The impact of rainfall and temperature on the spatial progression of cases during the chikungunya re-emergence in Thailand in 2008–2009

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Background: In 2008, chikungunya virus (CHIKV) re-emerged in Thailand after more than a decade of absence. Cases first appeared in the extreme southern region of the country and advanced northward approx. 300 km over the next 18 months. The spatial advance of CHIKV cases appeared to occur at two rates, initially progressing slowly and then increasing in speed. We hypothesize that climatic variation affected the transmission of CHIKV in the country.

Methods: To determine the effect of climate on CHIKV transmission, we evaluated models where climate affects the transmission rate from mosquitoes to humans; extrinsic incubation period; fertility rate of mosquitoes; and the mortality rate of mosquito larvae. We compared these models to models that did not include climate effects.

Results: The inclusion of climate data greatly improved model fit with models assuming climate affected the fertility rate of mosquitoes providing the best fit to data.

Conclusion: These results suggest that climatic variation contributed to the slower rate of incidence observed in March 2009. Overall, a gradient in transmission probability and mortality and fertility rates of mosquito is observed over the entire area with the most southern districts experiencing the most efficient transmission.

Keywords: Chikungunya, Emergence, Spatial, Thailand

Introduction

Chikungunya virus (CHIKV) is an *Alphavirus* transmitted by mosquitoes of the *Aedes* genus, particularly *Aedes albopictus* and *Aedes aegypti*.¹ The symptoms of CHIKV infection appear 1–12 days after infection² and include high fever, maculopapular rash and severe arthralgia.³ CHIKV was first isolated in Tanzania, Africa in 1952⁴; in Asia, CHIKV was first reported from Bangkok in 1965,⁵ followed by reports in Cambodia, Vietnam, Malaysia and Taiwan in subsequent years.⁶ After an absence of transmission for 10–15 years, an outbreak occurred in Thailand that corresponded with an increase in transmission in several countries in the Indian Ocean in 2006. Since 2006, CHIKV infections have appeared in many parts of the globe with cases increasing rapidly in many countries of the Caribbean, Central and South America.⁶ These introductions and emergences highlight the need to understand the conditions that might foster or impede efficient transmission of CHIKV when it is introduced to new areas.

Within Thailand, CHIKV has been detected in many locations. Cases were reported in Prachinburi in 1976, Surin in 1988, Khon

Khean in 1991, in Loei and Phrayao in 1993, and in 1995 in Nongkhai and Nakhon Si Thammarat.⁷ It is not clear to what extent transmission has persisted at low levels in intervening periods, but very few cases were detected between 1995 and 2008.³ The disease re-emerged in August 2008 and was first detected in the Yi-ngo district of Narathiwat province.⁸ Nationally, the incidence of CHIKV showed two distinct temporal peaks (Figure 1). Incidence increased until March 2009, receded, then increased again over the period from April to June 2009 (Figure 1), suggesting that transmissibility declined in the period between the two peaks. Over the next year, the disease spread throughout the entire country.⁹ Figure 2 shows cumulative incidence over the entire country and the week of onset for places as a function of their distance from Yi-ngo district (the first district where cases were detected). The spatial advance of cases was slow until June 2009, spreading quickly thereafter.

We hypothesize that this reduction in transmission is attributable to the impact of climate variation. The two peaks in incidence roughly correspond to peaks in rainfall. Ambient temperature also varies across this time period. Climate may play an important role

Figure 1. Time series of reported cases of chikungunya in selected provinces of southern Thailand. Provinces are color-coded as shown on map, time series and legend.

Figure 2. Cumulative incidence of chikungunya (blue curve, left axis) and distance from Yi-ngo (red circles, right axis), the district with the first outbreak in the south, shown as a function of time (cumulative incidence), or onset week (distance from Yi-ngo).

in disease transmission as it effects the mosquito life cycle, behavior and the time course of viral infection in the mosquito.^{10,11} In this work, we assess the impact of climate variation on the transmission of CHIKV during the emergence in 2008 using multiple competing mathematical models of the transmission dynamics of CHIKV.

We propose several mathematical models of CHIKV transmission that include an effect of climate on dynamics. We use these models to test whether climate is associated with the efficiency of transmission once CHIKV was introduced to particular districts in Thailand, and identify the climate factors that had the greatest impact on transmission.

We used genetic algorithms and Nelder-Mead optimization to find maximum log-likelihood estimates of parameters of four separate models that incorporate different assumptions of the relationship between climate and CHIKV transmission. We fit these models to reported data on CHIKV incidence by the Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health, Thailand.

Method

Data

Clinical cases of CHIKV in Thailand are reported to the national surveillance system administered by the Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health, Thailand. We analyzed all cases reported from August 2008 to October 2009. Incident cases were aggregated by week and by district (Administrative level 3). The first report of CHIKV in 2008 came from Yi-ngo district, Narathiwat province, on August 2008,⁸ then spread to neighboring areas. During the period of August 2008 to October 2009, cases were reported from 288 out of 928 total districts. These districts reside in 55 of the 76 total provinces in Thailand. We focused our analysis on the southern most 109 districts, where the majority of cases were reported. A time series of cases from all areas appears in Figure 1 as well as time series of cases from a selection of provinces. The total number of cases reported during this period was 48 919 cases.

We obtained data on rainfall and temperature variation in Thailand from the National Climate Data Center (NCDC). Data are available from 171 stations in Thailand, including 15 stations in the south of Thailand. We used the time series of weekly cumulative rainfall and weekly average of temperature¹² to build our models of CHIKV transmission. These time series were smoothed to eliminate discontinuities using natural splines. Data from the closest weather station were used for each of the 109 districts. Plots of rainfall (mm) and mean weekly temperature (°C) appear in Figure 3.

Description of transmission model

For the transmission model, we follow the model framework developed by Dumont et al. in 2008,¹³ used to model CHIKV outbreaks in France. We extended this framework to include the effect of changing climate (e.g., rainfall, temperature) on transmission dynamics. The state space of these models for both the mosquito and human are shown in Figure 4. Humans are classified into four states, susceptible (S_h), exposed (E_h), infectious (I_h), and immune (R_h). Susceptible humans (S_h) are infected with CHIKV by infectious mosquitoes (I_m) with probability of transmission (β_{mh}), and average daily biting rate (B). Susceptible humans who are infected transition to the E_h state. Following an intrinsic incubation period ($1/\nu_h$), infected humans transition from the E_h state to the I_h state and become immune after an infectious period of duration $1/\eta_h$. We assume that the total number of humans (N_h) is constant ($N_h = S_h + E_h + I_h + R_h$) over the period of the simulations, with equal birth rate and death rate. For the mosquito compartment, the number of eggs at each deposit per capita is μ_b . The mortality rate of larvae (L_m) is μ_L . The susceptible mosquito population (S_m) grows from larvae with maturation rate (η_L). Susceptible mosquitoes are infected by CHIKV by infectious humans (I_h) with probability of transmission (β_{hm}) and average daily biting rate (C). The exposed mosquito (E_m) stay uninfected for extrinsic incubation period ($1/\nu_m$) before becoming Infectious (I_m). The mean adult lifespan is $1/\mu_m$. Initially the size of the mosquito population is set to $S_m(0) = m \times N_h$ and $L_m(0) = k \times N_h$ where m is the number of mosquito per human and k is the number of larvae per human.

Climate has potential impacts on the mosquito life cycle and the efficiency of transmission of CHIKV.¹⁴ Warmer temperatures¹⁵

Figure 3. Chikungunya cases, rainfall (mm) and temperature (°C) in 109 districts of Thailand. Color map at the right of each graph shows the scale for the z-dimension.

lead to increased adult feeding behavior. Mortality rates of larvae have been found to be higher at higher temperatures.¹⁶ Temperature changes the length of the extrinsic incubation period of the virus.¹⁷ Rainfall may increase larval habitat,¹⁷ since mosquitoes require standing water for breeding.¹⁸ Reductions in rainfall may increase the number of eggs at each deposit, increasing competition between larvae for food.¹⁹

We created models to test different hypotheses of the impact of climate. In each model, it is assumed that climate affects different parts of the mosquito life cycle or disease transmission process. The four classes of models are:

Model 1: Transmission probability from infected mosquito (β_{mh}) is given by:

$$\beta_{mh}(t) = x_1^1 + x_2^1 \text{Rain}(t - \tau_1) + x_3^1 \text{Temp}(t - \tau_2)$$

Model 2: Number of eggs at each deposit per capita (μ_b) is given by:

$$[\mu_b(t) = x_1^2 + x_2^2 \text{Rain}(t - \tau_1) + x_3^2 \text{Temp}(t - \tau_2)]$$

Model 3: Extrinsic incubation period ($1/\nu_m$) is given by:

$$[\nu_m(t) = x_1^3 + x_2^3 \text{Rain}(t - \tau_1) + x_3^3 \text{Temp}(t - \tau_2)]$$

Model 4: The mortality rate for larvae (μ_L) is given by:

$$[\mu_L(t) = x_1^4 + x_2^4 \text{Rain}(t - \tau_1) + x_3^4 \text{Temp}(t - \tau_2)]$$

Where, x_1^i , x_2^i , and x_3^i are constant values of a linear function in model i , and τ_1 a time lag, varying from 0–6 weeks, and τ_2 from 0–2 weeks. We considered models individually, and models that use some combined set of the four elements above.

Parameterization of model

To estimate the parameters of these models, we used a genetic optimization algorithm implemented using the rgenoud package version 5.7–1 for R software version 2.11.1.²⁰ We found the values of the coefficients of the linear function that maximize the likelihood of the observed data. The rgenoud package implements an updated and extended version of the C program GENOUD.²¹ We

Figure 4. Compartmental model of Chikungunya infection among humans and mosquitoes. Full description of model appears in the ‘Description of transmission model’ section of the text.

set the population size to 500 and allowed for a maximum of 50 generations. We used boundaries to constrain parameters permissible ranges. We set other parameters of the transmission model to published values. These values and references for their values are given in Table 1. Table 1 also gives the range of values considered for those parameters estimated. The objective function we optimized is the Poisson log-likelihood²² between the observed values and the simulated values,

$$L(\lambda, x) = \prod_{i=1}^n \frac{\lambda^{x_i} e^{-\lambda}}{x_i!}.$$

We fit data on the impact of climate on CHIKV transmission only once cases had been detected in an area. We considered models where the 109 districts shared the same transmission parameters as well as models in which separate parameters were fit to each of the 109 districts. We first measured the fit of parameters at Yi-ngo (the first district where cases were detected) at multiple temporal lags of rainfall and temperature. We selected the lag that maximized the likelihood of the data and then used this lag for all other districts.

Human subjects

Data were collected as part of the Thai Ministry of Public Health public health surveillance and response. Data collection was approved by the Ethics Committee of the Ministry of Public Health of Thailand. Data collection was performed as part of public health response and thus consent was not required by the Ethics Committee and was not obtained from participants. Data were analyzed anonymously. The Institutional Review Boards of Johns Hopkins University and Mahidol University deemed this

Table 1. Epidemiological parameters with references

Parameters	Value
m : the number of mosquito per human	8
k : the number of larvae per human	5
B : average daily biting per day	1 ²³
C : average daily biting per day	1 ²³
β_{hm} : transmission probability from human to mosquito (per bite)	0.17
$1/\mu_h$: life span of human (in years)	73
$1/\eta_h$: infectious period (in days)	3 ¹²
$1/\nu_h$: intrinsic incubation period (in days)	3 ⁸
μ_m : Maturation rate from larvae to adult (per day)	0.2
$1/\mu_m$: adult lifespan of mosquito (in day)	7 ¹²
β_{mh} : transmission probability from mosquito to human (per bite)	0–1 (0.375 ²³) ^a
μ_b : Number of eggs at each deposit per capita (per day)	0.1–20 (6 ¹²) ^a
$1/\nu_m$: extrinsic incubation period (in days)	2–14 (4 ¹²) ^a
$1/\mu_L$: Natural mortality of larvae (per day)	0.1–14 (4 ¹²) ^a
Temperature time lag (in week)	0, 1, 2 ^a
Rainfall time lag (in week)	0, 1, ..., 6 ^a

Those values with just one value were not estimated in our model, but set to values given by the reference shown. Other parameters are fixed to values indicated. Where references are available they are shown. Fixed values without references were decided by authors.

^a Parameters estimated. Ranges considered for these parameters are shown here. Also shown for these parameters is a reference value appearing in the literature with reference number.

research not human subjects research as no personal identifiers were available to the researchers at JHU and Mahidol.

Results

The performance of four models at Yi-ngo, Narathiwat

Supplementary Figure 1 shows the log-likelihood of the observed data assuming models 1, 2, 3 and 4 using multiple time lags of temperature (0–2 weeks) and rainfall (0–6 weeks) data. Model 3 (extrinsic incubation period) did not fit well using climate data at any time lag. On the basis of the poor performance of model 3 at all lags, we did not consider model 3 for other locations. The log-likelihood of the observed data decreased in model 1 and 2 with increasing time lag of rainfall. Model 4 showed an opposite pattern. We found lags for rainfall of 3, 2, and 6 weeks for model 1, 2, and 4 respectively had the greatest likelihood with lags of 2, 0 and 0 used for temperature.

Comparing regional parameters and individual district level parameters

Using the best climate time-lag results for three models (models 1, 2 and 4), we fit the incidence case data in each of the 109 districts that had more than 50 cases over the period October 2008

to August 2009 (the time frame in which the overwhelming majority of cases occurred). We did not fit models to districts with fewer than 50 cases as these districts did not have sufficient data to robustly estimate parameters of models. We initialized simulations in the week when cases were first reported in each district with the number of cases reported in that week. We did not simulate the arrival process of cases going from zero to non-zero.

We tested 2 sets of models, one in which we identified three parameters for the entire region and one where each district was allowed to have different parameters dictating the relationship between climate and transmission (the total number of fitted parameters for each model is shown in Tables 2 and 3). Examples of the fit of example districts in regional parameter models and

district level parameters are shown in [Supplementary Figures 2 and 3](#), respectively. The estimated mean transmission probability and mean number of eggs at each deposit per capita for each district is shown in Figure 5A and 5B, respectively. The district level parameters fit statistically significantly better than using regional parameters. We found a spatial trend in the residuals for each district with larger residuals in the more northern districts, reflecting perhaps stochasticity in the seeding of outbreaks in these areas. Figure 6 shows the distribution of negative log-likelihoods in each of the 15 districts that had the largest total number of cases. Larger circle indicates worse fit (larger negative log-likelihoods). The districts that experienced cases last had the worst fit. We found that district level parameters improved the fit of the

Table 2. Fit of various models showing the degrees of freedom, log-likelihoods and χ^2 of fitted three models in regional parameters

	Df (#parameter)	Log-likelihood	χ^2 with Sat	χ^2 with Model 4	χ^2 with Model 2,4
Saturated	3926	-5.18x10 ³			
Regional parameters					
Model 1 (0,0)	3	-9.23x10 ⁴	p<0.001	NS	p<0.001
Model 1 (2,0)	3	-9.27x10 ⁴	p<0.001	NS	p<0.001
Model 1 (3,0)	3	-9.29x10 ⁴	p<0.001	NS	p<0.001
Model 1 (3,2)	3	-9.31x10 ⁴	p<0.001	NS	p<0.001
Model 2 (2,0)	3	-1.13x10 ⁵	p<0.001	NS	p<0.001
Model 4 (6,0)	3	-7.03x10 ⁴	p<0.001	NS	p<0.001
Model 1 and 2	6	-8.55x10 ⁴	p<0.001	NS	NS
Model 1 and 4	6	-7.13x10 ⁴	p<0.001	NS	NS
Model 2 and 4	6	-5.31x10 ⁴	p<0.001	p<0.001	NS
Model 1, 2 and 4	9	-5.28x10 ⁴	p<0.001	p<0.001	p<0.001

NS: not significant; p-values indicate those that fit statistically significantly worse than indicated model. Model numbers indicate models as described in the text with numbers in parentheses indicating the lag at which rainfall and temperature data are included.

Table 3. Degrees of freedom, log-likelihoods and χ^2 based p-values of fitted three models with district level parameters

	Df (#parameter)	Log-likelihood	χ^2 with Sat	χ^2 with Model 2	χ^2 with Model 1,4
Saturated	3926	-5.18x10 ³			
District level parameters					
Model 1 (0,0)	327	-3.17x10 ⁴	p<0.001	NS	p<0.001
Model 1 (2,0)	327	-3.19x10 ⁴	p<0.001	NS	p<0.001
Model 1 (3,0)	327	-3.27x10 ⁴	p<0.001	NS	p<0.001
Model 1 (3,2)	327	-3.34x10 ⁴	p<0.001	NS	p<0.001
Model 2 (2,0)	327	-3.13x10 ⁴	p<0.001	NS	p<0.001
Model 4 (6,0)	327	-3.22x10 ⁴	p<0.001	NS	p<0.001
Model 1 and 2	654	-2.80x10 ⁴	p<0.001	p<0.001	NS
Model 1 and 4	654	-2.26x10 ⁴	p<0.001	p<0.001	NS
Model 2 and 4	654	-2.58x10 ⁴	p<0.001	p<0.001	NS
Model 1, 2 and 4	981	-1.63x10 ⁴	p<0.001	p<0.001	p<0.001

NS: not significant; p-values show χ^2 probability of observed differences given no statistically significant difference in fit from model referred to in column headings.

Figure 5. Estimated mean transmission probabilities (A) and mean the number of eggs at each deposit per capita (B) for each of the districts with over 50 cases during November to December 2008.

Figure 6. Fit of model 1 (A) and Model 2 (B) with district level parameters in the 15 districts with the greatest number of cases. The radii of the red circles are proportional to the negative log-likelihood. Larger circles indicate worse fits to the data. Blue markers indicate the geographic centroid of each district.

model significantly as measured by a likelihood ratio test between models (Table 2). Comparing the models using all 109 districts and district level parameters, model 1 performed better than models 2 and 4.

We also estimated combined models with all combinations of models 1, 2 and 4. We found that the full model with all elements of models 1, 2 and 4 performed best, but was still statistically significantly different from a saturated model in performance.

Figure 7. Estimated transmission probabilities with district level parameters over 109 districts compared with the rainfall and temperature data.

The estimated transmission probabilities for all 109 models are shown in Figure 7 (top figure). The black line in each of the panels of Figure 7 indicates the first week when cases were over 10 cases/1000 individuals. The districts are ordered by latitude in each of the panels of Figure 7. The bottom left and bottom right panels of Figure 7 show the contributions of the rainfall and temperature terms to the transmission probability. In general, both rainfall and temperature were positively correlated with the transmission probability. Districts south of 6.9 degrees latitude had a high positive correlation with rainfall while districts north of 6.9 degrees latitude showed a greater positive correlation with temperature. As a result, transmission probabilities were higher in the extreme south during the rainy season than they were in the latitudes greater than 6.9 degrees. Transmission probabilities were lower in latitudes greater than 6.9 degrees during the period October 2008 to March 2009. Note that transmission probabilities were calculated from CHIKV, rainfall, and temperature data mostly after March 2009 because cases did not appear in the districts north of 6.9 degrees latitude until then.

The number of eggs at each deposit and mortality rates of larvae showed similar patterns, with higher numbers of eggs and

lower mortality rates in latitudes south of 6.9 degrees latitude in the period from October 2008 to March 2009.

We found that the model that assumes that temperature and rainfall affects the fertility of mosquitoes using rainfall at a lag of 3 weeks and using district level covariates provides the best fit to data from the 109 districts in southern Thailand (Table 1).

Discussion

We find that the inclusion of climate information significantly improves the fit of transmission models of the outbreak of CHIKV in southern Thailand in 2008–2009. Our results suggest that climate affected the speed of the transmission and incidence in particular areas of Thailand, leading to a slowing of the spatial advance of CHIKV during the cool, rainy season from November 2008 to February 2009. Transmission in the latitudes greater than 6.9 degrees experienced an increase as temperatures warmed during the period from March 2009 to August 2009.

We considered models where climate affected the transmission probability, the egg deposition rate of mosquitoes, the

extrinsic incubation period and the mortality rate of larvae. We found that models where climate changed the transmission probability, the mortality rate of larvae and the egg deposition performed similarly but better than a model in which the length of the extrinsic incubation period was associated with rainfall and temperature. A model that incorporated all of these elements outperformed all other models. The fit of this model is strong by visual inspection and the increased complexity of this model was justified by a likelihood ratio test.

We found that models that lag rainfall performed better than models without a time lag. Models performed best using temperature data with a zero time lag. This is consistent with our intuition that rainfall might have an effect on the quality of breeding sites for some period of time while the effect of temperature should be instantaneous.

We considered two kinds of models, one set with regional parameters and one set with individual district level parameters. The inclusion of district level parameters improves the fit of the model. The effect of climate was different in different districts, which may be attributable to the wide variation in climate conditions in this mountainous peninsula. Our modeling effort was constrained by the limited amount of climate data available to fit the case data. If data were available from more weather stations, we might have been able to more effectively resolve the micro-scale impact of climate.

The processes affecting the spatial spread of CHIKV cases may have affected our results. Our models performed worse in districts that experienced cases later. Model 1, in which the transmission rate from mosquitoes to humans was associated with climate, was the best model when we considered district level parameters. The transmission intensities were high in all parts of southern Thailand at the time of emergence and then decreased due to changes in climate conditions. The spatial spread resumed the next season when rainfall totals and mean daily temperature increased.

The quality of surveillance could have also affected our results. Our models and the fit to cases depending greatly on the temporal distribution of the data (rather than absolute numbers) and so we expect our results to be robust to differences in reporting efficiency across districts. However, temporal changes in reporting efficiency could have greatly affected our results.

In this study, we have not considered a number of non-climate related covariates that could be important determinants of CHIKV incidence including population density, land-use, host and vector movement. The focus of our analysis was on temporal changes on climate on patterns of incidence. It could be that other covariates affect or confound the relationship of climate with CHIKV transmission. However, given that our results show that the specific temporal patterns of climate variation is associated with CHIKV, we do not expect that the inclusion of static ecological or sociological factors would change our inferences.

Our results are consistent with other studies that have found links between climate and chikungunya,^{22,23} however the impact of climate on chikungunya in Thailand, particular, the mechanistic impact of changes in temperature and rainfall have been unclear.^{24–26}

Conclusions

We find that the model that assumes that temperature and rainfall affects the fertility of mosquitoes using rainfall at a lag of three weeks provides the best fit to data from the 109 districts in

southern Thailand. However, the fit to all 109 districts with just three parameters was poor. The inclusion of district specific parameters greatly improved fit. We also find evidence that CHIKV transmission intensities were high in all parts of southern Thailand at the time of emergence and then decreased to low transmission levels in response to changes in climate conditions. Increases in rainfall totals and mean daily temperature during the next season were accompanied by a resumed spatial proliferation of CHIKV.

Supplementary data

Supplementary data are available at Transactions online (<http://trstmh.oxfordjournals.org/>).

Authors' contributions: SC and DATC conceived the study; SC and DATC designed the study protocol; SI collated the data and performed analysis; SI and WT reviewed the manuscript. SC and DATC drafted the manuscript; DATC critically revised the manuscript for intellectual content. All authors read and approved the final manuscript. SC and DATC are guarantors of the paper.

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