Title Page

Spatiotemporal patterns and climatic drivers of severe dengue in Thailand

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All authors declared that they have no any actual or potential conflict of interest.

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This study has not been published previously. It is not under consideration for publication elsewhere, and its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

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Dear Reviewer,

Thanks very much for your valuable comments on our manuscript. We've amended the manuscript accordingly and all revisions have been marked red.

Reviewer #1: 1. Introduction:

Line 93: Should use Aedes aegypti and Ae. albopictus.

Response: We've amended it accordingly (Line 93).

Line 101: Information about DF and climatic factors, should add more previous work about this in Thailand (e.g. Wongkoon et al., 2013: Weather factors influencing the occurrence of dengue factor in Nakhon Si Thammarat, Thailand).

Response: Thanks for the information provided. We've added this reference into the revision (Line 101).

Line 116: Add reference after "Lauer et al."

Response: Done (Line 116). Thanks.

2. Methods:

2.1 Data collection:

- Why the data collection except Bueng Kan? please explain.

Response: We obtained the data from the supplementary materials of a published paper (*Lauer et al. Proceedings of the National Academy of Science 2018; 115 (10) E2175-E2182*). Data in Bueng Kan were not available in the supplementary materials of this *PNAS* paper, and the authors did not explain why. We believe that not including Bueng Kan in the study did not affect our results as the main results of dengue spatiotemporal patterns were presented by province.

- Explain more details about sampling technique for sample 51 provinces from 77 provinces, Is it cover all regions of Thailand?

Response: We chose these 51 provinces because only these provinces had complete climate data and had less than 20% missing data on severe dengue (Lines 142-144). Yes, the selected 51 provinces cover all regions of Thailand, and the information on the corresponding region each province belongs to has been provided in Table S1 (Lines 144-146).

- What's the proportion from each region?

Response: The proportions of the available provinces in all provinces of each region have been presented in the revision (Lines 146-150). We've acknowledged that only having 51 provinces in the climate-dengue association assessment is a limitation of this study (Lines 354-356).

2.2 Data Analysis

- Should add more details about the Poisson regression model in the form of equation with DF and climatic factors, it's easy to understand.

Response: Done (Lines 177-183). Thanks.

3. Results

- Should add the results from the goodness of fit analysis with R^2 and residual plot.

Response: Thanks for the comment. We've added the residual plots for the main models in the revision (Figure S3 and Lines 237-239). Generalized linear model (GLM) combined with distributed lag non-linear model (DLNM) does not produce R^2 value. We have tried generalized additive model (GAM) with DLNM, and have presented the R^2 values for the main models in the below table for your reference. We did not show this result in the revision as we used GLM combined with DLNM in the main analysis.

Model	Lag 3 months	Lag 2 months	Lag 1 month
Mean temperature	0.724	0.722	0.721
Relative humidity	0.756	0.752	0.737

- Should add more information about the estimated coefficients in Poisson regression model

Response: Thanks for the comment. Figures 4A, 4B, 5A, and 5B have presented the log (RR) for the Poisson regression models.

Reference:

Shoud add more research on DHF and climatic factors in Thailand, e.g. Wongkoon et al., 2016: Spatio-temporal climate-based model of dengue infection in Southern Thailand.

Response: We’ve added this in the Discussion section as suggested (Lines 311-313).

Best regards,

Zhiwei Xu (On behalf of all co-authors)

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Abstract

Objectives: The burden of dengue fever in Thailand is considerable, yet there are few large-scale studies exploring the drivers of transmission. This study aimed to investigate the spatiotemporal patterns and climatic drivers of severe dengue in Thailand.

Methods: Geographic Information System (GIS) techniques and spatial cluster analysis were used to visualize the spatial distribution and detect high-risk clusters of severe dengue in 76 provinces of Thailand from January 1999 to December 2014. The seasonal patterns of severe dengue cases in different provinces were identified. A two-stage modelling approach combining a generalized linear model with a distributed lag non-linear model was used to quantify the effects of monthly mean temperature and relative humidity on the occurrence of severe dengue cases in 51 provinces of Thailand.

Results: Significant severe dengue clustering was detected, especially during epidemic years, and the location of these clusters showed substantial inter-annual variation. Severe dengue cases in Northern and Northeastern Thailand peaked in June to August and this pattern was stable across the study period, whereas the seasonality of severe dengue cases in other regions (especially Central Thailand) was less predictable. The risk of the occurrence of severe dengue cases increased with an increase in mean temperature in Northeastern Thailand, Central Thailand, and Southern Thailand, with peaks occurring between 24 °C to 30 °C in Northeastern Thailand and 27 °C to 29 °C in Southern Thailand West Coast, respectively. Relative humidity significantly affected the occurrence of severe dengue cases in Northeastern and Central Thailand, with optimal ranges observed for each region.

Conclusions: Our findings substantiate the potential for developing climate-based dengue early warning systems for Thailand, and have implications for informing pre-emptive vector control.

Keywords: Relative humidity; Severe dengue; Temperature; Thailand

1. Introduction

Dengue fever (DF), the most important arboviral disease in the world in terms of numbers affected (Bhatt et al., 2013), has caused substantial health and economic burdens to households, health care systems and governments (Castro et al., 2017; Shepard et al., 2016). More than half of the world's population is living in areas at risk of DF (Castro et al., 2017). Countries located in the tropics and subtropics, such as Thailand, are particularly prone, causing considerable costs that are both direct (e.g., medical cost) and indirect (e.g., reduced workplace productivity), of greatest burden to people who are at socioeconomic disadvantage (Lee et al., 2017b; Tozan et al., 2017). Dengue infection causes flu-like illness, and occasionally it develops into a life-threatening complication called severe dengue (also known as dengue hemorrhagic fever).

Understanding the spatial pattern of DF and identifying its dominant determinants will help facilitate judicious resource allocation, especially for resource-constrained countries and regions, and will help the development of tailored DF control and prevention programs (Acharya et al., 2016; Wangdi et al., 2018). The transmission of DF involves a complex interaction of the dengue virus, mosquitoes (mainly *Aedes aegypti* and *Ae. albopictus*) and susceptible people. Currently, DF prevention is largely reliant on vector control. Hence, the identification of seasonal DF pattern is a critical step in informing optimal timing of vector control intensification. Prior studies have widely reported distinct seasonal pattern of DF (Hu et al., 2010; Wangdi et al., 2018). However, studies explicitly exploring the dynamic change of DF seasonality across different years are still limited (Stoddard et al., 2014).

The potential drivers of DF transmission are multiple, but, as with all major vector-borne disease, climatic factors (e.g., temperature, relative humidity, and rainfall) are known to be strongly associated with DF transmission (Morin et al., 2013; Wongkoon et al., 2013b). These climatic factors affect DF transmission through their impacts on dengue virus replication and transmission, vector ecology, as well as human behaviors (Morin et al., 2013; Xu et al., 2017). However, due to the complex nature of climate-DF relationship, the dominant climatic drivers of DF transmission may vary regionally (Lauer et al., 2018) and this association is often non-linear (Wu et al., 2018; Xu et al., 2017). Large-scale studies are required to inform projections of DF risk areas under climate change scenarios (Ebi and Nealon, 2016) and yet there are relatively few examples of these (Johansson et al., 2009; Lee et al., 2017a).

Seventy percent of severe dengue occurs in Asia (Bhatt et al., 2013), and the disease and economic burdens of severe dengue in Thailand are considerable (Bhatt et al., 2013; Lee et al., 2017b; Tozan et al., 2017). The tropical climate of Thailand encourages very high mosquito density and is ideal for the transmission of DF. Further, Thailand is a popular tourist spot in Asia, a source of labor for other countries and increasingly industrialized. The increased human movement associated with these characteristics will increase the importations of virus from other endemic areas and may contribute to seeding dengue epidemics (Tian et al., 2017). Regarding the associations between climatic factors and severe dengue in Thailand, Lauer et al. (2018) used models with severe dengue incidence only and models with the inclusion of climatic covariates to forecast several dengue incidence in Thailand, and found the inclusion of climatic covariates did not consistently add value to the forecasts compared with the incidence-only models. They speculated that this finding was either because the associations of climate covariates with dengue differ across time and space, or because the associations are spurious. No study has substantiated their speculations so far, and we attempted to fill this gap in the present study.

This study used monthly data on severe dengue cases in Thailand between January 1999 and December 2014 to address three objectives: 1) Identify the possible high-risk clusters of severe dengue in Thailand; 2) Compare the inter-annual seasonality of severe dengue in different provinces of Thailand from 1999 to 2014; and 3) Quantify the associations of mean temperature and relative humidity with severe dengue in Thailand and regions within it.

2. Methods

2.1 Data collection

Thailand is situated in the tropical area of Southeast Asia between latitudes 5° 37' N to 20° 27' N and longitudes 97° 22' E to 105° 37' E. Its climate is under the influence of seasonal monsoon winds. Thailand can be divided into six subnational regions according to the climate pattern and meteorological conditions, namely Northern Thailand, Northeastern Thailand, Central Thailand, Eastern Thailand, Southern Thailand West Coast, and Southern Thailand East Coast (Supplementary Figure S1).

Thailand has 77 provinces. Monthly data on severe dengue cases and yearly population data from 1999 to 2014 for each province of Thailand, except for Bueng Kan, were obtained from a published paper (Lauer et al., 2018). Daily data on relative humidity and mean temperature for 61 provinces, from 1999 to 2008, were supplied by Meteorological Department, Ministry of Digital Economy and Society, Thailand. We aggregated the daily data on relative humidity and mean temperature into monthly data by calculating the mean of the daily values. To quantify the associations of mean temperature and relative humidity with severe dengue, 51 provinces with complete climate data and less than 20% missing data on severe dengue were selected. Details of these 51 provinces (the corresponding subnational region it belongs to, average value of mean temperature, and average value of relative humidity) were given in Supplementary Table S1. The proportions of these 51 provinces in all provinces of Northern Thailand, Northeastern Thailand, Central Thailand, Eastern Thailand, Southern Thailand West Coast, and Southern Thailand East Coast were 60% (9/15), 60% (12/20), 50% (9/18), 75% (6/8), 83% (5/6), and 100% (10/10), respectively.

2.2 Data analysis

The spatiotemporal pattern analysis used the whole data set from 76 provinces. As there were missing values of monthly severe dengue data in some provinces, it was not possible for us to sum the monthly severe dengue data into annual estimates for each province. As such, for each year, we divided the average value of severe dengue case numbers in available months by yearly population to obtain the severe dengue incidence for every province. Spatial cluster analysis was conducted to identify the randomly distributed severe dengue cases and to explore high-risk clusters. A Poisson regression model was performed to compute the mean relative risk of severe dengue for each cluster (Qi et al., 2012).

Current evidence suggests that the associations of mean temperature and relative humidity with the occurrence of DF cases can be non-linear (Wu et al., 2018). Therefore we used a generalized linear model and a distributed lag non-linear model to examine the effects of mean temperature and relative humidity on the occurrence of severe dengue cases (Gasparrini et al., 2010). One to three months of lag were used in the analysis based on the findings of prior studies in Guangzhou, China, and Mekong Delta region, Vietnam (Phung et al., 2016; Wu et al., 2018). Specifically, there were two stages in the analysis. Herein, we use mean temperature as an example to clarify the details. Stage I: for each province, the relationship between mean temperature and the occurrence of severe dengue cases was modelled using a cross-basis. The cross-basis was defined by a B-spline with two degrees of freedom (*df*s) for the space of mean temperature. The spline for mean temperature was centered at the value corresponding to the point of minimum severe dengue risk. Month and year were included as dummy variables in the model to control for seasonality and long-term trend. Stage II: multivariate meta-analysis was used to pool the association of mean temperature with the occurrence of severe dengue case (Gasparrini and Armstrong, 2013). Finally, we obtained the associations between mean temperature and occurrence of severe dengue cases across three lags (one, two, and three months) for subnational regions (i.e., Northern, Northeastern, Central, Eastern, Southern Thailand West Coast, and Southern Thailand East Coast) and for the whole of Thailand. The following equation was used in the stage I analysis:

$Y_t \sim \text{Poisson}(\mu_t)$

$\text{Log}(\mu_t) = \alpha + \beta T_{t,l} + \eta_1 \text{Month} + \eta_2 \text{Year}$

Where t is the month of the observation, Y_t is the observed monthly dengue number in month t, α is the model intercept, $T_{t,l}$ is a matrix obtained by applying the DLNM to temperature, β is the vector of coefficients for $T_{t,l}$ and l is the lag months. Sensitivity analysis for severe dengue seasonality assessment was performed by filling in missing severe dengue data using imputation approach. Visualization of monthly severe dengue incidence and identification of high-risk clusters was conducted using ArcGIS 10.5 (ESRI Inc., Redlands, CA, USA) and SaTScan. Modelling the association of mean temperature and relative humidity with severe dengue was done using "dlnm" (Gasparini, 2011) and "mvmeta" packages, and missing data were filled in using the "zoo" package in R 3.4.4.

3. Results

Temporal pattern of severe dengue cases in Thailand and subnational regions

Analysis of decomposed pattern of monthly severe dengue cases in Thailand from 1999 to 2014 suggested that there were severe dengue epidemics in 2001, 2002, 2010, and 2013 (Figure 1A). A distinct seasonality of severe dengue occurrence in Thailand was observed in Figure 1A with considerable inter-annual variation in the regions affected (Figure 1B).

Spatial patterns of severe dengue incidence across different years

Figure 2A illustrated the spatial pattern of monthly severe dengue incidence in Thailand each year and Figure 2B illustrated the spatial shifting in the primary cluster each year. Monthly severe dengue incidence in provinces of Southern Thailand (i.e., Southern Thailand West Coast and Southern Thailand East Coast) appeared to be consistently high across different epidemic years. Monthly severe dengue incidence in Central Thailand was amongst the highest in 2001 but remained low during other epidemic years (i.e., 2002, 2010, and 2013).

Seasonality of severe dengue cases in Thailand and subnational regions

Figure 3A delineated the seasonal patterns of severe dengue cases in all 76 selected provinces (from top to bottom: Northern Thailand to Southern Thailand West Coast), suggesting that there was a distinct seasonality of severe dengue cases for most provinces of Thailand. Specifically, severe dengue cases peaked in June to August in Northern and Northeastern Thailand. The seasonality of severe dengue cases in Central Thailand was less distinct than upper Thailand (i.e., Northern and Northeastern Thailand). Severe dengue cases in Eastern Thailand, Southern Thailand East Coast, and Southern Thailand West Coast consistently peaked in May to August.

Sensitivity analysis results showed that the seasonal patterns of severe dengue cases in these 76 provinces did not change substantially after filling in the missing data (Figure S2).

Figure 3B showed the year to year change in the seasonality of severe dengue cases in subnational regions, indicating that the seasonality of severe dengue cases in Northern and Northeastern Thailand was stable across years. In comparison, the seasonality of severe dengue cases in Central Thailand changed substantially from year to year. The seasonality of severe dengue cases in Eastern Thailand, Southern Thailand West Coast, and Southern Thailand East Coast also changed from year to year, although not as dramatically as Central Thailand.

Effects of mean temperature and relative humidity on the occurrence of severe dengue cases in Thailand and subnational regions

Figures 4 (A and B) and 5 (A and B) presented the effects of mean temperature and relative humidity on the occurrence of severe dengue cases. Complete results (log (RR) and 95% confidence interval) for three-month lag were presented because this lag corresponded to the lowest quasi Akaike's Information Criterion (QAIC).

In general, mean temperature significantly affected the occurrence of severe dengue cases in Thailand (Figure 4A). Specifically, the occurrence of severe dengue cases in Central Thailand was most sensitive to mean temperature effect, followed by Southern Thailand East Coast, Southern Thailand West Coast, and Northeastern Thailand (Figure 4B). Interestingly, the shape of the relationship between mean temperature and the occurrence of severe dengue, as well as the threshold temperature (i.e., temperature corresponding to the lowest risk of severe dengue case occurrence) varied across different regions. Relative humidity also had a significant effect on the occurrence of severe dengue cases in Thailand (Figure 5A). The occurrence of severe dengue cases in Northeastern Thailand was most sensitive to relative humidity effect, followed by Central Thailand (Figure 5B). The shape of the relationship between relative humidity and the occurrence of severe dengue cases, as well as the threshold relative humidity (i.e., relative humidity corresponding to the lowest risk of severe dengue case occurrence) also varied across these two sensitive regions. Figure S3 presented the residual plots of the mean temperature and relative humidity models in Figure 4A and Figure 5A. We did not observe distinct patterns in these residual plots.

4. Discussion

This study presents one of the two attempts to analyze the spatiotemporal patterns of severe dengue in Thailand (Lauer et al., 2018). Results demonstrate that while local severe dengue clusters arise in different locations year-to-year making them difficult to predict, consistent regional patterns were identified and these can be exploited in developing forecasting tools. Severe dengue cases consistently peaked from June to August in Northern and Northeastern Thailand. Additionally, severe dengue was driven by mean temperature in Central and Southern Thailand, whereas it was more driven by relative humidity in Northeastern Thailand. The heterogeneous associations of mean temperature and relative humidity with severe dengue in different regions of Thailand suggest that considering regional heterogeneity when including climatic covariates in the incidence-only model to forecast dengue incidence may increase the accuracy of the forecasting (Lauer et al., 2018).

The intensity of severe dengue transmission depends on the circulating serotype of dengue virus, mosquito density, the immunity level of population, and the environment. As such, we tried to understand the possible reasons behind the shifting pattern of high-risk cluster across different epidemic years in Thailand from these four aspects. Although the increase in average age of severe dengue patients in Thailand has been widely documented (Cummings et al., 2009), children remained the predominant group affected by severe dengue (Limkittikul et al., 2014), and therefore the varying high-risk cluster was unlikely to be caused by spatial change in herd immunity. The proportions of different dengue virus serotypes (i.e., DENV-1, DENV-2, DENV-3, and DENV-4) had an appreciable change from 2005 to 2009 and there was an increase in the proportion of DENV-2 in all subnational regions (Limkittikul et al., 2014). Due to the lack of mosquito density data, we were unable to identify the roles that mosquito density played in driving the spatiotemporal pattern of severe dengue, but Xu et al. have found that mosquito density and climate variation largely explained the temporal dynamic of DFs in Guangzhou, China (Xu et al., 2017). Hu et al. have also observed that maximum temperature and rainfall affected spatial pattern of DFs in Queensland, Australia (Hu et al., 2012). Thus, we could not rule out the possibility that mosquito density and climatic factors may work independently or interactively to affect the spatial pattern change of severe dengue in Thailand.

Monsoon weather pattern predominates in Thailand, and the peak season of severe dengue cases in Thailand that we observed in this study coincided with Thailand's rainy season (May/June to October). A study in Sisaket, Thailand, has observed that numbers of *Aedes* larvae were higher in the rainy season than in the winter and summer seasons (Wongkoon et al., 2013a). However, Johansson et al. found that the effect of rainfall on DF in Thailand was not stable (Johansson et al., 2009). Regarding the possible entomological factors that caused dengue seasonality in Thailand, Hartley et al. found that vector mortality and biting rate stood out (Hartley et al., 2002). The distinct and stable seasonality in Northern and Northeastern Thailand observed in this study suggest that pre-season vector control in these regions might ease severe dengue burden (Vogel, 2018). The less-distinct and temporally-varying severe dengue seasonality in Central Thailand could partially be attributable to the fact that water containers were present all year around (Tonn et al., 1969). Climatic factors may also play a role in driving severe dengue seasonality in Central Thailand (Do et al., 2014), especially in light of the significant findings on the effects of mean temperature and relative humidity on the occurrence of severe dengue cases in Central Thailand in this study.

In general, increased ambient temperature speeds up dengue virus replication rate within the mosquitos and shortens its extrinsic incubation period, facilitating its transmission (Morin et al., 2013). Ambient temperature also acts as an important regulator of mosquito development and survival, as well as mosquito reproductive behavior (Morin et al., 2013). The complexity of temperature impacts on dengue viruses and mosquitoes, as well as the findings from previous studies (Wu et al., 2018; Xu et al., 2017), motivated us to assess the possible non-linear relationship between temperature and the occurrence of severe dengue cases. We observed that generally there was an optimal temperature range for the occurrence of severe dengue cases in Thailand, although we also observed heterogeneity in terms of this temperature range across different regions. Specifically, the occurrence of severe dengue cases roughly favoured an ambient mean temperature range of 24°C to 30°C in Northeastern Thailand, and 27°C to 29°C in Southern Thailand West Coast. In Central Thailand and Southern Thailand East Coast, the risk of the occurrence of severe dengue cases increased when temperature increased, and remained stable or dipped slightly when temperature reached high level. Prior studies in Thailand have also found significant effect of temperature on the occurrence of DF cases or severe dengue cases (Johansson et al., 2009; Nitatpattana et al., 2007; Promprou et al., 2005; Thammapalo et al., 2005), although all of them assumed a linear relationship between temperature and dengue occurrence. Rueda et al. have found that the development rates of immature *Aedes aegypti* increased with incubation temperatures to 34 °C and then slowed, and *Ae. aegypti* survival peaked at 27°C (Rueda et al., 1990), which also indicated that there may be an optimal temperature range for dengue transmission (Mordecai et al., 2017).

The present study has also found significant effect of relative humidity on the occurrence of severe dengue cases in Northeastern Thailand and Central Thailand. Similar to temperature, there were also optimal relative humidity ranges that the occurrence of severe dengue cases favoured. Promprou et al. have found a significant relationship between relative humidity and the occurrence of severe dengue cases in Southern Thailand using correlation analysis and linear regression analysis (Promprou et al., 2005). Wongkoon et al. have also observed that relative humidity was an important climate predictor of dengue case number in Southern Thailand (Wongkoon et al., 2018). Studies conducted in Manila (Philippines) (Sumi et al., 2016), Mekong Delta region (Vietnam) (Dung et al., 2016), and Singapore (Earnest et al., 2011) have found an increase of DF cases with the increase of relative humidity, but Xiang et al. have found that, when relative humidity was beyond 78.9%, DF cases decreased when relative humidity increased (Xiang et al., 2017). The heterogeneous findings in these studies might partially be due to the assumption made on the nature of relative humidity and DF relationship prior to data analysis. Biologically, *Ae. aegypti* eggs can tolerate a wide range of relative humidity values, but *Ae. albopictus* eggs favor high relative humidity (Juliano et al., 2002). Nevertheless, mosquitoes may bite more at low humidity, possibly increasing the transmission of dengue virus (Wu et al., 2009). Thoroughly understanding how climatic factors affect the transmission of dengue virus and the occurrence of severe dengue cases is of great significance because climate change will increase global surface temperature and may alter the distribution of relative humidity among regions.

The associations between climatic factors and the occurrence of severe dengue cases that we found in this study suggest the possibility of developing a dengue early warning system based on climate, and the appreciable heterogeneity of these associations across different regions indicates that region-specific early warning might be more ideal. Optimal lead time is a pivotal factor in developing dengue early warning system. The three-month-optimal-lag that we observed in this study is consistent with findings from Cambodia (Choi et al., 2016) but inconsistent with findings from the Mekong Delta region, Vietnam (Dung et al., 2016), and Guangzhou, China (Xiang et al., 2017). A prior study in Singapore reported that a dengue early warning forecast given three months prior to the onset of a possible epidemic would give local authorities enough time to mitigate an outbreak (Hii et al., 2012). The heterogeneous lag patterns across different countries observed in existing literature suggested that optimal lead time for dengue early warning might be country- or region-specific.

This study has two major strengths. First, we explored the dynamic spatial patterns of severe dengue incidence across different years in Thailand, and described regional differences in terms of the seasonality of severe dengue cases, facilitating future dengue prevention and control resource allocation and implementation of vector control. Second, we quantified the effects of mean temperature and relative humidity on the occurrence of severe dengue cases. The identifications of climate-sensitive regions and optimal ranges of mean temperature and relative humidity for the occurrence of severe dengue cases may shed some light on adequately understanding how climate change may affect the occurrence of severe dengue cases in Thailand in the future. However, projecting future severe dengue burden under climate change scenarios still needs to consider many other factors (e.g., mosquito density and future shifting in demographics, etc.). Three weaknesses of this study should also be acknowledged. First, we were unable to examine how mosquito density may affect the spatiotemporal patterns of severe dengue as we did not have mosquito data. Second, we also did not have data on rainfall and evaporation, which restricted us from exploring the relationship between rainfall, evaporation and the occurrence of severe dengue cases in Thailand, although a recent study has found that relative humidity appeared to be the most important climatic factor in predicting the temporal pattern of dengue incidence in Manila, the Philippines (Carvajal et al., 2018). Third, we were only able to quantify the associations of mean temperature and relative humidity with severe dengue in 51 provinces due to data unavailability.

5. Conclusion

Severe dengue in Thailand clustered in certain provinces, especially during epidemic years. The high-risk cluster changed across years, calling for further research to understand the fundamental reasons behind this pattern. Pre-season vector control in Northern and Northeastern Thailand could potentially ease severe dengue burden. Regional heterogeneity existed in terms of the effects of mean temperature and relative humidity on the occurrence of severe dengue cases in Thailand. As climate change continues, severe dengue burden in Central Thailand, Northeastern Thailand, and Southern Thailand may change in the future, and evaluating the magnitude of this possible change may help future dengue resource allocation in Thailand.

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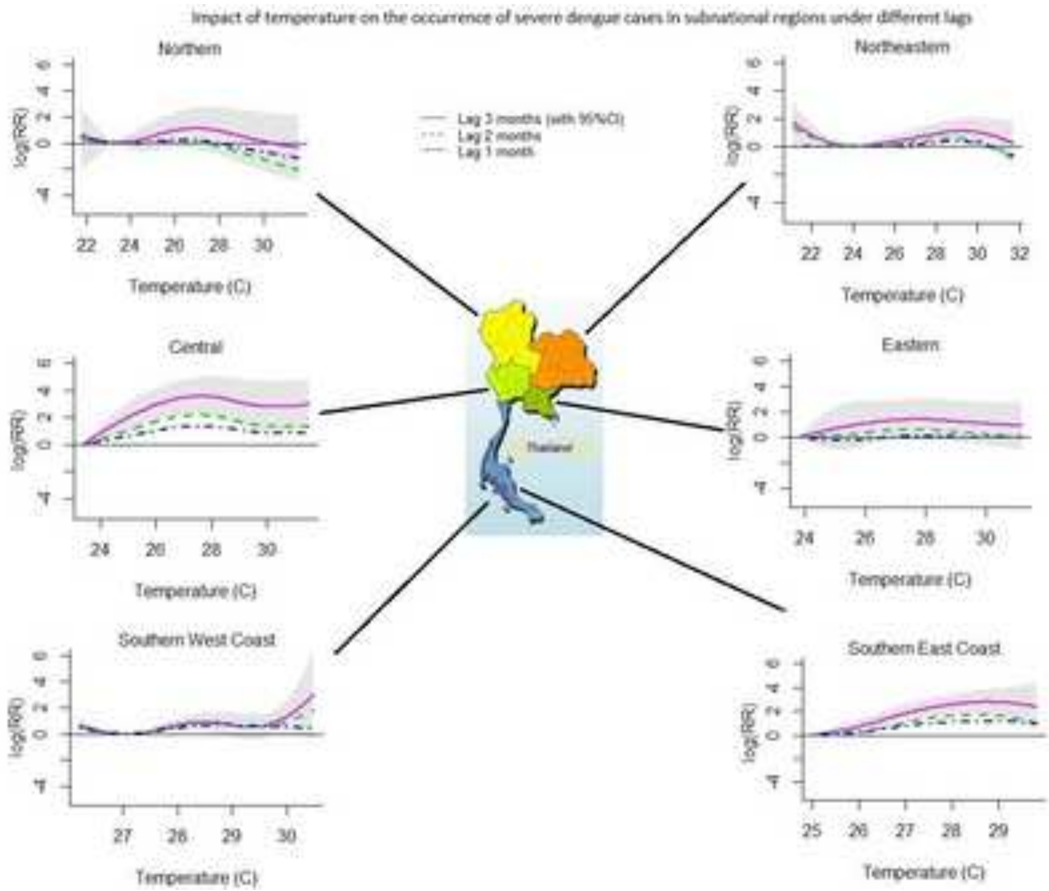
*Graphical Abstract



***Highlights (for review : 3 to 5 bullet points (maximum 85 characters including spaces per bullet point)**

Highlights

1. High risk cluster of severe dengue in Thailand showed substantial inter-annual variation;
2. Severe dengue cases peaked in June to August in Northern and Northeastern Thailand and this seasonal pattern was stable across years;
3. Mean temperature affected the occurrence of severe dengue cases in Northeastern, Central and Southern Thailand;
4. Relative humidity affected the occurrence of severe dengue cases in Northeastern and Central Thailand.

Spatiotemporal patterns and climatic drivers of severe dengue in Thailand

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Abstract

Objectives: The burden of dengue fever in Thailand is considerable, yet there are few large-scale studies exploring the drivers of transmission. This study aimed to investigate the spatiotemporal patterns and climatic drivers of severe dengue in Thailand.

Methods: Geographic Information System (GIS) techniques and spatial cluster analysis were used to visualize the spatial distribution and detect high-risk clusters of severe dengue in 76 provinces of Thailand from January 1999 to December 2014. The seasonal patterns of severe dengue cases in different provinces were identified. A two-stage modelling approach combining a generalized linear model with a distributed lag non-linear model was used to quantify the effects of monthly mean temperature and relative humidity on the occurrence of severe dengue cases in 51 provinces of Thailand.

Results: Significant severe dengue clustering was detected, especially during epidemic years, and the location of these clusters showed substantial inter-annual variation. Severe dengue cases in Northern and Northeastern Thailand peaked in June to August and this pattern was stable across the study period, whereas the seasonality of severe dengue cases in other regions (especially Central Thailand) was less predictable. The risk of the occurrence of severe dengue cases increased with an increase in mean temperature in Northeastern Thailand, Central Thailand, and Southern Thailand, with peaks occurring between 24 °C to 30 °C in Northeastern Thailand and 27 °C to 29 °C in Southern Thailand West Coast, respectively. Relative humidity significantly affected the occurrence of severe dengue cases in Northeastern and Central Thailand, with optimal ranges observed for each region.

Conclusions: Our findings substantiate the potential for developing climate-based dengue early warning systems for Thailand, and have implications for informing pre-emptive vector control.

Keywords: Relative humidity; Severe dengue; Temperature; Thailand

1. Introduction

Dengue fever (DF), the most important arboviral disease in the world in terms of numbers affected (Bhatt et al., 2013), has caused substantial health and economic burdens to households, health care systems and governments (Castro et al., 2017; Shepard et al., 2016). More than half of the world's population is living in areas at risk of DF (Castro et al., 2017). Countries located in the tropics and subtropics, such as Thailand, are particularly prone, causing considerable costs that are both direct (e.g., medical cost) and indirect (e.g., reduced workplace productivity), of greatest burden to people who are at socioeconomic disadvantage (Lee et al., 2017b; Tozan et al., 2017). Dengue infection causes flu-like illness, and occasionally it develops into a life-threatening complication called severe dengue (also known as dengue hemorrhagic fever).

Understanding the spatial pattern of DF and identifying its dominant determinants will help facilitate judicious resource allocation, especially for resource-constrained countries and regions, and will help the development of tailored DF control and prevention programs (Acharya et al., 2016; Wangdi et al., 2018). The transmission of DF involves a complex interaction of the dengue virus, mosquitoes (mainly *Aedes aegypti* and *Ae. albopictus*) and susceptible people. Currently, DF prevention is largely reliant on vector control. Hence, the identification of seasonal DF pattern is a critical step in informing optimal timing of vector control intensification. Prior studies have widely reported distinct seasonal pattern of DF (Hu et al., 2010; Wangdi et al., 2018). However, studies explicitly exploring the dynamic change of DF seasonality across different years are still limited (Stoddard et al., 2014).

The potential drivers of DF transmission are multiple, but, as with all major vector-borne disease, climatic factors (e.g., temperature, relative humidity, and rainfall) are known to be strongly associated with DF transmission (Morin et al., 2013; Wongkoon et al., 2013b). These climatic factors affect DF transmission through their impacts on dengue virus replication and transmission, vector ecology, as well as human behaviors (Morin et al., 2013; Xu et al., 2017). However, due to the complex nature of climate-DF relationship, the dominant climatic drivers of DF transmission may vary regionally (Lauer et al., 2018) and this association is often non-linear (Wu et al., 2018; Xu et al., 2017). Large-scale studies are required to inform projections of DF risk areas under climate change scenarios (Ebi and Nealon, 2016) and yet there are relatively few examples of these (Johansson et al., 2009; Lee et al., 2017a).

Seventy percent of severe dengue occurs in Asia (Bhatt et al., 2013), and the disease and economic burdens of severe dengue in Thailand are considerable (Bhatt et al., 2013; Lee et al., 2017b; Tozan et al., 2017). The tropical climate of Thailand encourages very high mosquito density and is ideal for the transmission of DF. Further, Thailand is a popular tourist spot in Asia, a source of labor for other countries and increasingly industrialized. The increased human movement associated with these characteristics will increase the importations of virus from other endemic areas and may contribute to seeding dengue epidemics (Tian et al., 2017). Regarding the associations between climatic factors and severe dengue in Thailand, Lauer et al. (2018) used models with severe dengue incidence only and models with the inclusion of climatic covariates to forecast several dengue incidence in Thailand, and found the inclusion of climatic covariates did not consistently add value to the forecasts compared with the incidence-only models. They speculated that this finding was either because the associations of climate covariates with dengue differ across time and space, or because the associations are spurious. No study has substantiated their speculations so far, and we attempted to fill this gap in the present study.

This study used monthly data on severe dengue cases in Thailand between January 1999 and December 2014 to address three objectives: 1) Identify the possible high-risk clusters of severe dengue in Thailand; 2) Compare the inter-annual seasonality of severe dengue in different provinces of Thailand from 1999 to 2014; and 3) Quantify the associations of mean temperature and relative humidity with severe dengue in Thailand and regions within it.

2. Methods

2.1 Data collection

Thailand is situated in the tropical area of Southeast Asia between latitudes 5^{o} 37' N to 20^{o} 27' N and longitudes 97^{o} 22' E to 105^{o} 37' E. Its climate is under the influence of seasonal monsoon winds. Thailand can be divided into six subnational regions according to the climate pattern and meteorological conditions, namely Northern Thailand, Northeastern Thailand, Central Thailand, Eastern Thailand, Southern Thailand West Coast, and Southern Thailand East Coast (Supplementary Figure S1).

Thailand has 77 provinces. Monthly data on severe dengue cases and yearly population data from 1999 to 2014 for each province of Thailand, except for Bueng Kan, were obtained from a published paper (Lauer et al., 2018). Daily data on relative humidity and mean temperature for 61 provinces, from 1999 to 2008, were supplied by Meteorological Department, Ministry of Digital Economy and Society, Thailand. We aggregated the daily data on relative humidity and mean temperature into monthly data by calculating the mean of the daily values. To quantify the associations of mean temperature and relative humidity with severe dengue, 51 provinces with complete climate data and less than 20% missing data on severe dengue were selected. Details of these 51 provinces (the corresponding subnational region it belongs to, average value of mean temperature, and average value of relative humidity) were given in Supplementary Table S1. The proportions of these 51 provinces in all provinces of Northern Thailand, Northeastern Thailand, Central Thailand, Eastern Thailand, Southern Thailand West Coast, and Southern Thailand East Coast were 60% (9/15), 60% (12/20), 50% (9/18), 75% (6/8), 83% (5/6), and 100% (10/10), respectively.

2.2 Data analysis

The spatiotemporal pattern analysis used the whole data set from 76 provinces. As there were missing values of monthly severe dengue data in some provinces, it was not possible for us to sum the monthly severe dengue data into annual estimates for each province. As such, for each year, we divided the average value of severe dengue case numbers in available months by yearly population to obtain the severe dengue incidence for every province. Spatial cluster analysis was conducted to identify the randomly distributed severe dengue cases and to explore high-risk clusters. A Poisson regression model was performed to compute the mean relative risk of severe dengue for each cluster (Qi et al., 2012).

Current evidence suggests that the associations of mean temperature and relative humidity with the occurrence of DF cases can be non-linear (Wu et al., 2018). Therefore we used a generalized linear model and a distributed lag non-linear model to examine the effects of mean temperature and relative humidity on the occurrence of severe dengue cases (Gasparrini et al., 2010). One to three months of lag were used in the analysis based on the findings of prior studies in Guangzhou, China, and Mekong Delta region, Vietnam (Phung et al., 2016; Wu et al., 2018). Specifically, there were two stages in the analysis. Herein, we use mean temperature as an example to clarify the details. Stage I: for each province, the relationship between mean temperature and the occurrence of severe dengue cases was modelled using a cross-basis. The cross-basis was defined by a B-spline with two degrees of freedom (*df*s) for the space of mean temperature. The spline for mean temperature was centered at the value corresponding to the point of minimum severe dengue risk. Month and year were included as dummy variables in the model to control for seasonality and long-term trend. Stage II: multivariate meta-analysis was used to pool the association of mean temperature with the occurrence of severe dengue case (Gasparrini and Armstrong, 2013). Finally, we obtained the associations between mean temperature and occurrence of severe dengue cases across three lags (one, two, and three months) for subnational regions (i.e., Northern, Northeastern, Central, Eastern, Southern Thailand West Coast, and Southern Thailand East Coast) and for the whole of Thailand. The following equation was used in the stage I analysis:

$$Y_t \sim \text{Poisson}(\mu_t)$$

$$\text{Log}(\mu_t) = \alpha + \beta\, T_{t,l} + \eta_1\, \text{Month} + \eta_2 \text{Year}$$

Where t is the month of the observation, Y_t is the observed monthly dengue number in month t, α is the model intercept, $T_{t,l}$ is a matrix obtained by applying the DLNM to temperature, β is the vector of coefficients for $T_{t,l}$ and l is the lag months. Sensitivity analysis for severe dengue seasonality assessment was performed by filling in missing severe dengue data using imputation approach. Visualization of monthly severe dengue incidence and identification of high-risk clusters was conducted using ArcGIS 10.5 (ESRI Inc., Redlands, CA, USA) and SaTScan. Modelling the association of mean temperature and relative humidity with severe dengue was done using “dlnm” (Gasparini, 2011) and “mvmeta” packages, and missing data were filled in using the “zoo” package in R 3.4.4.

3. Results

Temporal pattern of severe dengue cases in Thailand and subnational regions

Analysis of decomposed pattern of monthly severe dengue cases in Thailand from 1999 to 2014 suggested that there were severe dengue epidemics in 2001, 2002, 2010, and 2013 (Figure 1A). A distinct seasonality of severe dengue occurrence in Thailand was observed in Figure 1A with considerable inter-annual variation in the regions affected (Figure 1B).

Spatial patterns of severe dengue incidence across different years

Figure 2A illustrated the spatial pattern of monthly severe dengue incidence in Thailand each year and Figure 2B illustrated the spatial shifting in the primary cluster each year. Monthly severe dengue incidence in provinces of Southern Thailand (i.e., Southern Thailand West Coast and Southern Thailand East Coast) appeared to be consistently high across different epidemic years. Monthly severe dengue incidence in Central Thailand was amongst the highest in 2001 but remained low during other epidemic years (i.e., 2002, 2010, and 2013).

Seasonality of severe dengue cases in Thailand and subnational regions

Figure 3A delineated the seasonal patterns of severe dengue cases in all 76 selected provinces (from top to bottom: Northern Thailand to Southern Thailand West Coast), suggesting that there was a distinct seasonality of severe dengue cases for most provinces of Thailand. Specifically, severe dengue cases peaked in June to August in Northern and Northeastern Thailand. The seasonality of severe dengue cases in Central Thailand was less distinct than upper Thailand (i.e., Northern and Northeastern Thailand). Severe dengue cases in Eastern Thailand, Southern Thailand East Coast, and Southern Thailand West Coast consistently peaked in May to August.

Sensitivity analysis results showed that the seasonal patterns of severe dengue cases in these 76 provinces did not change substantially after filling in the missing data (Figure S2).

Figure 3B showed the year to year change in the seasonality of severe dengue cases in subnational regions, indicating that the seasonality of severe dengue cases in Northern and Northeastern Thailand was stable across years. In comparison, the seasonality of severe dengue cases in Central Thailand changed substantially from year to year. The seasonality of severe dengue cases in Eastern Thailand, Southern Thailand West Coast, and Southern Thailand East Coast also changed from year to year, although not as dramatically as Central Thailand.

Effects of mean temperature and relative humidity on the occurrence of severe dengue cases in Thailand and subnational regions

Figures 4 (A and B) and 5 (A and B) presented the effects of mean temperature and relative humidity on the occurrence of severe dengue cases. Complete results (log (RR) and 95% confidence interval) for three-month lag were presented because this lag corresponded to the lowest quasi Akaike's Information Criterion (QAIC).

In general, mean temperature significantly affected the occurrence of severe dengue cases in Thailand (Figure 4A). Specifically, the occurrence of severe dengue cases in Central Thailand was most sensitive to mean temperature effect, followed by Southern Thailand East Coast, Southern Thailand West Coast, and Northeastern Thailand (Figure 4B). Interestingly, the shape of the relationship between mean temperature and the occurrence of severe dengue, as well as the threshold temperature (i.e., temperature corresponding to the lowest risk of severe dengue case occurrence) varied across different regions. Relative humidity also had a significant effect on the occurrence of severe dengue cases in Thailand (Figure 5A). The occurrence of severe dengue cases in Northeastern Thailand was most sensitive to relative humidity effect, followed by Central Thailand (Figure 5B). The shape of the relationship between relative humidity and the occurrence of severe dengue cases, as well as the threshold relative humidity (i.e., relative humidity corresponding to the lowest risk of severe dengue case occurrence) also varied across these two sensitive regions. Figure S3 presented the residual plots of the mean temperature and relative humidity models in Figure 4A and Figure 5A. We did not observe distinct patterns in these residual plots.

4. Discussion

This study presents one of the two attempts to analyze the spatiotemporal patterns of severe dengue in Thailand (Lauer et al., 2018). Results demonstrate that while local severe dengue clusters arise in different locations year-to-year making them difficult to predict, consistent regional patterns were identified and these can be exploited in developing forecasting tools. Severe dengue cases consistently peaked from June to August in Northern and Northeastern Thailand. Additionally, severe dengue was driven by mean temperature in Central and Southern Thailand, whereas it was more driven by relative humidity in Northeastern Thailand. The heterogeneous associations of mean temperature and relative humidity with severe dengue in different regions of Thailand suggest that considering regional heterogeneity when including climatic covariates in the incidence-only model to forecast dengue incidence may increase the accuracy of the forecasting (Lauer et al., 2018).

The intensity of severe dengue transmission depends on the circulating serotype of dengue virus, mosquito density, the immunity level of population, and the environment. As such, we tried to understand the possible reasons behind the shifting pattern of high-risk cluster across different epidemic years in Thailand from these four aspects. Although the increase in average age of severe dengue patients in Thailand has been widely documented (Cummings et al., 2009), children remained the predominant group affected by severe dengue (Limkittikul et al., 2014), and therefore the varying high-risk cluster was unlikely to be caused by spatial change in herd immunity. The proportions of different dengue virus serotypes (i.e., DENV-1, DENV-2, DENV-3, and DENV-4) had an appreciable change from 2005 to 2009 and there was an increase in the proportion of DENV-2 in all subnational regions (Limkittikul et al., 2014). Due to the lack of mosquito density data, we were unable to identify the roles that mosquito density played in driving the spatiotemporal pattern of severe dengue, but Xu et al. have found that mosquito density and climate variation largely explained the temporal dynamic of DFs in Guangzhou, China (Xu et al., 2017). Hu et al. have also observed that maximum temperature and rainfall affected spatial pattern of DFs in Queensland, Australia (Hu et al., 2012). Thus, we could not rule out the possibility that mosquito density and climatic factors may work independently or interactively to affect the spatial pattern change of severe dengue in Thailand.

Monsoon weather pattern predominates in Thailand, and the peak season of severe dengue cases in Thailand that we observed in this study coincided with Thailand's rainy season (May/June to October). A study in Sisaket, Thailand, has observed that numbers of *Aedes* larvae were higher in the rainy season than in the winter and summer seasons (Wongkoon et al., 2013a). However, Johansson et al. found that the effect of rainfall on DF in Thailand was not stable (Johansson et al., 2009). Regarding the possible entomological factors that caused dengue seasonality in Thailand, Hartley et al. found that vector mortality and biting rate stood out (Hartley et al., 2002). The distinct and stable seasonality in Northern and Northeastern Thailand observed in this study suggest that pre-season vector control in these regions might ease severe dengue burden (Vogel, 2018). The less-distinct and temporally-varying severe dengue seasonality in Central Thailand could partially be attributable to the fact that water containers were present all year around (Tonn et al., 1969). Climatic factors may also play a role in driving severe dengue seasonality in Central Thailand (Do et al., 2014), especially in light of the significant findings on the effects of mean temperature and relative humidity on the occurrence of severe dengue cases in Central Thailand in this study.

In general, increased ambient temperature speeds up dengue virus replication rate within the mosquitos and shortens its extrinsic incubation period, facilitating its transmission (Morin et al., 2013). Ambient temperature also acts as an important regulator of mosquito development and survival, as well as mosquito reproductive behavior (Morin et al., 2013). The complexity of temperature impacts on dengue viruses and mosquitoes, as well as the findings from previous studies (Wu et al., 2018; Xu et al., 2017), motivated us to assess the possible non-linear relationship between temperature and the occurrence of severe dengue cases. We observed that generally there was an optimal temperature range for the occurrence of severe dengue cases in Thailand, although we also observed heterogeneity in terms of this temperature range across different regions. Specifically, the occurrence of severe dengue cases roughly favoured an ambient mean temperature range of 24°C to 30°C in Northeastern Thailand, and 27°C to 29°C in Southern Thailand West Coast. In Central Thailand and Southern Thailand East Coast, the risk of the occurrence of severe dengue cases increased when temperature increased, and remained stable or dipped slightly when temperature reached high level. Prior studies in Thailand have also found significant effect of temperature on the occurrence of DF cases or severe dengue cases (Johansson et al., 2009; Nitatpattana et al., 2007; Promprou et al., 2005; Thammapalo et al., 2005), although all of them assumed a linear relationship between temperature and dengue occurrence. Rueda et al. have found that the development rates of immature *Aedes aegypti* increased with incubation temperatures to 34 °C and then slowed, and *Ae. aegypti* survival peaked at 27°C (Rueda et al., 1990), which also indicated that there may be an optimal temperature range for dengue transmission (Mordecai et al., 2017).

The present study has also found significant effect of relative humidity on the occurrence of severe dengue cases in Northeastern Thailand and Central Thailand. Similar to temperature, there were also optimal relative humidity ranges that the occurrence of severe dengue cases favoured. Promprou et al. have found a significant relationship between relative humidity and the occurrence of severe dengue cases in Southern Thailand using correlation analysis and linear regression analysis (Promprou et al., 2005). Wongkoon et al. have also observed that relative humidity was an important climate predictor of dengue case number in Southern Thailand (Wongkoon et al., 2018). Studies conducted in Manila (Philippines) (Sumi et al., 2016), Mekong Delta region (Vietnam) (Dung et al., 2016), and Singapore (Earnest et al., 2011) have found an increase of DF cases with the increase of relative humidity, but Xiang et al. have found that, when relative humidity was beyond 78.9%, DF cases decreased when relative humidity increased (Xiang et al., 2017). The heterogeneous findings in these studies might partially be due to the assumption made on the nature of relative humidity and DF relationship prior to data analysis. Biologically, *Ae. aegypti* eggs can tolerate a wide range of relative humidity values, but *Ae. albopictus* eggs favor high relative humidity (Juliano et al., 2002). Nevertheless, mosquitoes may bite more at low humidity, possibly increasing the transmission of dengue virus (Wu et al., 2009). Thoroughly understanding how climatic factors affect the transmission of dengue virus and the occurrence of severe dengue cases is of great significance because climate change will increase global surface temperature and may alter the distribution of relative humidity among regions.

The associations between climatic factors and the occurrence of severe dengue cases that we found in this study suggest the possibility of developing a dengue early warning system based on climate, and the appreciable heterogeneity of these associations across different regions indicates that region-specific early warning might be more ideal. Optimal lead time is a pivotal factor in developing dengue early warning system. The three-month-optimal-lag that we observed in this study is consistent with findings from Cambodia (Choi et al., 2016) but inconsistent with findings from the Mekong Delta region, Vietnam (Dung et al., 2016), and Guangzhou, China (Xiang et al., 2017). A prior study in Singapore reported that a dengue early warning forecast given three months prior to the onset of a possible epidemic would give local authorities enough time to mitigate an outbreak (Hii et al., 2012). The heterogeneous lag patterns across different countries observed in existing literature suggested that optimal lead time for dengue early warning might be country- or region-specific.

This study has two major strengths. First, we explored the dynamic spatial patterns of severe dengue incidence across different years in Thailand, and described regional differences in terms of the seasonality of severe dengue cases, facilitating future dengue prevention and control resource allocation and implementation of vector control. Second, we quantified the effects of mean temperature and relative humidity on the occurrence of severe dengue cases. The identifications of climate-sensitive regions and optimal ranges of mean temperature and relative humidity for the occurrence of severe dengue cases may shed some light on adequately understanding how climate change may affect the occurrence of severe dengue cases in Thailand in the future. However, projecting future severe dengue burden under climate change scenarios still needs to consider many other factors (e.g., mosquito density and future shifting in demographics, etc.). Three weaknesses of this study should also be acknowledged. First, we were unable to examine how mosquito density may affect the spatiotemporal patterns of severe dengue as we did not have mosquito data. Second, we also did not have data on rainfall and evaporation, which restricted us from exploring the relationship between rainfall, evaporation and the occurrence of severe dengue cases in Thailand, although a recent study has found that relative humidity appeared to be the most important climatic factor in predicting the temporal pattern of dengue incidence in Manila, the Philippines (Carvajal et al., 2018). Third, we were only able to quantify the associations of mean temperature and relative humidity with severe dengue in 51 provinces due to data unavailability.

5. Conclusion

Severe dengue in Thailand clustered in certain provinces, especially during epidemic years. The high-risk cluster changed across years, calling for further research to understand the fundamental reasons behind this pattern. Pre-season vector control in Northern and Northeastern Thailand could potentially ease severe dengue burden. Regional heterogeneity existed in terms of the effects of mean temperature and relative humidity on the occurrence of severe dengue cases in Thailand. As climate change continues, severe dengue burden in Central Thailand, Northeastern Thailand, and Southern Thailand may change in the future, and evaluating the magnitude of this possible change may help future dengue resource allocation in Thailand.

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Figure

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Figure 1A. Monthly severe dengue cases in Thailand from 1999 to 2014

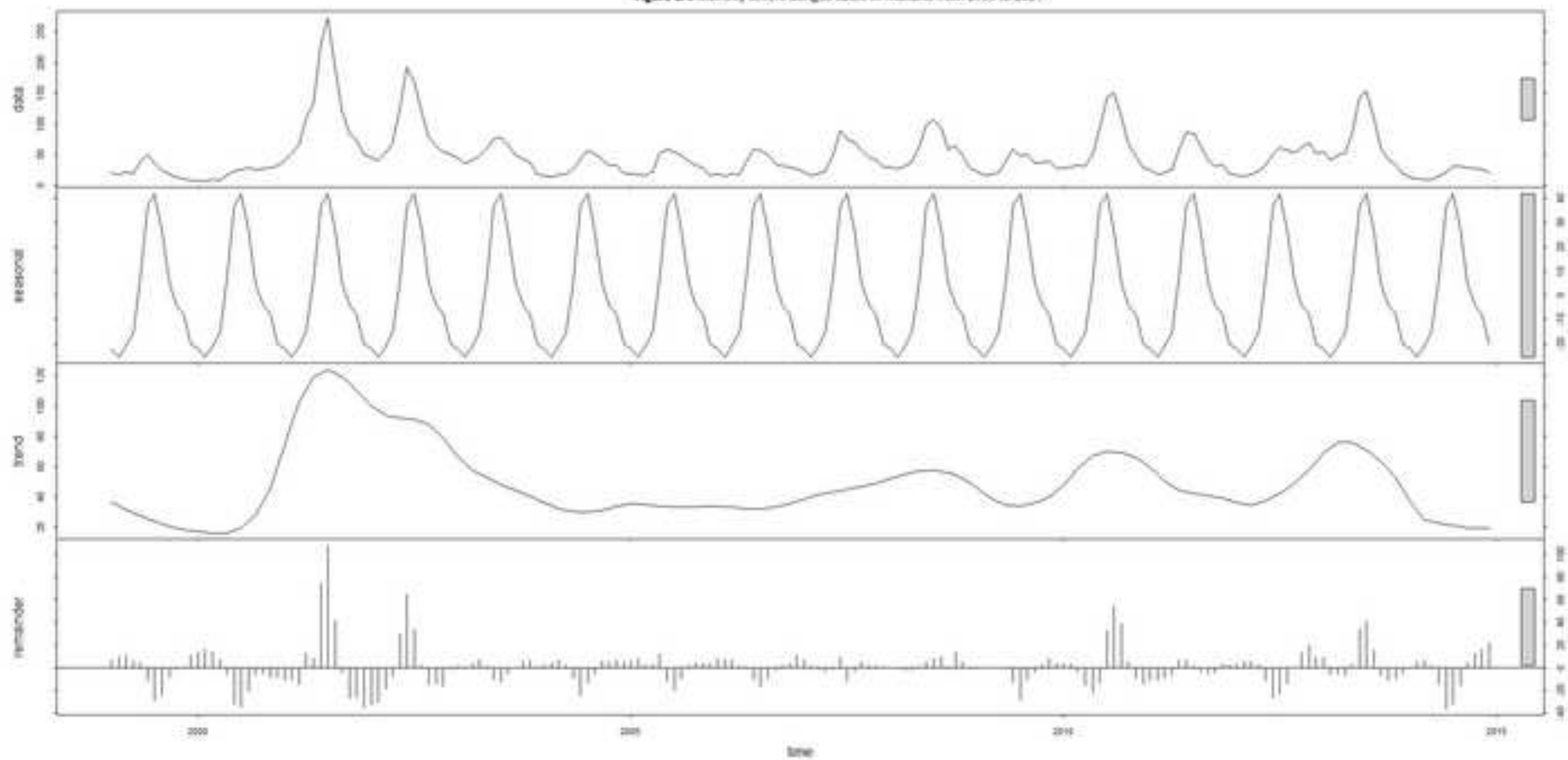

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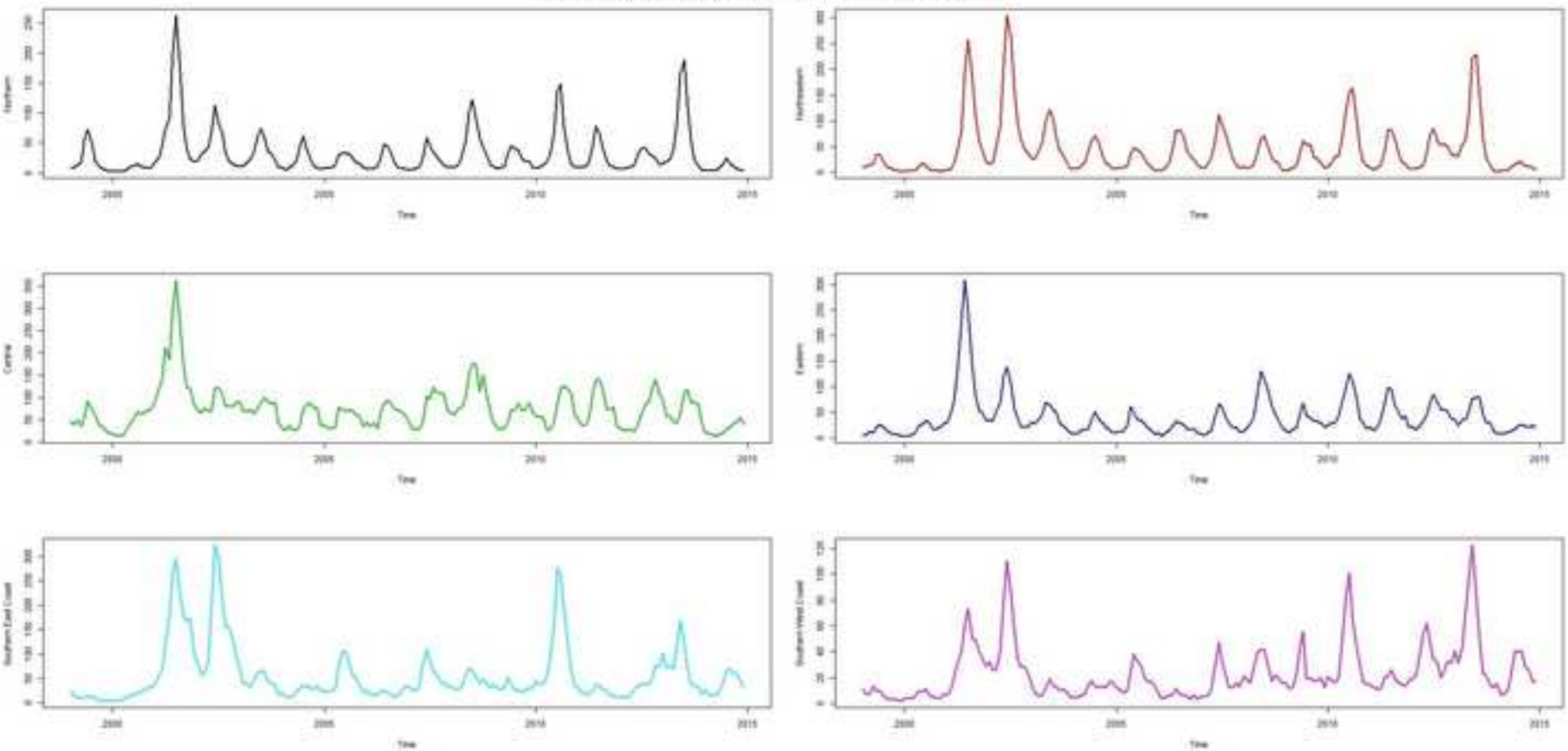
Figure 18. Monthly severe dengue cases in subnational regions from 1999 to 2014



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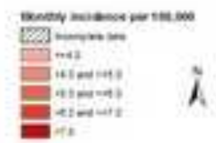

Figure 2A. Spatial distributions of severe dengue incidence in Thailand across different years

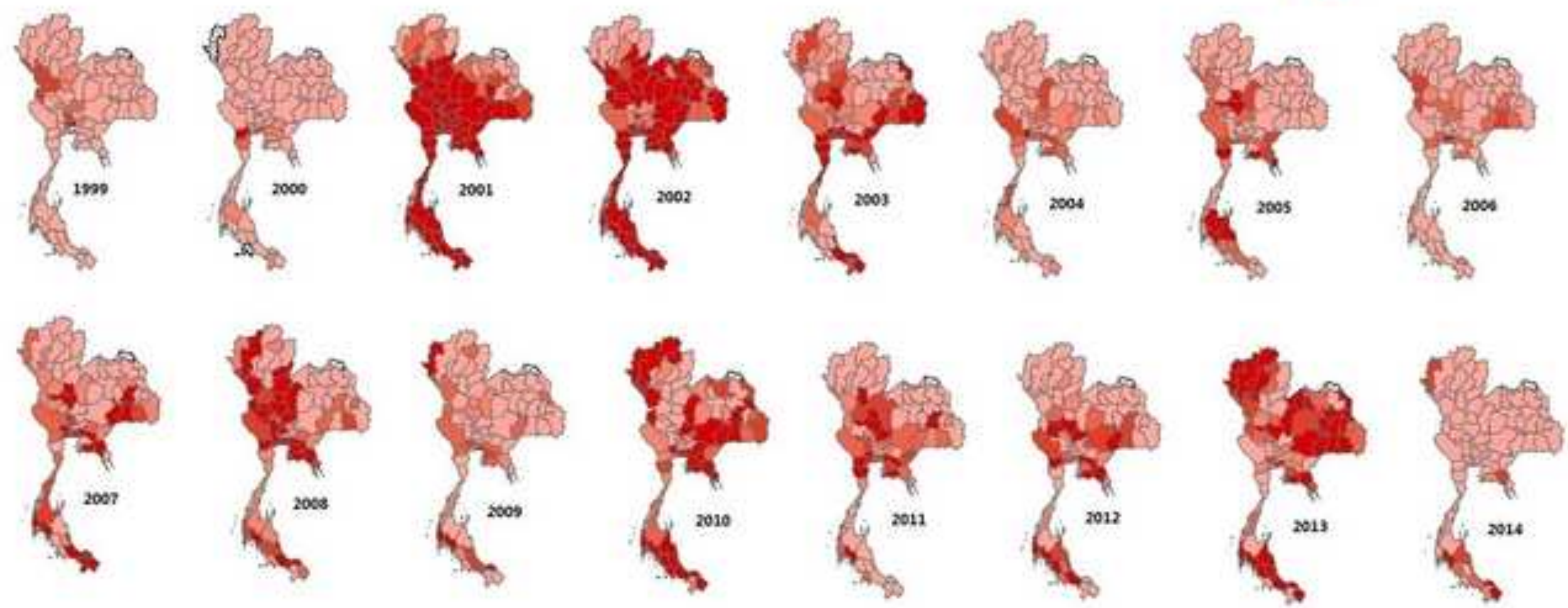

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Figure 2B. Primary clusters of severe dengue in Thailand across different years

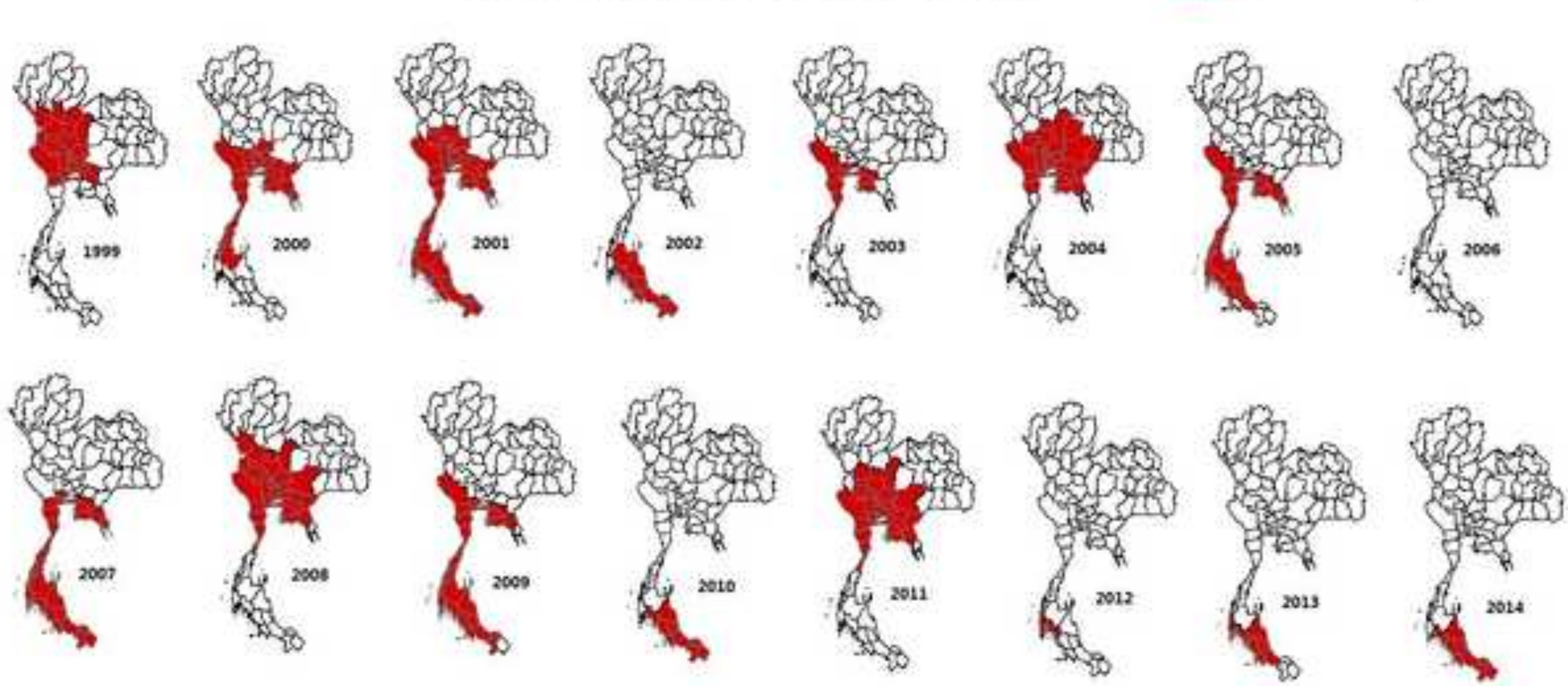

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Figure 3A. Seasonality of severe dengue cases in different provinces of Thailand

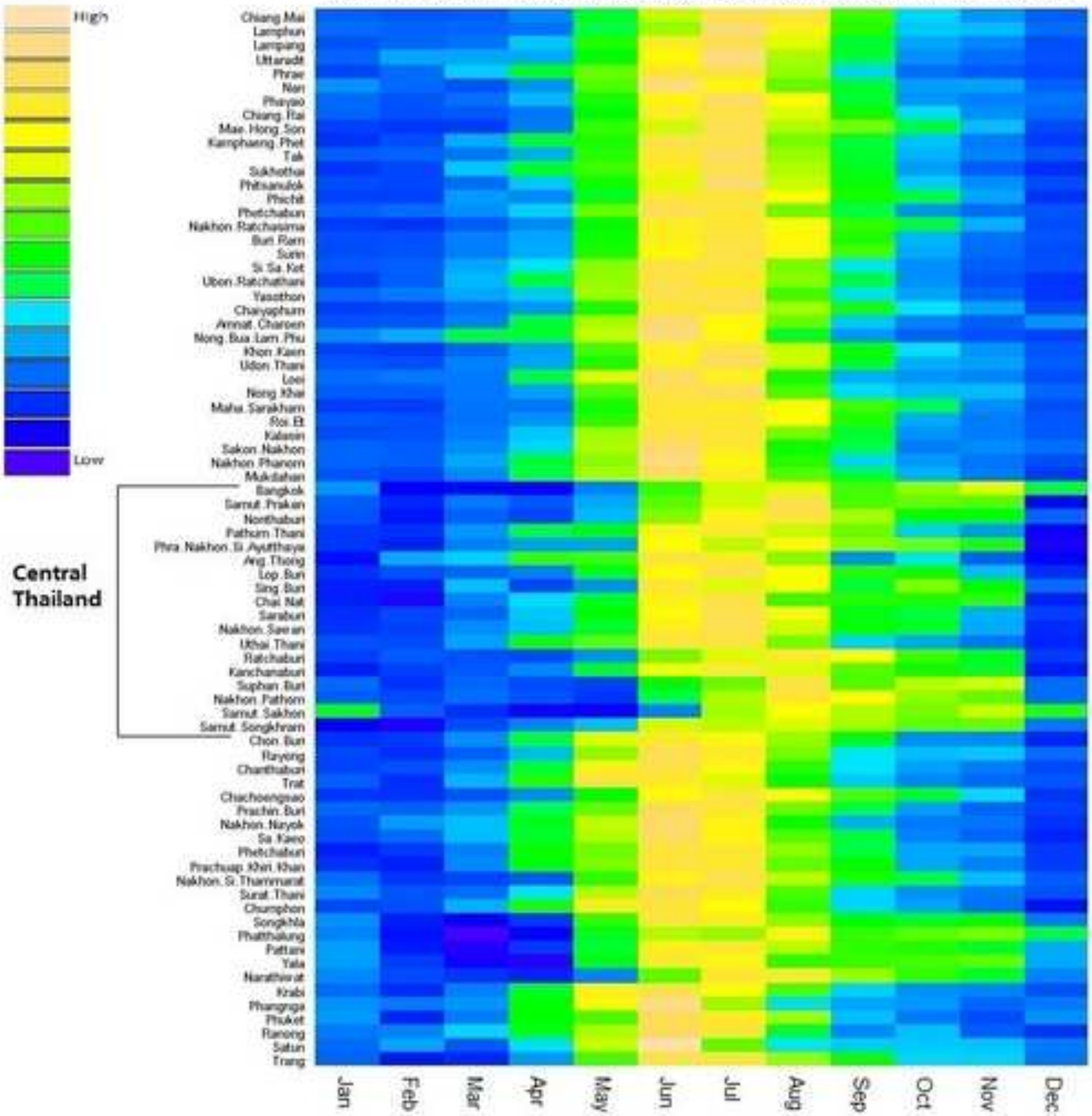

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Figure 3B. Severe dengue seasonality change across different years in subnational years

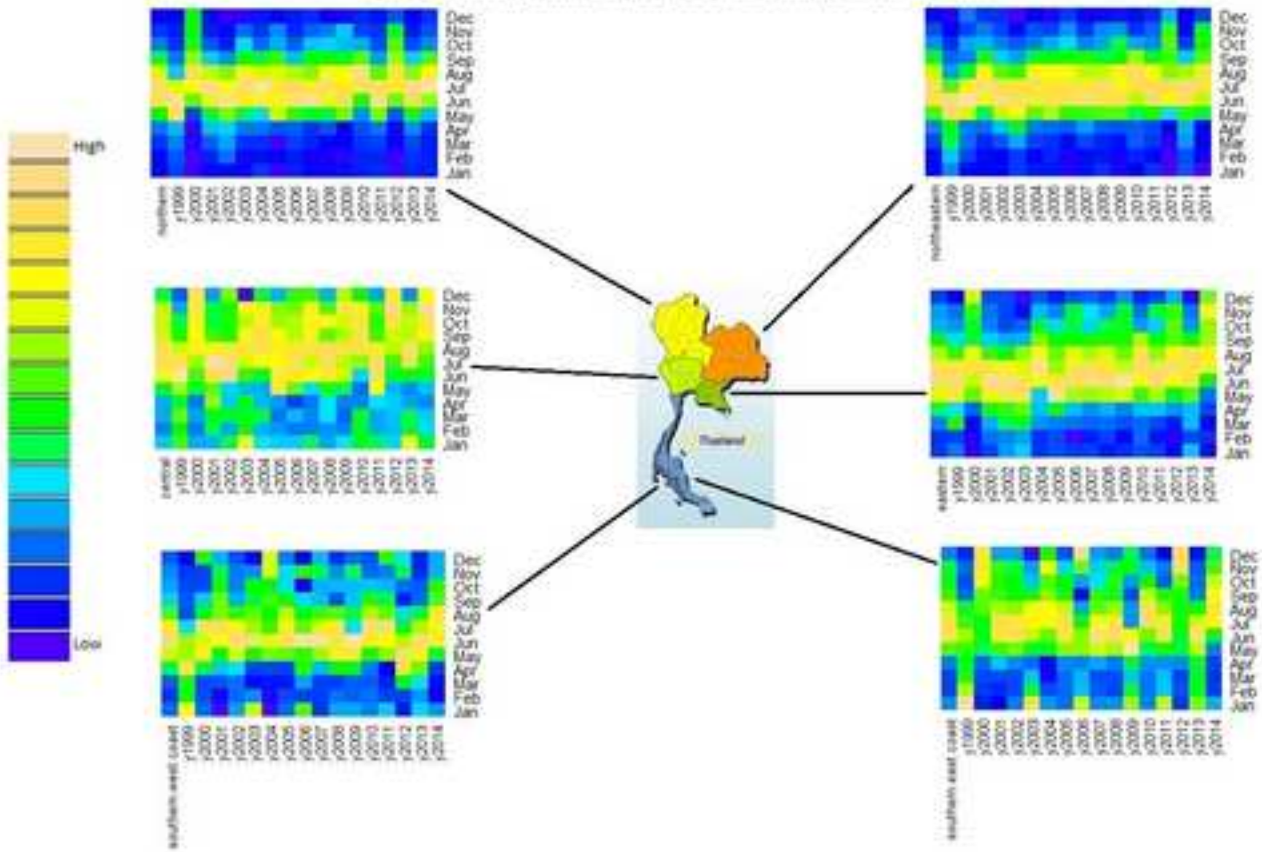

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Figure 4A. Impact of temperature on the occurrence of severe dengue cases in Thailand under different lags

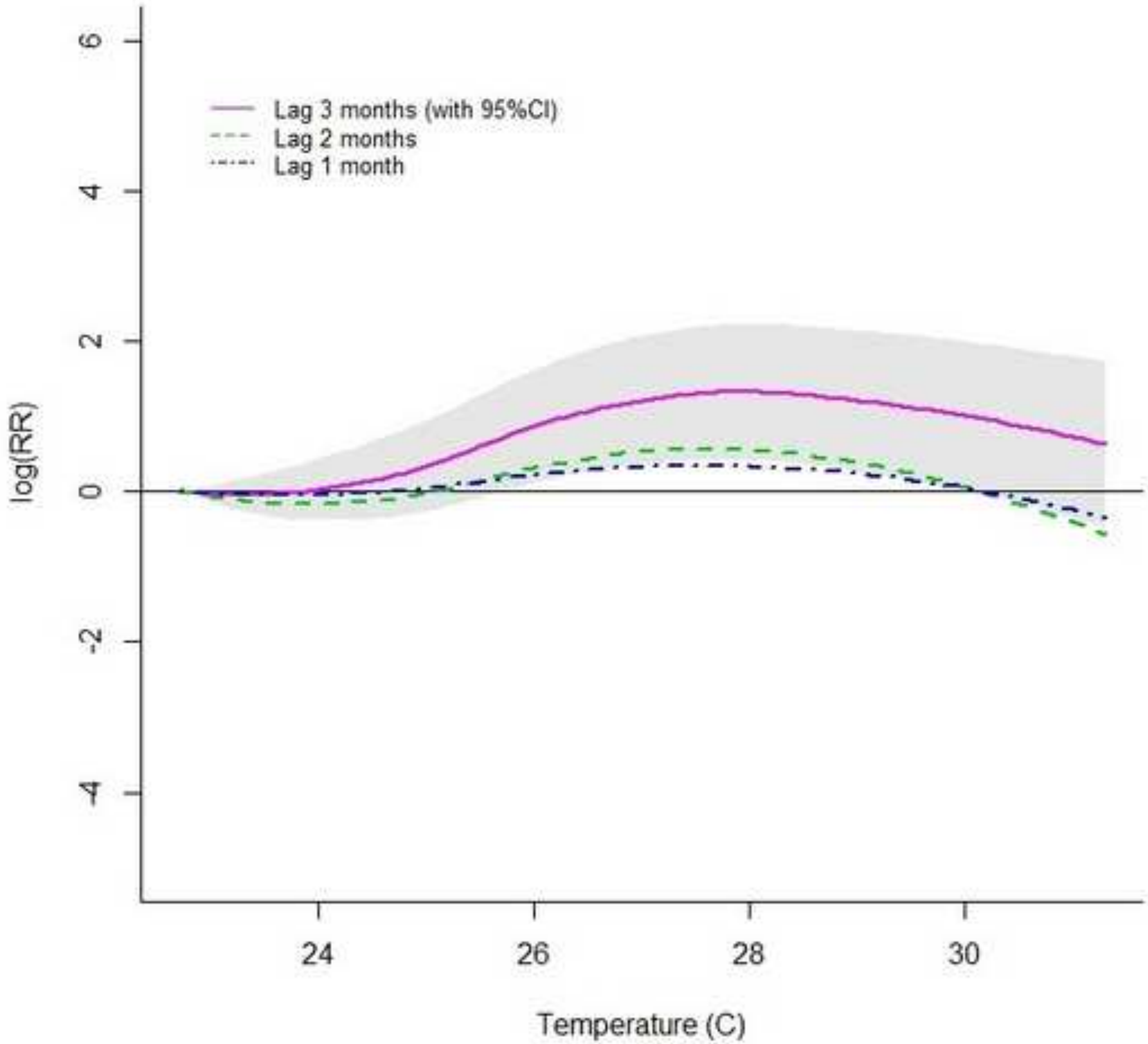

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Figure 4B. Impact of temperature on the occurrence of severe dengue cases in subnational regions under different lags

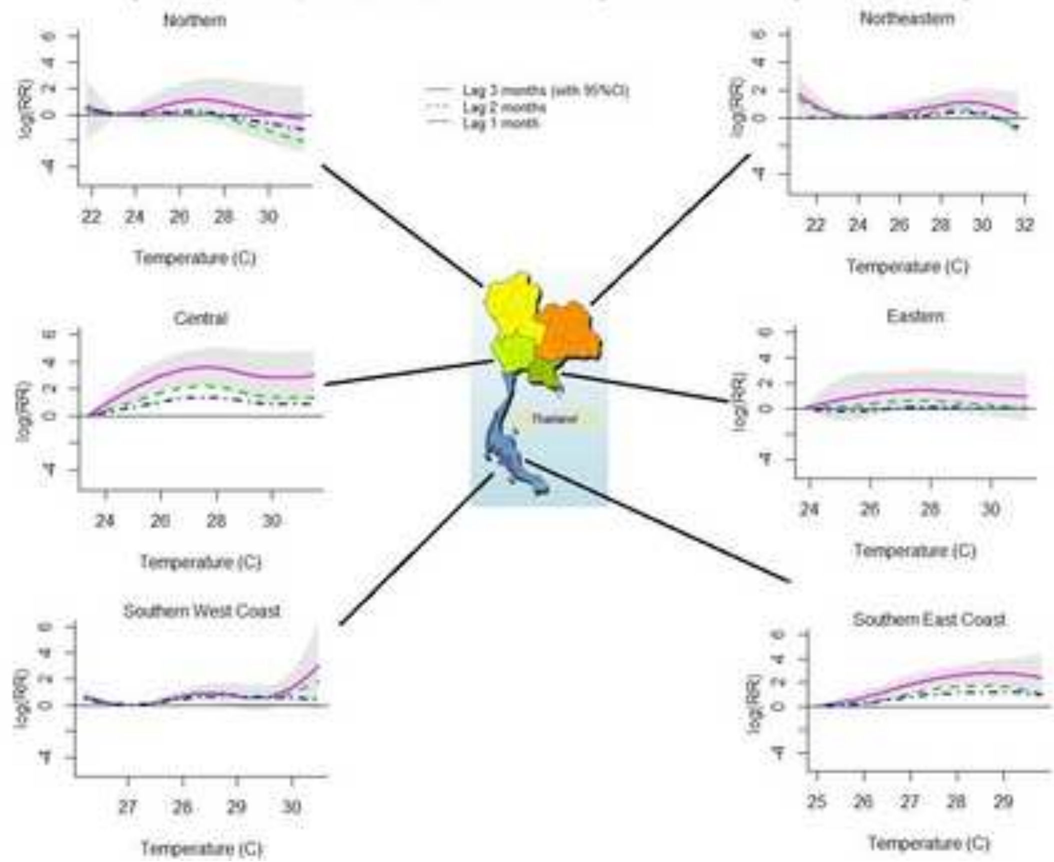

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Figure 5A. Impact of relative humidity on the occurrence of severe dengue cases in Thailand under different lags

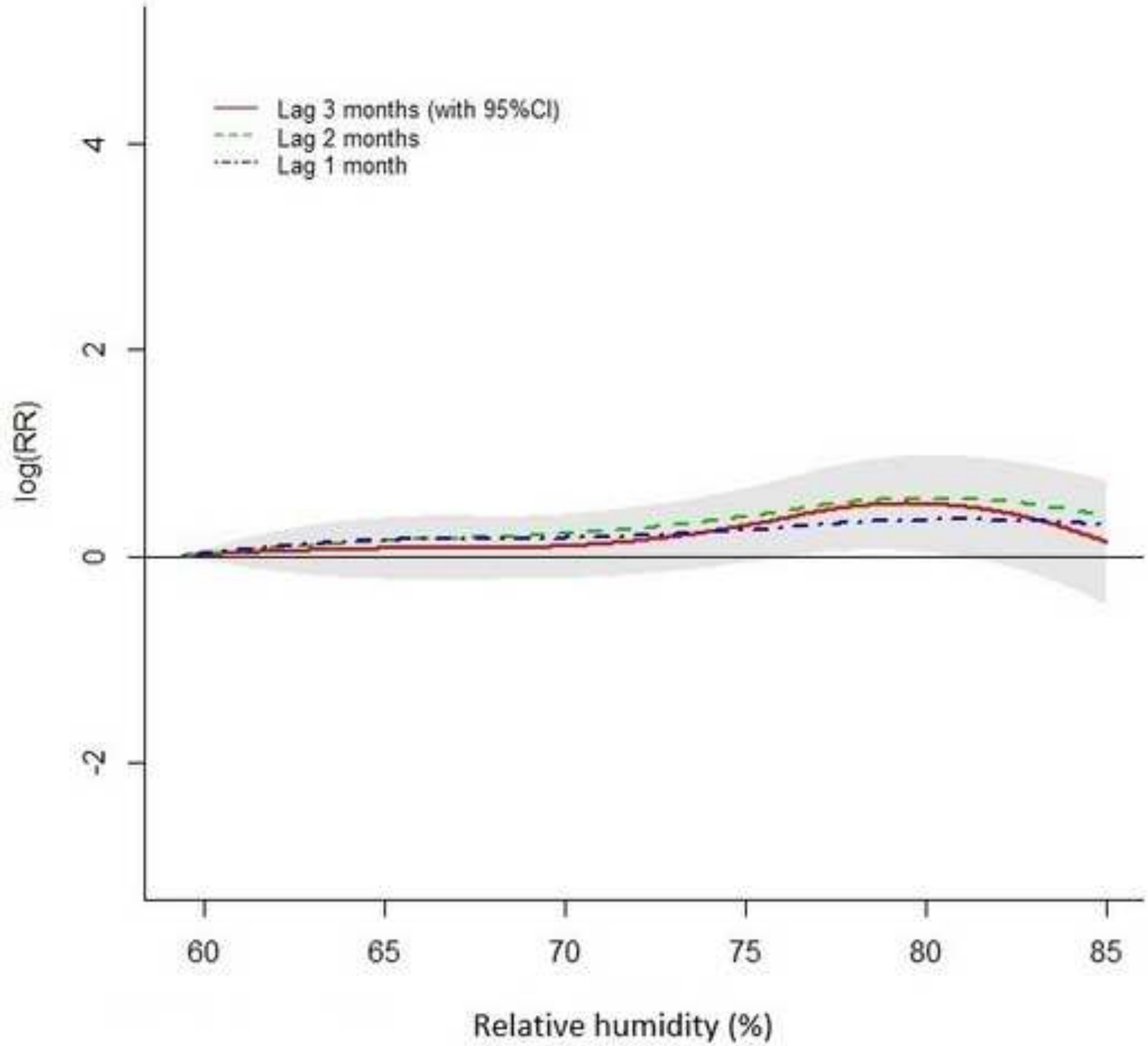

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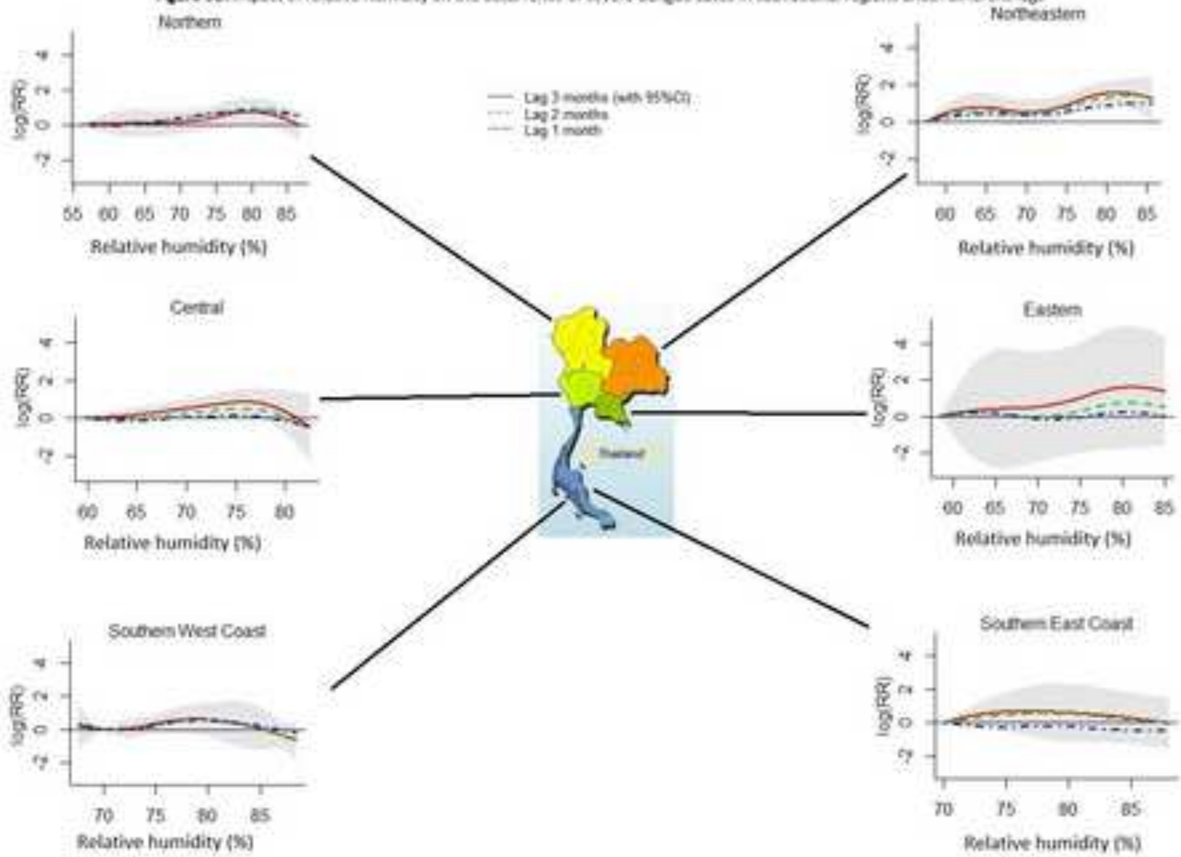
Figure S8. Impact of relative humidity on the occurrence of severe dengue cases in subnational regions under different lags



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