage. Both factors show significant impact to mosquito population and dengue transmission dynamics. Our simulations confirm the impact of climate to dengue transmission is significant and suggest that the greatest potential of dengue transmission in Thailand occur in June to August which average temperature is 28-29^{o}C in the mid of rain season. This study provides one possibility how dengue transmission could change as global climate changing. Reducing the contact with mosquito is the best way to control dengue outbreak.

APPENDIX

The disease free equilibrium point is as follow
$S_H = \frac{\lambda_h N_H}{\mu_h}$, $S_E = \frac{\mu_m K_E(a-(s+\mu_e))}{as}$, $S_M = \frac{K_E(a-(s+\mu_e))}{a}$
R_0 can be obtained by using the method introduced by van den Driessche (2002). We write the system of differential equation as $\psi' = f - v$ where

$$\varphi = \begin{bmatrix} I_H \\ I_E \\ L_M \\ I_M \end{bmatrix}, f = \begin{bmatrix} \frac{bb_m I_M S_H}{N_H} \\ a(1-\frac{S_E+I_E}{K_E})\gamma I_H \\ \frac{bb_m S_M I_H}{N_H} \\ 0 \end{bmatrix}, v = \begin{bmatrix} (\mu_h+r)I_H \\ (s+\mu_e)I_E \\ (\mu_m+c)L_M \\ -cL_M - sI_E + \mu_m I_M \end{bmatrix} \quad (7)$$

The jacobian matrices F and V, associated with f and v respectively, at the disease free equilibrium are.

$$F = \begin{bmatrix} 0 & 0 & 0 & bb_m \\ 0 & 0 & 0 & a\gamma(1-\frac{S_E}{K_E}) \\ bb_m\frac{N_M}{N_H} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

$$V = \begin{bmatrix} \mu_h+r & 0 & 0 & 0 \\ 0 & s+\mu_e & 0 & 0 \\ 0 & 0 & \mu_m+c & 0 \\ 0 & -s & -c & \mu_m \end{bmatrix} \quad (8)$$

and the next generation matrix $G = FV^{-1}$ is:

$$G = \begin{bmatrix} 0 & 0 & \frac{b_m c}{(\mu_m+c)\mu_m} & \frac{b_m h}{\mu_m} \\ 0 & 0 & \frac{a\gamma(K_E-S_E)c}{K_E(\mu_m+c)\mu_m} & \frac{a\gamma(K_E-S_E)}{K_E\mu_m} \\ \frac{\mu_m+c}{\mu_h+r} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \quad (9)$$

R_0 is then the spectral radius of the next generation matrix, $R_0 = \rho(G)$, the largest eigenvalue of G. Thus:

$$R_0 = \frac{\alpha}{2} + \sqrt{\frac{\alpha^2}{4} + \beta} \quad (10)$$

where

$$\alpha = a\left(1 - \frac{N_E}{K_E}\right)\frac{sr}{(s+\mu_e)\mu_m}$$
$$\beta = \frac{b^2 b_h b_m N_m c}{N_h(\mu_m + e)(\mu_h + r)}$$

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