Published in final edited form as:

Int J Parasitol. 2011 January ; 41(1): 109–116. doi:10.1016/j.ijpara.2010.08.005.

Social and environmental determinants of malaria in space and time in Viet Nam

Bui H. Manh^a, Archie C.A. Clements^{b,c,*}, Nguyen Q. Thieu^d, Nguyen M. Hung^d, Le X. Hung^d, Simon I. Hay^e, Tran T. Hien^a, Heiman F.L. Wertheim^{a,f}, Robert W. Snow^{f,g}, and Peter Horby^{a,f}

^aOxford University Clinical Research Unit, Viet Nam

^bUniversity of Queensland, School of Population Health, Herston 4006, Queensland, Australia

^cAustralian Centre for International and Tropical Health, Queensland Institute of Medical Research, Herston 4006, Queensland, Australia

^dNational Institute of Malariology, Parasitology and Entomology, Hanoi, Viet Nam

^eSpatial Ecology and Epidemiology Group, Tinbergen Building, Department of Zoology, University of Oxford, South Parks Road, Oxford, UK

^fCentre for Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK

^gMalaria Public Health and Epidemiology Group, Centre for Geographic Medicine, KEMRI – University of Oxford – Wellcome Trust Collaborative Programme, Nairobi, Kenya

Abstract

The malaria burden in Viet Nam has been in decline in recent decades, but localised areas of high transmission remain. We used spatiotemporal analytical tools to determine the social and environmental drivers of malaria risk and to identify residual high-risk areas where control and surveillance resources can be targeted. Counts of reported *Plasmodium falciparum* and *Plasmodium vivax* malaria cases by month (January 2007–December 2008) and by district were assembled. Zero-inflated Poisson regression models were developed in a Bayesian framework. Models had the percentage of the district's population living below the poverty line, percent of the district covered by forest, median elevation, median long-term average precipitation, and minimum temperature included as fixed effects, and terms for temporal trend and residual district-level spatial autocorrelation. Strong temporal and spatial heterogeneity in counts of malaria cases was apparent. Poverty and forest cover were significantly associated with an increased count of malaria cases but the magnitude and direction of associations between climate and malaria varied by socio-ecological zone. There was a declining trend in counts of malaria cases during the study period. After accounting for the social and environmental fixed effects, substantial spatial heterogeneity was still evident. Unmeasured factors which may contribute to this residual variation include malaria control activities, population migration and accessibility to health care. Forest-related activities and factors encompassed by poverty indicators are major drivers of malaria incidence in Viet Nam.

Keywords

Malaria; Spatial epidemiology; Surveillance; Bayesian statistics; *Plasmodium falciparum*; *Plasmodium vivax*; Poverty; Forest cover

1. Introduction

Following large epidemics in the early 1990s, malaria control in Viet Nam was intensified and over the past 20 years the incidence of malaria in Viet Nam has been greatly reduced (Hung et al., 2002; Barat, 2006). In 2008, 11,355 confirmed cases and 25 deaths were reported, compared with over one million cases and 4500 deaths in 1991 (Ettling, 2002). The decline is probably a consequence of the synergy between a strengthened malaria control program and extensive socio-economic development (Ettling, 2002; Hung et al., 2002; Van Nam et al., 2005). However, malaria remains a problem in some areas, particularly the central highlands, despite control efforts that include enhanced health services, early diagnosis and free treatment with artemisinin derivatives, and free insecticide-treated nets (Ettling, 2002; Van Nam et al., 2005; Thang et al., 2009). The factors believed to have been associated with the persistence of risk in these areas include remoteness and difficulty in delivering and sustaining control efforts; presence in the central highlands of the exophagic and exophilic vector *Anopheles dirus sensu stricto*; poor living and education standards; low perception of risk; and forest-related activities (Erhart et al., 2004, 2005; Sanh et al., 2008; Abe et al., 2009; Morrow et al., 2009; Peeters Grietens et al., 2010). Forest-related activities have been identified as an especially important risk factor for malaria (Guerra et al., 2006), with a population-attributable fraction of 53% estimated in one study in Viet Nam (Erhart et al., 2004). Poverty is also consistently identified as a risk factor for malaria in Viet Nam and reflects the fact that the burden of malaria is greatest in poor ethnic minority communities living in remote areas in close proximity to forests (Erhart et al., 2005; Sanh et al., 2008).

Despite the successes, malaria control remains a high priority for Viet Nam due to the threat of recrudescence or reintroduction into areas where control has been successful and due to evidence of declining efficacy of artemisinin based treatments in parts of the Mekong sub-region (Delacollette et al., 2009; Dondorp et al., 2010). Spatial epidemiological tools are increasingly being used to estimate and represent malaria risk, and identify environmental correlates of risk (Brooker et al., 2006; Childs et al., 2006; Noor et al., 2008; Clements et al., 2009; Hay et al., 2009; Reid et al., 2010). At the national level, maps of disease risk can be powerful tools for advocacy and engaging policy makers and funders. At a sub-national level, maps can assist malaria control program managers to mobilise and allocate resources whilst spatial analysis can provide new insights into the determinants of malaria transmission risk and help predict the impact on malaria transmission of new developments, such as infrastructure projects or changes in land use.

We conducted a spatial analysis of the association between counts of malaria cases and indicators of climate, poverty and forest cover. The aim was to identify high-risk areas in Viet Nam where surveillance and control resources can be concentrated. By examining variation explained and unexplained by the aforementioned factors, we also aimed to generate hypotheses regarding additional potential drivers of malaria risk at a time when the overall burden is in decline and the focus of interventions is moving towards active elimination of transmission in localised, high-risk areas.

2. Materials and methods

2.1. Study area

Viet Nam is elongated in a north-south direction and has wide variability in elevation from the coast to the central and northern highland areas (Fig. 1). The country has been divided by the General Statistics Office (GSO; <http://www.gso.gov.vn>) of Viet Nam into eight socio-ecological zones: Northwest, bordering Lao P.D.R. (and with a short border with China); Northeast, a partly mountainous region near the border with China and the Gulf of Tonkin; Red River delta, a densely populated region containing the major cities of Hanoi and Haiphong; North Central Coast, between Lao P.D.R. and the coast; South Central Coast, between the Central Highlands and the coast, and containing the major city of Danang; Central Highlands, a mountainous area bordering Cambodia; Southeast, containing Ho Chi Minh City; and Mekong River Delta in the far south. Each of these zones has a distinct climate by virtue of its latitude and topography. The first administrative division of Viet Nam is the province ($n = 64$) and these are sub-divided into districts ($n = 670$).

2.2. Malaria data

The numbers of reported cases of *Plasmodium falciparum* and *Plasmodium vivax* malaria by month from January 2007–December 2008, and by district, were provided by the National Institute of Malariology, Parasitology and Entomology (NIMPE), Viet Nam. In Viet Nam, malaria diagnosis is mostly based on microscopy but sometimes it was done by rapid diagnostic test (RDT). Data on the number of cases were missing in some districts for some months, for each type of malaria. The number of missing observations was 531 out of a total of 16,080 district/months (3.3%). These missing values were imputed by averaging the values from the two adjacent months in which data were collected; in most cases, these numbers were zero.

2.3. Demographic, social and environmental data

Population data by district were available from the GSO for 2006 and 2007. The district populations were imputed by month as follows: the difference in the district population in 2006 and 2007 was calculated and divided by 12 to give a monthly population increase (I). The 2007 population was assumed to apply to January 2007 and for subsequent months $i = (1, 2, \dots, 23)$, the population (P) in district j was calculated as follows: $P_{ij} = P_{i-1,j} + I_j$.

Temperature and precipitation data were obtained from the WORLDCLIM project (<http://www.worldclim.org/>). These are long-term average values collected at weather stations, interpolated using geostatistics to a 1 km² global grid. Digital elevation data were obtained from the Shuttle Radar Topography Mission (SRTM; <http://www2.jpl.nasa.gov/srtm/>) of the US National Geospatial-Intelligence Agency and the US National Aeronautics and Space Administration (Farr et al., 2007). These data were sampled at 3 arc-s (approximately 90 m). Data on forest cover from 2005 were obtained from the Ministry of Agriculture and Rural Development (MARD), Viet Nam. MARD updates land cover maps every 5 years based on LandSat and other remote sensing data, which are then ground-truthed by MARD staff. The original MARD map consisted of 17 different land cover categories that were collapsed into forest and non-forest categories. Each of these environmental variables, available electronically in raster (i.e. grid) format, was imported into the geographical information system (GIS) GRASS 6.4 (Neteler and Mitasova, 2007) using the *r.in.gdal* module.

District-level estimates of the percentage of the population living below the “overall poverty line” (defined as the expenditure required to purchase 2100 kcal per person per day, plus a modest allowance for non-food expenditures) were obtained from the International Food Policy Research Institute (IFPRI) (<http://gisweb.ciat.cgiar.org/povertymapping/>). These data

were based on small area estimates from household surveys and the national census (Minot and Baulch, 2005).

Administrative boundaries in GIS format were downloaded from the website of the International Steering Committee for Global Mapping (<http://www.iscgm.org>). The malaria, demographic and poverty data were linked to these administrative maps on the basis of the district name. Administrative boundaries often change in Viet Nam. Whilst the malaria data matched the administrative boundary map, there were 670 districts in the malaria data set compared with 614 in the poverty data set (which used older administrative divisions). Districts were reconciled to match across each data set, with priority given to preserving the highest resolution possible for the malaria data. For new districts that were created by splitting old districts, the same proportion of the population below the poverty line was assumed for each of the new districts as for the old district. For new districts that were created by merging multiple old districts, the proportion of the population below the poverty line of the old district that contained the largest proportion of the area of the new district was used. For new districts that had expanded in area by including parts of adjacent districts, the proportion of the population below the poverty line of the original district was used.

Spatial median values of temperature, precipitation and elevation were calculated for each district using the GRASS module *r.statistics*. The percentage of the area of each district covered by forest was also calculated in the GIS using this module.

2.4. Analysis

Of the 16,080 observations in the final data sets, there were 12,870 (80.0%) zero counts for *P. falciparum* and 14,241 (88.6%) zero counts for *P. vivax*. Zero counts can arise from two processes: “true zeros” (also called structural zeros), which occur in districts that could not have supported malaria transmission during the study period, and “random zeros”, which occur in districts that could have supported malaria transmission but for some (or possibly all) months, did not have any reported cases.

Zero-inflated Poisson regression models were developed in the Bayesian statistical software WinBUGS version 1.4 (Medical Research Council, Cambridge, UK and Imperial College London, UK) for *P. falciparum* and *P. vivax*. They contain a mixing probability ω that the observation is a true zero count. Due to co-linearity with minimum temperature (Pearson's correlation coefficient $>|0.7|$), maximum temperature was excluded from the models. Preliminary analyses suggested different effects of climate (rainfall and minimum temperature) in different socio-ecological zones of Viet Nam. Therefore, the models had separate coefficients for these climate effects in each zone.

For the count of malaria cases Y in district i , month j , the mixture was specified as follows:

$$P(Y_{ij}=y_{ij}) = \begin{cases} \omega + (1 - \omega) e^{-\mu}, & y_{ij}=0 \\ (1 - \omega) e^{-\mu} \mu^{y_{ij}} / y_{ij}!, & y_{ij}>0; \end{cases} \quad (1)$$

and the regression on the social and environmental effects against the modelled mean count, μ , had the following form:

$$\log(\mu_{ij}) = \log(E_{ij}) + \alpha + \beta^T \chi_i + \gamma_N W_{ij} + \delta_N Z_{ij} + v_i + \theta t_j; \quad (2)$$

where E_{ij} is a population offset (calculated as the product of the district population in month j and the total number of malaria cases divided by the total person months at risk in Viet Nam over the entire study period); α is the intercept; β is a vector of T coefficients for the district-level covariates x_j (elevation, percent of the population below the poverty line and

percent forest cover); γ_N and δ_N are socio-ecological zone-specific coefficients for precipitation (w_{ij}) and minimum temperature (z_{ij}), respectively; ν_i are spatially auto-correlated district-level random effects; and θ is a coefficient representing temporal trend, where t_j are the months 1, 2, ..., 24. Non-informative priors were used for the unknown model parameters, including: $\alpha \sim \text{uniform}(-\infty, \infty)$, $\beta, \gamma, \delta, \theta \sim N(0, 1000)$ and $\omega \sim \text{beta}(1, 1)$. The spatially auto-correlated random effect ν_i was modelled using a conditional autoregressive prior structure (Besag et al., 1991), where spatial relationships between districts were defined according to a simple adjacency weights matrix. If two counties shared a border, the weight = 1 and if they did not, the weight = 0.

The models were run for an initial 1000 iterations and the values from these iterations were discarded. They were then run in blocks of 10,000 iterations after which the posterior chains of the unknown model parameters were examined for convergence. Due to slow convergence (at approximately 100,000 iterations), with poor mixing and auto-correlated chains, it was ultimately decided to thin the chains by a factor of 50 iterations. Ten-thousand values from the posterior distributions of each of the unknown model parameters were then stored for subsequent analysis. These were summarised by the posterior mean and 95% credible intervals (CrI). For the co-variate effects, an odds ratio that is significant at the 5% level is one for which the 95% CrI excludes 1.0. To determine what percentage of spatial variation was explained by the social and environmental covariates, the models were also run without the covariates and the variance of the spatial random effect ν_i was calculated and compared for the models with and without the covariates.

3. Results

3.1. Descriptive analysis

In the final data sets (including imputed missing data), there were 18,034 cases of *P. falciparum* malaria (10,205 in 2007 and 7829 in 2008) and 5178 cases of *P. vivax* malaria (3209 in 2007 and 1969 in 2008). This gives an overall incidence of 1.05 and 0.30 cases per 10,000 person years at risk for *P. falciparum* and *P. vivax*, respectively. *Plasmodium falciparum* infections displayed a strong seasonal pattern with peaks in cases in September 2007 and November 2008; whereas the nationally aggregated *P. vivax* data did not show such an obviously seasonal pattern, with a small peak in November 2007 and no clear peak in 2008 (Fig. 2). Both types of malaria were highly heterogeneously distributed across the country (Figs. 3 and 4). Despite only having 0.5% of the population, four districts (Quang Tri district, Huong Hoa Province, North Central Coast; Quang Nam district, Nam Tra My Province, South Central Coast; Binh Phuoc district, Bu Dang Province, Southeast; and Binh Phuoc district, Phuoc Long Province, Southeast) reported 26.2% of all *P. falciparum* and 27.3% of all *P. vivax* cases during the study period. This concentration of cases in few districts and a high proportion of zero-count districts, resulted in extreme over-dispersion of malaria cases.

3.2. Spatiotemporal model

The count of malaria cases due to both *P. falciparum* and *P. vivax* was positively associated with percentage forest cover of the district and percentage of the population living below the poverty line (Table 1). The magnitude of the association between both types of malaria and percent forest cover was remarkably similar, but there was a stronger association between *P. falciparum* malaria and percentage of the population living below the poverty line (log Relative Risk 0.36, 95% CrI 0.21–0.52) than for *P. vivax* (log Relative Risk 0.17, 95% CrI 0.02–0.33). There was a negative association with both types of malaria and median elevation of the district, but this was not significant at the 5% level. The association between counts of malaria cases and the climate variables – long-term average precipitation and

minimum temperature – varied in direction and magnitude across the eight socio-ecological zones of Viet Nam. In the Northwest, North Central Coast, South Central Coast and Central Highlands, there was a positive association between both types of malaria and precipitation (i.e. as precipitation increased, the count of malaria cases increased), although for *P. vivax* this was only significant at the 5% level in the North Central Coast zone. By contrast, there was a negative association between both types of malaria and precipitation (i.e. as precipitation increased, the count of malaria cases decreased) in the Southeast and Mekong Delta zones. There was a significant, negative relationship between minimum temperature and both types of malaria (i.e. as minimum temperature increased, the count of malaria cases decreased) in the Northwest, Central Highlands and Southeast. However, there were significant, positive associations between *P. falciparum* malaria and minimum temperature (i.e. as minimum temperature increased, the count of malaria cases increased) in the Northeast and North Central Coast, and between *P. vivax* malaria and minimum temperature in the North Central Coast and Mekong Delta zones. There was a significant, negative temporal trend in counts of cases of both types of malaria over the study period.

The spatially auto-correlated random effect (ν_j) smoothes the spatial pattern of residual variation in counts of malaria cases after taking into account the social and environmental fixed effects (Fig. 5). Both types of malaria show areas of lower than average malaria risk that is unexplained by the model fixed effects (low residual risk) around the major urban centres of Hanoi (in the Red River delta) and Ho Chi Minh City (in the Southeast). Low residual risk was also apparent in the coastal areas of the Northeast zone, and the western half of the Mekong delta. There was a corridor of low residual risk of *P. falciparum* malaria in the northwest of Viet Nam, running from the border of Yunnan Province, China, to the Lao P.D.R. For both types of malaria, areas of higher than average malaria risk unexplained by the model fixed effects (i.e. high residual risk) included the far Northwest and Northeast and most of the North Central Coast, South Central Coast, Central Highlands, Southeast (excluding the Ho Chi Minh City metropolitan area) and coastal areas of the Mekong delta.

The variance of the spatial random effect (ν_j) in the models with the co-variables was 7.0 (95% CrI 5.9–8.6) for *P. falciparum* and 9.4 (95% CrI 7.8–11.5) for *P. vivax*. In the models without co-variables, the variance was 8.5 (95% CrI 7.2–10.2) for *P. falciparum* and 10.6 (95% CrI 8.9–12.8) for *P. vivax*. This indicates that the social and environmental co-variables explained 17.8% of the spatial variability of *P. falciparum* and 11.8% of the spatial variability of *P. vivax* malaria counts.

4. Discussion

Malaria risk continues to decline in Viet Nam and is now very heterogeneous, with most cases concentrated in a relatively small number of districts. Malaria incidence is strongly associated with social and environmental factors that can be summarised by the percentage of the population living under the poverty line and the percentage of forest cover. However we found a variable association between counts of malaria cases and climate (precipitation and minimum temperature) in different socio-ecological zones. This variable relationship demonstrates the difficulties in making predictions about the influence of climate change scenarios on malaria transmission. The variation in the association between climate and malaria epidemiology may result from a combination of spatial differences in the predominant vector species and their favored ecological conditions, and the limitations of the climate data (Trung et al., 2004; Garros et al., 2008). Unmeasured risk modifiers, such as malaria control activities, socio-economic development, localised behavioural patterns and population mobility, may also drive a partial dissociation between climate and risk, reflecting similar observations at a global scale (Gething et al., 2010).

The magnitude of the random effects shown in Fig. 5 demonstrates the residual presence of influences on counts of malaria cases after accounting for the effects of poverty, forest cover, climate and elevation. These additional, unmeasured factors are likely to be highly important given the relatively modest percentage of spatial variability explained by the model covariates. Unmeasured factors that could contribute to the residual spatial variation in risk include systematically better case ascertainment in some areas due to greater awareness, effective malaria control interventions, differences in accessibility to preventive and curative services, locally prevalent behavioural risk factors for malaria, and migration of cases across the border from high-risk areas in neighbouring countries. Labourers and traders may migrate into Viet Nam from malaria endemic areas of Laos and Cambodia: migrant workers are known to be at particularly high risk of malaria and may have poor knowledge of malaria and poor access to preventive and therapeutic services (Xu and Liu, 1997; Wiwanitkit, 2002; Kitvatanachai et al., 2003; Chaveepojnkamjorn and Pichainarong, 2004; Van Nam et al., 2005).

A major limitation of any attempt to use routine case reports to measure risk is the completeness and representativeness of such data sources. It has been shown that routine reporting of malaria cases through the health system in Viet Nam substantially underestimates the true number of cases (Erhart et al., 2007). Whether these factors affect the validity of our analysis depends on whether the extent of under-reporting systematically differs between areas. The use of enhanced case detection and early treatment as a control measure in high-risk areas would suggest that such a bias, if present, would tend to underestimate malaria risk in low transmission areas (Thang et al., 2009). Whilst poverty is a commonly used proxy measure for many risks, it cannot capture the complexity of non-biological pathways to illness, such as health system quality and accessibility, community perceptions and behaviours, and access to information (Morrow et al., 2009). Whilst mapping of accessibility to care and information may be feasible, mapping of community beliefs and perceptions is a much more challenging task.

Although the resolution of the spatial analysis presented here is relatively high compared with many other analyses, field surveys demonstrate heterogeneity in malaria risk at smaller scales than the district (Erhart et al., 2005). The application of spatial statistics to geo-referenced malariometric survey data offers opportunities for finer discrimination of risk. As the traditionally remote areas of Viet Nam become more open to agricultural development and the use of natural resources, and as economic corridors are opened throughout the Mekong sub-region, the role of population movements in modulating malaria risk requires greater consideration. Additionally, the most recent, available forest cover data were collected in 2005; future model refinement could involve the addition of more up-to-date forest cover data, and variables that describe dynamic changes in forest cover (e.g. due to deforestation and regeneration efforts). As a longer time-series of malaria surveillance data becomes available we will be able to investigate temporal variability (including inter-annual variability) in malaria incidence in more detail.

The distribution of counts of malaria cases throughout Viet Nam in 2007 and 2008 are partially explained by the distribution of poverty and forest cover. However, significant unexplained risk remains. Spatial analysis can help focus attention on areas where additional surveillance, sampling and research is needed to better define this unexplained variation.

Acknowledgments

A.C.A.C. is supported by a Career Development Award from the Australian National Health and Medical Research Council (#631619); S.I.H. is supported by a Senior Research Fellowship from the Wellcome Trust (#079091); and R.W.S. is a recipient of a Wellcome Trust Principal Research Fellowship (#079080). The project was funded by the Li Ka Shing Foundation through a grant to University of Oxford, U.K. It forms part of the output of the Malaria

Atlas Project (MAP, <http://www.map.ox.ac.uk>), principally funded by the Wellcome Trust, U.K. We thank Pete Gething and Anand Patil, University of Oxford, for their comments on the statistical analysis.

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Fig. 1. Location of Viet Nam, showing the eight socio-ecological zones recognised by the General Statistics Office: (1) Red River Delta; (2) Northeast; (3) Northwest; (4) North Central Coast; (5) South Central Coast; (6) Central Highlands; (7) Southeast; and (8) Mekong River Delta.

Fig. 2. Time series of numbers of reported cases of malaria due to *Plasmodium falciparum* and *Plasmodium vivax*, Viet Nam, January 2007–December 2008.

Fig. 3. Number of cases of malaria caused by *Plasmodium falciparum* reported by district in Viet Nam in: (a) 2007; and (b) 2008. District i = Quang Tri district, Huong Hoa Province; ii = Quang Nam district, Nam Tra My Province; iii = Binh Phuoc district, Bu Dang Province; and iv = Binh Phuoc district, Phuoc Long Province.

Fig. 4. Number of cases of malaria caused by *Plasmodium vivax* reported by district in Viet Nam in: (a) 2007; and (b) 2008.

Fig. 5. Spatial random effects for counts of malaria cases caused by: (a) *Plasmodium falciparum*; and (b) *Plasmodium vivax*. Values are derived from zero-inflated Poisson regression models of the number of cases of malaria caused by each species, reported by month and district in Viet Nam, 2007–2008, and are on a scale of log relative risk.

Table 1

Values derived from zero-inflated Poisson regression models of counts of malaria cases caused by *Plasmodium falciparum* and *Plasmodium vivax*, reported by month and district, Viet Nam, 2007–2008. Estimates of co-variate effects are on the scale of log relative risk

Variable	<i>Plasmodium falciparum</i> Mean (95% CrI)	<i>Plasmodium vivax</i> Mean (95% CrI)
Elevation (100 m increase)	-0.12 (-0.27 to 0.03)	-0.02 (-0.15 to 0.10)
Percent living under poverty line (10% increase)	0.36 (0.21 to 0.52) ^a	0.17 (0.02 to 0.33) ^a
Percent forest cover (10% increase)	0.33 (0.16 to 0.50) ^a	0.39 (0.26 to 0.52) ^a
<i>Precipitation (100 mm increase)</i>		
Red River Delta	0.19 (-0.19 to 0.57)	0.09 (-0.29 to 0.44)
Northeast	-0.10 (-0.46 to 0.26)	0.08 (-0.14 to 0.30)
Northwest	0.45 (0.17 to 0.72) ^a	0.02 (-0.12 to 0.16)
North Central Coast	0.22 (0.19 to 0.25) ^a	0.15 (0.08 to 0.22) ^a
South Central Coast	0.24 (0.21 to 0.28) ^a	0.06 (-0.01 to 0.13)
Central Highlands	0.30 (0.26 to 0.34) ^a	0.04 (-0.07 to 0.14)
Southeast	-0.11 (-0.14 to -0.07) ^a	-0.09 (-0.16 to -0.03) ^a
Mekong Delta	-0.19 (-0.32 to -0.06) ^a	-0.32 (-0.53 to -0.12) ^a
<i>Minimum temperature (1 °C increase)</i>		
Red River Delta	-0.06 (-0.17 to 0.04)	-0.01 (-0.11 to 0.10)
Northeast	0.10 (0.00 to 0.21) ^a	0.04 (-0.02 to 0.10)
Northwest	-0.24 (-0.32 to -0.17) ^a	-0.07 (-0.11 to -0.03) ^a
North Central Coast	0.13 (0.12 to 0.15) ^a	0.05 (0.02 to 0.08) ^a
South Central Coast	0.01 (-0.02 to 0.04)	0.02 (-0.02 to 0.06)
Central Highlands	-0.23 (-0.26 to -0.20) ^a	-0.10 (-0.17 to -0.03) ^a
Southeast	-0.14 (-0.17 to 0.11) ^a	-0.13 (-0.19 to 0.07) ^a
Mekong Delta	-0.16 (-0.31 to 0.00)	0.24 (0.02 to 0.45) ^a
Trend (per month)	-0.01 (-0.01 to -0.00) ^a	-0.03 (-0.03 to -0.02) ^a
Intercept	-2.65 (-2.82 to -2.47)	-1.77 (-1.99 to -1.56)
ω	0.11 (0.09 to 0.14)	0.28 (0.25 to 0.32)

Variable	<i>Plasmodium falciparum</i> Mean (95% CrI)	<i>Plasmodium vivax</i> Mean (95% CrI)
Variance CAR random effect	7.00 (5.88 to 8.61)	9.37 (7.79 to 11.48)

CrI, Bayesian credible interval; CAR, conditional autoregressive.

^aSignificant co-variables at 5% level.