

Original article

Regional Differences in the Growing Incidence of Dengue Fever in Vietnam Explained by Weather Variability

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Abstract: Dengue fever is a major health problem in Vietnam, but its incidence differs from province to province. To understand this at the local level, we assessed the effect of four weather components (humidity, rainfall, temperature and sunshine) on the number of dengue cases in nine provinces of Vietnam. Monthly data from 1999 to 2009 were analysed by time-series regression using negative binomial models. A test for heterogeneity was applied to assess the weather-dengue association in the provinces. Those associations were significantly heterogeneous (for temperature, humidity, and sunshine: $P < 0.001$ heterogeneity test; for rainfall: $P = 0.018$ heterogeneity test). This confirms that weather components strongly affect dengue transmission at a lag time of 0 to 3 months, with considerable variation in their influence among different areas in Vietnam. This finding may promote the strategic prevention of dengue disease by suggesting specific plans at the local level, rather than a nationally unified approach.

Key words: Dengue, temperature, rainfall, humidity, sunshine, weather variability

INTRODUCTION

Dengue is a mosquito-borne viral disease of increasing public-health concern worldwide. In recent decades, the incidence has increased 30-fold and has expanded to new geographic regions, spreading between countries and from urban to rural areas [1]. Dengue diseases are now widely dispersed in the tropics and subtropics and expose more than 2.5 billion people in over 100 countries to the risk of dengue [2]. The dengue virus belongs to the genus *Flavivirus*, family Flaviviridae and includes four serotypes, DEN-1 through DEN-4. There is no cross-protective immunity between the four serotypes, although immunity to one serotype can give life-long protection against the serotype [3].

Dengue is transmitted via the bite of infective mosquitoes, primarily *Aedes aegypti* and secondarily *Ae. albopictus* [4, 5]. Previous studies have demonstrated a strong correlation between dengue cases and modelled *Ae. Aegypti* and *Ae. Albopictus* populations [6, 7]. Vietnam has a typical Southeast Asian tropical monsoon climate, and the territory of Vietnam stretches over areas approximately three-quarters hilly and mountainous. The topography and monsoon climate lead to differences in the temperature-

humidity regime among regions in Vietnam. For instance, there is a cold winter with little rain in the northern region, wet and dry seasons in the southern and highland region, and rainy winter season in the central region [8]. The diversity of climatic conditions could affect the differences in vector population size and distribution in Vietnam [5] and thereby play an important role in dengue epidemics [1]. In 1959, the early dengue epidemics in Vietnam were reported in Ha Noi and Hai Phong. Since then, the disease has become endemic throughout Vietnam in spite of the existing diversity in climate in the country [9].

Several studies have assessed the impact of weather and climate on dengue in Vietnam and in other parts of the world, but the majority focused on a single region [10–12] or municipalities in a single region [13, 14], or took a global approach in multiple countries [6, 15]. Few studies have considered the spatial heterogeneity of weather components and its impact on vector populations to predict dengue incidence, particularly in Vietnam.

The aim of this study was to identify the meteorological factors responsible for the spatial and temporal heterogeneity in the incidence of dengue fever in Vietnam while considering the regimes of each weather variable, i.e., rain-

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fall, temperature, humidity, and hours of sunshine. For instance, temperature may not always be positively associated with the incidence of dengue fever, and it is useful to assess the heterogeneous temperature regime in Vietnam in order to establish an effective method of projection in the future. We used meteorological and dengue incidence data collected from nine provinces over a period of 11 years. The parameters included in the analysis were humidity, temperature, rainfall, and hours of sunshine. To interpret the results, we referred to data on the dispersal of the different carriers in these provinces. This information may assist the National Program for Dengue Surveillance and Control in planning strategies to control the spread of dengue fever.

MATERIALS AND METHODS

Study location

The National Program for Dengue Surveillance and Control was established in 1999 and expanded to include all the provinces of Vietnam by 2005. This system of surveillance, management and administration has been synchronized and strengthened into a unified effort to control Dengue Fever and Dengue Hemorrhagic Fever (DF/DHF) as part of a national strategy [16]. Based on available meteorological and dengue incidence data from 1999 to 2009, nine provinces were selected for the study: Ha Noi, Da Nang, Binh Dinh, Khanh Hoa, Gia Lai, Lam Dong, Ho Chi Minh, Ba Ria Vung Tau and Ca Mau (Fig. 1). In 2008, the Ha Tay and old Ha Noi provinces merged into one province. Hence, the Ha Noi province data include data from Ha Tay and old Ha Noi before 2008 and data from Ha Noi since 2008. The nine provinces belong to one surveillance system for DF/DHF.

Data sources

Monthly data on dengue cases for each province from 1999 to 2009 were collected from the National Institute of Hygiene and Epidemiology and the Department of Preventive Medicine. Data were based on the established surveillance system and published in the Statistical Yearbook of Infectious Diseases. The cases included DF and DHF, which had been clinically diagnosed based on the WHO criteria of 1997 [17]. Only 16–27% of reported cases were confirmed in the laboratory during the period of from 2001 through 2007 in Vietnam [16].

Meteorological data, including monthly total rainfall (mm), monthly mean air temperature (°C), monthly mean humidity (per cent) and monthly total sunshine duration (hour) from 1999 to 2009 were extracted from the Statistical Yearbook of Vietnam, published by the General Statistics Office in Hanoi from 2001 to 2010. Meteorological data of

Ho Chi Minh province were obtained from the website of the statistical office in Ho Chi Minh city [18].

Statistical analysis

The monthly cases of dengue were treated as a dependent variable, and the meteorological variables as independent variables. The associations between them were estimated using negative binomial generalized linear models [19]. Some missing data in the rainfall records, altogether less than 8%, were extrapolated and complemented using the generalized linear model. To account for seasonality in the number of dengue cases, natural cubic splines for months of the year with 3 degrees of freedom (df) were included in the model. Indicator variables for the years of the study were also incorporated into the model to allow for long-term trends and other variation between the years. To control for autocorrelation, an autoregressive term of order 1 was incorporated into the models [20].

Models for rainfall, temperature, humidity and sunshine

Rainfall, temperature, humidity and sunshine were analyzed because we hypothesized that these weather components potentially influence the incidence of dengue cases based on previous studies looking at climate and infectious diseases [21, 22]. Based on exploratory analyses, data from the literature, Akaike's Information Criterion (AIC) [23] and considerations concerning the interpretation difficulty associated with long time lags, we analyzed lag times (delay in the effect of each weather component on the number of dengue cases) of up to 3 months. In our initial analyses, we fitted a natural cubic spline 3 df to the average over lag periods of 0–3 months [24], which means the average of 4-month weather components, namely the average of those in the month when the dengue case reported and 3 months prior to the month. When each weather component was analyzed, we also included other weather components as natural cubic splines (3 df) in the model to allow for the effects of confounding variables, with a lag time of 0–3 months. In real life, weather is a synergy of weather variables. Hence, we decided to analyze the impacts by multivariate analysis.

In summary, the model took the following form:

$$\log[E(Y)] = \alpha + NS(\text{rain}_{0-3}, 3 \text{ df}) + NS(\text{temp}_{0-3}, 3 \text{ df}) \\ + NS(\text{hum}_{0-3}, 3 \text{ df}) + NS(\text{sun}_{0-3}, 3 \text{ df}) \\ + NS(\text{time}, 3 \text{ df}/\text{year}) + i.\text{year},$$

where $E(Y)$ is the expected monthly case count and 'rain', 'temp', 'hum', 'sun' and 'time' indicate the average monthly rainfall, temperature, relative humidity, sunshine hours and month of the year, respectively. NS indicates a natural cubic spline function and $i.\text{year}$ represents indicator variables of year.

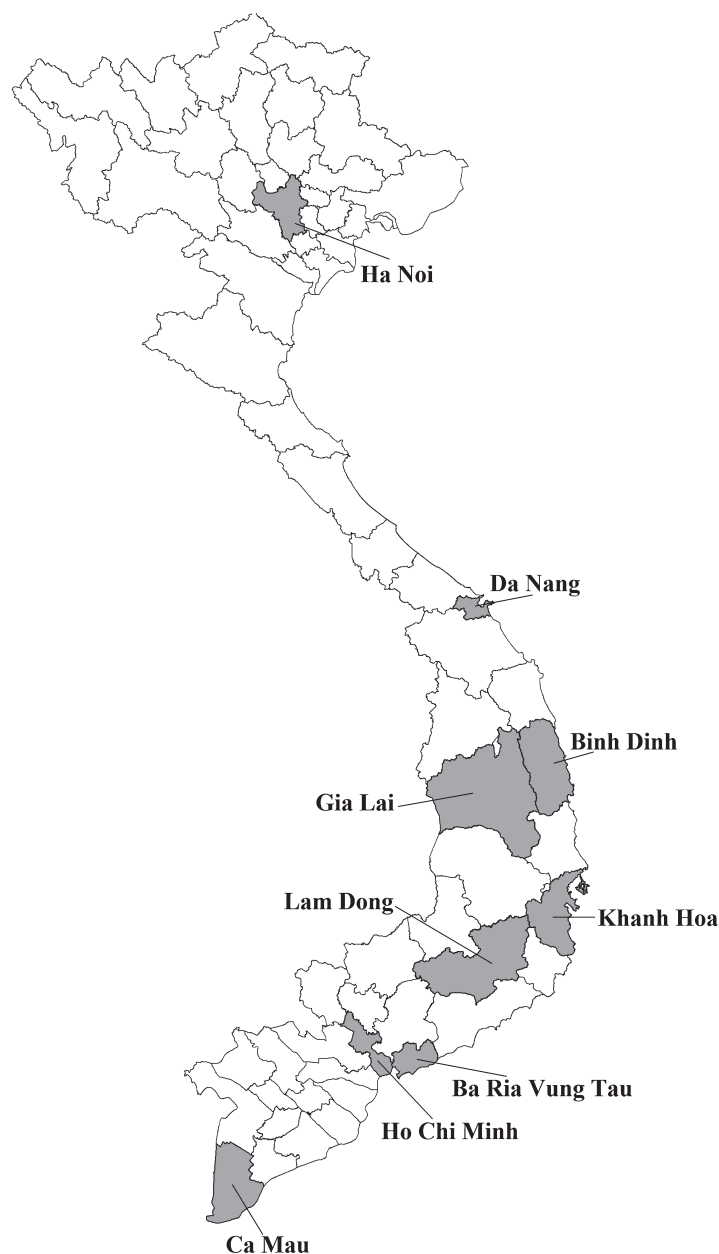


Fig. 1. The nine provinces of Vietnam selected for the study. The study sites are shaded in gray on the map.

Graphs of the predicted number of dengue cases plotted as smoothed functions of each weather component were created by natural cubic splines [24]. These graphs were used to visually assess whether the functional form of the relationship was linear across the full range of independent variables. Because there was no obvious U- or V-shaped risk-response relationship in the smoothed graphs, we chose a linear model for simplicity.

Change in the number of dengue cases associated with 1 mm, 1°C, 1% and 1 hour changes in rainfall, temperature, humidity and sunshine, respectively, (estimated as coeffi-

icients from the regression model) was reported as a percentage change with corresponding 95% confidence intervals (CIs). Coefficient and 95% CIs of the regression between weather components and dengue cases for each province were analyzed to assess variability using the chi-square test for heterogeneity. Sensitivity of the estimates to the seasonal control was examined by replacing the natural cubic splines terms with an indicator variable of season (3-month seasonal terms: spring, summer, autumn and winter), month, Fourier terms of three to five harmonics per year and natural cubic splines for months of the year with 4 df. The

smallest value of AIC was set as the standard to identify the best model [23]. All statistical analyses were performed using Stata 11.1 (Stata Corporation, College Station, TX, USA).

RESULTS

Weather and dengue incidence in each region

From 1999 to 2009, a total of 187,171 dengue cases were reported in the nine provinces. The number of cases was highest in Ho Chi Minh City (84,089) and lowest in Lam Dong province (1,673). There was considerable variability in rainfall, temperature, humidity and sunshine hours among the regions. In the northern region, Ha Noi (Fig. 2a), it was relatively cool with short durations of sunshine. In the central region, Da Nang, Binh Dinh and Khanh Hoa (Fig. 2b), it was hot with the highest rainfall. In the highlands region, Gia Lai (Fig. 2c) and Lam Dong, it was cool with the highest humidity. In the southern region, Ho Chi Minh (Fig. 2d), Ba Ria Vung Tau and Ca Mau, it was the hottest with long durations of sunshine. The number of monthly dengue cases increased during the study period in Ha Noi, Ho Chi Minh, and Ba Ria Vung Tau. The yearly peaks in all provinces were seen mainly in June to December.

Model selection

To select the best model, we performed the sensitivity analysis by comparing the seven models as indicated in Table 1. Since the AIC of model 7 (adjusted for natural cubic spline with 3df) was the smallest, we selected it as the best model. Fig. 3 presents both observed and predicted monthly dengue incidences during the period of 11 years in all the nine provinces. The predicted dengue cases were calculated using model 7. Although the R^2 of model 7 ranged between 6% and 20% (Table 1), Fig. 3 demonstrates almost the same trend in the dengue incidence observed over the 11-year period.

Association between weather components and dengue incidence based on the model 7

Based on the parameters, Fig. 4 demonstrates the association between the four weather components and dengue incidence. With a lag of 0–3 months, there were significant associations between average rainfall and dengue cases in Ha Noi and Ba Ria Vung Tau (Fig. 4a). The increase in the number of dengue cases per 1 mm increase in rainfall with a lag of 0–3 months adjusted for natural cubic spline with 3df was 0.7% (95% CI: 0.2% to 1.2%, $P = 0.009$) and -0.5% (95% CI: -0.9% to -0.1% , $P = 0.014$), respectively.

The dengue cases showed a significant positive associ-

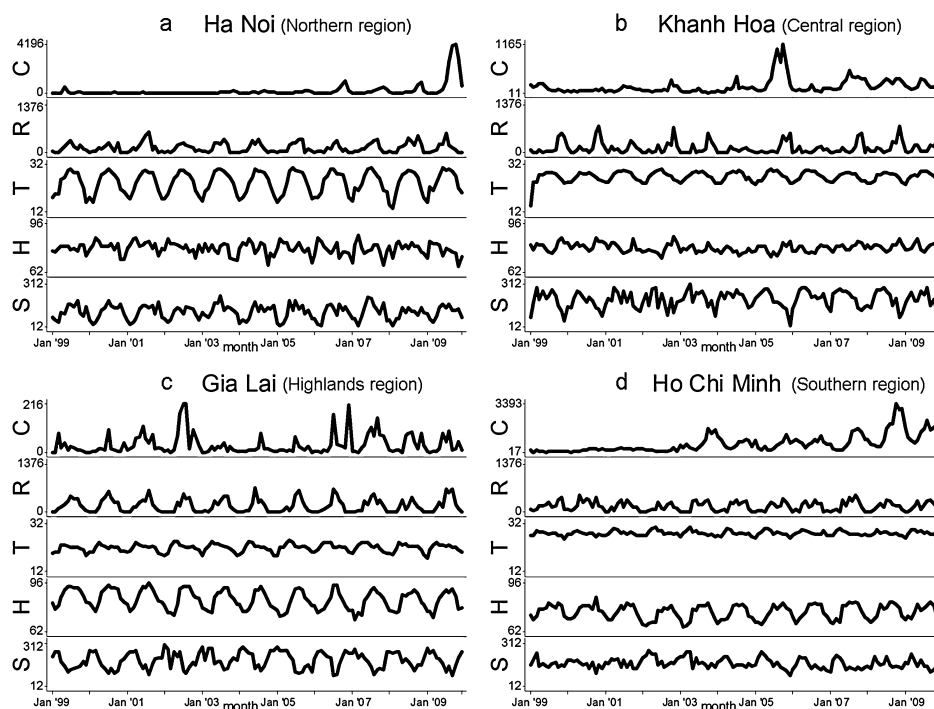


Fig. 2. Dengue cases and meteorological data in Ha Noi, Khanh Hoa, Gia Lai and Ho Chi Minh, from 1999 to 2009. C: dengue cases (monthly total), R: rainfall (monthly total; mm), T: temperature (monthly average; °C), H: humidity (monthly average; %), S: sunshine (monthly total; hour).

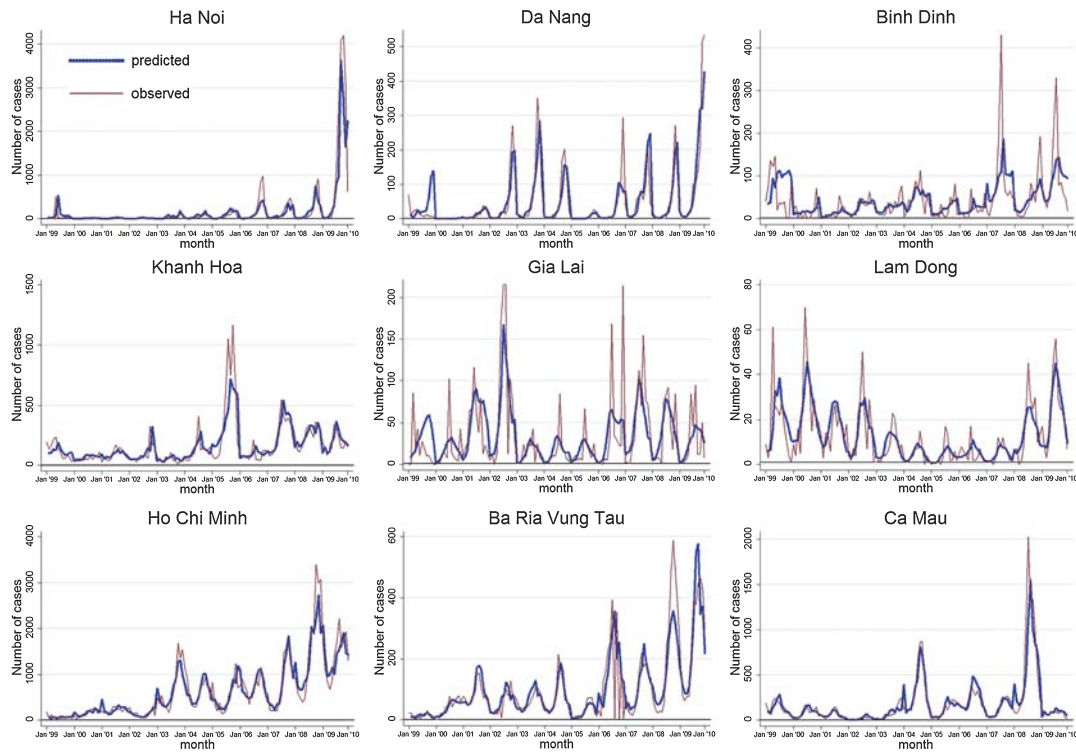


Fig. 3. Predicted and observed time series plots in the nine provinces.

Table 1. The AIC values and paseudo R-square (indicated in parentheses) in the model

Model	Ha Noi	Da Nang	Binh Dinh	Khanh Hoa	Gia Lai	Lam Dong	Ho Chi Minh	Ba Ria Vung Tau	Ca Mau
model 1	1249 (0.175)	953 (0.195)	1215 (0.057)	1448 (0.113)	1111 (0.089)	834 (0.151)	1710 (0.145)	1330 (0.122)	1379 (0.173)
model 2	1241 (0.191)	954 (0.209)	1222 (0.064)	1428 (0.136)	1117 (0.098)	838 (0.164)	1713 (0.151)	1336 (0.129)	1346 (0.203)
model 3	1239 (0.191)	952 (0.208)	1221 (0.063)	1426 (0.136)	1116 (0.097)	837 (0.163)	1712 (0.151)	1337 (0.127)	1344 (0.203)
model 4	1238 (0.189)	950 (0.207)	1217 (0.063)	1429 (0.132)	1113 (0.096)	834 (0.162)	1710 (0.150)	1335 (0.125)	1345 (0.200)
model 5	1237 (0.186)	952 (0.201)	1217 (0.060)	1428 (0.130)	1112 (0.094)	833 (0.159)	1709 (0.148)	1332 (0.125)	1345 (0.197)
model 6	1250 (0.176)	943 (0.206)	1213 (0.060)	1429 (0.126)	1112 (0.090)	829 (0.158)	1708 (0.147)	1330 (0.123)	1357 (0.188)
model 7	1245 (0.177)	946 (0.201)	1212 (0.059)	1441 (0.118)	1113 (0.088)	830 (0.156)	1707 (0.147)	1329 (0.123)	1366 (0.181)

AIC: Akaike’s information criterion. Model 1: adjusted for season, Model 2: adjusted for month, Model 3: adjusted for Fourier term of five harmonics per year, Model 4: adjusted for Fourier term of four harmonics per year, Model 5: adjusted for Fourier term of three harmonics per year, Model 6: adjusted for natural cubic spline with 4df, Model 7: adjusted for natural cubic spline with 3df.

ation with temperature in four provinces and a significant negative association in one province (Fig. 4b). The percentage changes in the number of dengue cases per 1°C increase in average temperature over a lag of 0–3 months were 135.1% (95% CI: 79.3% to 208.3%, $P < 0.001$) in Ha Noi,

62.7% (95% CI: 3.8% to 155.2%, $P = 0.034$) in Da Nang, 82.8% (95% CI: 20.2% to 178.0%, $P = 0.005$) in Lam Dong, 43.0% (95% CI: 8.0% to 89.4%, $P = 0.012$) in Ca Mau and –28.7% (95% CI: –43.2% to –10.4%, $P = 0.004$) in Ho Chi Minh.

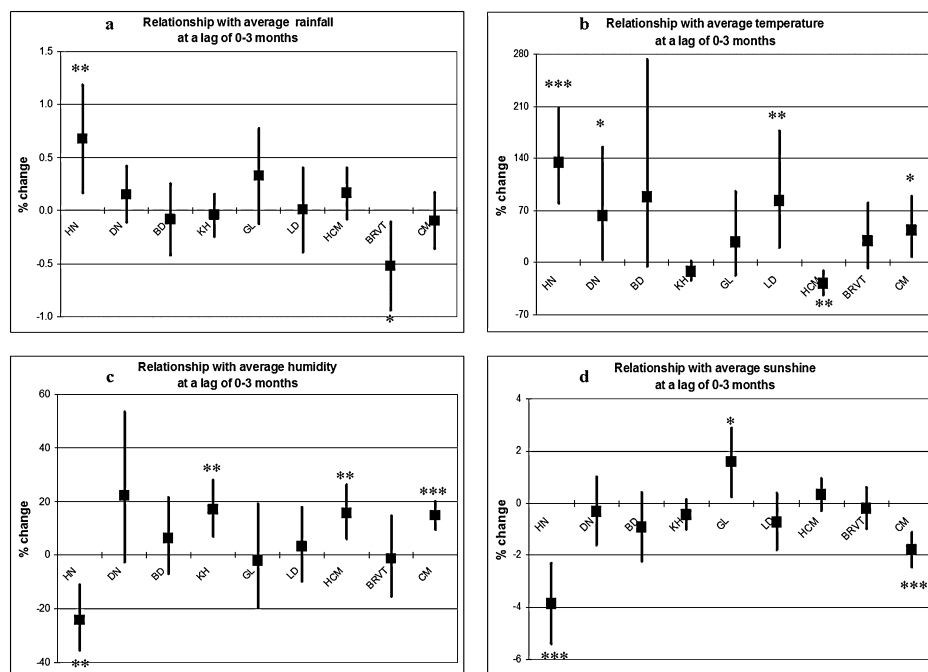


Fig. 4. Percentage change (and 95% CI) in number of dengue cases (a) per 1 mm increase in average rainfall; (b) per 1°C increase in average temperature; (c) per 1% increase in average humidity; (d) per 1 hour increase in average sunshine with a lag of 0–3 months after adjusting for natural cubic splines for months of the year with 3 degrees of freedom.

HN: Ha Noi, DN: Da Nang, BD: Binh Dinh, KH: Khanh Hoa, GL: Gia Lai, LD: Lam Dong, HCM: Ho Chi Minh, BRVT: Ba Ria Vung Tau, CM: Ca Mau.

*: $P < 0.05$; **: $P < 0.01$; ***: $P < 0.001$.

The relationship between the number of dengue cases and average humidity in the nine provinces with a lag of 0–3 months is shown in Fig. 4c. A significant positive association was observed in Khanh Hoa, Ho Chi Minh and Ca Mau: with a 1% increase in humidity, the number of dengue cases increased 17.0% (95% CI: 6.8% to 28.1%, $P = 0.001$), 15.7% (95% CI: 6.0% to 26.3%, $P = 0.001$) and 14.7% (95% CI: 9.5% to 20.2%, $P < 0.001$), respectively. However, a significant negative association was found in Ha Noi; with a 1% increase in humidity, the number of dengue cases decreased –24.1% (95% CI: –35.5% to –10.8%, $P = 0.001$).

There was a significant negative association between dengue cases and the hours of sunshine in Ha Noi and Ca Mau, but a significant positive association in Gia Lai (Fig. 4d); the percentage changes were –3.9% (95% CI: –5.4% to –2.3%, $P < 0.001$), –1.8% (95% CI: –2.5% to –1.1%, $P < 0.001$) and 1.6% (95% CI: 0.2% to 2.9%, $P = 0.02$), respectively.

Test for heterogeneity

The association of humidity, rainfall, temperature, and sunshine with dengue in the different provinces was found

to be significantly heterogeneous, $\chi^2_{8df} = 38.6$, $P < 0.001$, $\chi^2_{8df} = 18.4$, $P = 0.018$, $\chi^2_{8df} = 67.5$, $P < 0.001$ and $\chi^2_{8df} = 48.8$, $P < 0.001$, respectively.

DISCUSSION

In our results, the test of heterogeneity indicated that the impacts of each weather component on dengue cases varied from one area to another. Although Vietnam lies entirely in the tropical monsoon region, it exhibits considerable climatic and topographic diversity from north to south over different latitudes [8]. This contributes to the diversity in the association between weather components and dengue incidence among the nine provinces. Weather and climate variability can induce variation in dengue incidence via the development and survival of vectors or dengue viruses [21, 22]. Moreover, the spatial distribution of both vectors (*Ae. aegypti* and *Ae. albopictus*) of dengue transmission to humans in Vietnam was reportedly influenced by weather components. In fact, the density of mosquitoes varied between geographic regions, namely, with *Ae. aegypti* mainly found in the southern and central regions and *Ae. albopictus* mainly found in the northern region, because *Ae. albopictus*

prefer cooler temperatures than do *Ae. Aegypti* [5]. Also, it is said that the dengue transmission rate of *Ae. aegypti* is much higher than that of *Ae. albopictus* [25]. Therefore, the diversity of climatic conditions is correlated to the difference in dengue incidence.

A significant association was observed between monthly average temperature and the monthly number of dengue cases with a lag of 0–3 months in five provinces (Fig. 3b). These results confirmed previous findings. For example, a positive association was found in Mexico [13], Puerto Rico [14] and Thailand [26], and a negative association was found in Taiwan [11], while no significant correlation was noted in Trinidad [27] or the Philippines [28]. Temperature strongly influences dengue transmission and epidemic potential because increased temperature accelerates transmission risk by shortening the extrinsic incubation period of the pathogen, the expansion in geographical range and the distribution of vectors [21, 22] or by increasing the survival rate and larva growth [29]. However, increased temperature up to a certain point reduces the mosquito population by hampering egg production and increasing the daily mortality rate among adult mosquitoes [30, 31]. The complexity of these factors is consistent with the results of the present study, that is, four out of nine study areas showed a positive association and a negative association in one area, illustrating that the intensity of climatic impact, particularly temperature, differed between areas. The negative association in Ho Chi Minh province could be explained by a different proportion of vector species: *Ae. albopictus* is the major vector in Ho Chi Minh, while the major vector in the other provinces of the southern region is *Ae. Aegypti* [5]. Since *Ae. albopictus* prefers cooler temperatures, the higher temperature in Ho Chi Minh might cause a decrease in the *Ae. albopictus* population and thus lead to a reduction in the number of dengue cases.

In our study, humidity and dengue showed both positive and negative associations. A previous study pointed to the synergic effect of humidity and temperature on the reproductive rate and survival of female mosquitoes, egg production, and the authors emphasized that survival decreased when temperature increased from 25°C to 35°C, with constant 80% relative humidity, and that the oviposition rate was even lower at 35°C and 60% relative humidity [30]. Humidity could affect dengue transmission by exerting a desiccative effect and thus impact survival: high humidity increases vector survival while low humidity decreases vector survival [22]. Variations in humidity and rainfall also play an important role and relate to temperature in terms of their effects on the mosquito population [32]. The differences in combinations of humidity, temperature, and rainfall might have positively and negatively influenced vector

population size as well as dengue incidence in an alternate manner.

Also, it is known that rainfall affects dengue incidence by changing the vector population size in combination with other weather components. Our results showed a significant positive association between rainfall and dengue incidence in Ha Noi, but a significant negative association in Ba Ria Vung Tau, findings consistent with those of previous studies [14]. Although in general rainfall may serve to increase the mosquito population by providing more mosquito breeding sites, heavy rainfall should reduce the population by destroying those breeding sites [22]. In fact, some study areas other than Ha Noi and Ba Ria Vung Tau had heavy rainfall in some seasons; hence, no significant association was observed with dengue cases. Furthermore, the variability of available water containers and water storage practices affects the association between rainfall and *Ae. aegypti* abundance, and it could also cause the association between rainfall and dengue transmission to vary among areas [33].

The intensity and duration of sunshine exerts an effect on the metabolism and energy of vectors, as they do on the physiological processes of other living organisms. In fact, the light-induced killing of mosquito larvae in *Aedes aegypti* has been reported [34]. Moreover, *Ae. aegypti* is a day-biting species, with biting occurring mainly from two hours after sunrise to several hours before sunset [4]. A previous study in another area of Vietnam—Dak Lak province—revealed a negative association between sunshine duration and the number of dengue cases [35]. Our study shows the heterogeneity of the sunshine-dengue association among areas, with a negative association in Ha Noi and Ca Mau, a positive association in Gia Lai and no significant association in other areas. Sunshine is also closely linked to other ecological factors such as temperature and humidity and thereby might affect the dengue incidence. Therefore, the synergy of sunshine and the other weather components could cause variability in the association with dengue incidence among studied areas.

Some possible weaknesses are inherent in this study. One is the under-reporting of cases. Because asymptomatic or atypical cases could not be identified by the current reporting system, cases without clinical symptoms were excluded from this study. Another is diagnostic accuracy, although misdiagnosis is unlikely because the diagnoses were based on WHO criteria [17] and because dengue is a common disease in these areas, and training in diagnosis and treatment is conducted regularly [16, 36]. A third weakness is the limited number of study sites, particularly the northern region where only Ha Noi was included. Although dengue cases were reported, a lack of complete meteorological data in the other provinces made it impossible to include

them in this study. Furthermore, we did not consider non-weather components that might influence the distribution and prevalence of the disease, such as socio-demography, urbanization, vector-control activities and human behavior that could influence mosquito populations and contact between susceptible humans and mosquito vectors. Although such factors do not vary over the short- to medium-term, they might be important long-term modifiers of the association between weather and dengue fever.

Our study findings confirm that weather components play an important role in the transmission of dengue fever. In particular, temperature, rainfall, humidity and sunshine showed both negative and positive impacts on dengue incidence. However, the direction and degree of its influence on dengue incidence differs when latitude and topography differ even within the same country. The heterogeneous nature of this association might require DF/DHF control measures to be tailored specifically at the local level in Vietnam.

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