The relationship between rising temperatures and malaria incidence in Hainan, China, from 1984 to 2010: a longitudinal cohort study

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Summary

Background **The influence of rising global temperatures on malaria dynamics and distribution remains controversial, especially in central highland regions. We aimed to address this subject by studying the spatiotemporal heterogeneity of malaria and the effect of climate change on malaria transmission over 27 years in Hainan, an island province in China.**

Methods **For this longitudinal cohort study, we used a decades-long dataset of malaria incidence reports from Hainan, China, to investigate the pattern of malaria transmission in Hainan relative to temperature and the incidence at increasing altitudes. Climatic data were obtained from the local meteorological stations in Hainan during 1984–2010 and the WorldClim dataset. A temperature-dependent R_0 model and negative binomial generalised linear model were used to decipher the relationship between climate factors and malaria incidence in the tropical region.**

Findings **Over the past few decades, the annual peak incidence has appeared earlier in the central highland regions but later in low-altitude regions in Hainan, China. Results from the temperature-dependent model showed that these long-term changes of incidence peak timing are linked to rising temperatures (of about 1·5°C). Further, a 1°C increase corresponds to a change in cases of malaria from –5·6% (95% CI –4·5 to –6·6) to –9·2% (95% CI –7·6 to –10·9) from the northern plain regions to the central highland regions during the rainy season. In the dry season, the change in cases would be 4·6% (95% CI 3·7 to 5·5) to 11·9% (95% CI 9·8 to 14·2) from low-altitude areas to high-altitude areas.**

Interpretation **Our study empirically supports the idea that increasing temperatures can generate opposing effects on malaria dynamics for lowland and highland regions. This should be further investigated and incorporated into future modelling, disease burden calculations, and malaria control, with attention for central highland regions under climate change.**

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Introduction

In the past 20 years, the world has made great progress in fighting malaria. Despite this progress, malaria remains one of the most serious challenges to global health. In 2020, there were 241 million cases of malaria worldwide resulting in an estimated 627 000 deaths.[1] The WHO African region has the largest burden of malaria morbidity, with 228 million cases (95%) in 2020, followed by the WHO South-East Asia region (2%).[1] The seasonality and spatial distribution of malaria cases are affected by climatic factors, particularly temperature,[2–4] which affects the population dynamics and biting rates of mosquitoes that transmit the disease.[5,6] Temperature also affects the sporogonic cycle of these mosquitoes. A study showed that the extrinsic incubation period (the time for parasites to reach their infectious stage) was shortest at 34°C and increased at cooler temperatures by pairing of *Anopheles stephensi* and *Plasmodium falciparum*.[7] The influences of temperature variability on mosquito-borne viruses, such as dengue and Zika, are well described and accepted.[8,9] However, the possible effects of temperature on malaria incidence are controversial.[10–12] Rising temperatures above a critical minimum (approximately 18°C for extrinsic incubation period of *P falciparum* and 15°C for *Plasmodium vivax*)[13] might contribute, directly or indirectly, to malaria transmission, whereas temperatures higher than a critical maximum (approximately 32°C for extrinsic incubation period of *P falciparum* and 31°C for *P vivax*)[13] might decrease the survival of mosquitoes and parasites and reduce transmission.[13,14] The role of rising temperatures

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Research in context

Evidence before this study

We searched PubMed for studies on temperature and spatiotemporal heterogeneity of malaria transmission from Jan 1, 2000, to May 1, 2021, using the search terms "malaria transmission", "temperature", and "modeling". The effect of rising temperatures on the scale of malaria transmission has been explored extensively. However, empirical evidence on the effect of rising temperatures on seasonal malaria transmission is scarce, particularly for China.

Added value of this study

We use a 27-year dataset to show that malaria epidemic trends on a tropical island with more than 9 million inhabitants are sometimes inconsistent with model-based predictions of climate effects. By using mechanistic models, we showed how the intensity of malaria transmission is explained by the temperature on the island with spatial heterogeneity. We found that a trend of increasing temperature over several decades has shaped current patterns of malaria transmission in Hainan. Specifically, the annual peak incidence came earlier in the highland regions but later in lowland regions. The increasing temperature is associated with fewer cases during the rainy season, but more cases in the dry season.

Implications of all the available evidence

This study further shows the diverse effects of rising temperatures on malaria epidemic trends in tropical regions with great heterogenicity in altitude. Our results indicate the specific and precise mitigation and control for malaria, both in low-altitude regions and in the central highland regions, with appropriate timing and strength of control measures.

in increasing malaria incidence (especially malaria in highland areas) in Africa has been debated[15–17] and is unclear because of the presence of confounding factors, such as antimalarial treatment, human migration, changes of land use, and time-changing sampling criteria for different locations.

Climate conditions, such as temperature and rainfall, affect malaria transmission largely through changes in the lifecycles of mosquitoes and parasites,[13,14,18] as calculated with specific models. For example, the degree-day model was widely used to characterise the influence of temperature on extrinsic incubation period.[14] A study found a lower thermal limit for the development of *P falciparum* in *A stephensi* and *Anopheles gambiae* based on laboratory experiments.[19] Mechanistic models have also been developed to measure the influence of climatic factors on the intensity of malaria transmission, with a focus on the effect of temperature change.[4,5,8] This framework uses the results of laboratory studies to parameterise the non-linear temperature responses of mosquito and parasite life-history traits and synthesises these into estimates of the basic reproductive number (R_0) of malaria through time and space. These studies have improved our understanding of the potential responses of malaria transmission to climate change and of the heterogeneity in malaria risk among regions. Long-term incidence of malaria involving climate factors was also under investigation, with focus on malaria forecasts in Botswana based on an operational seasonal climate model,[20] observed increases in malaria driven by raised temperatures in the Kenyan highlands,[3] or establishing the link between the decreases in malaria epidemics in the Ethiopian highlands and the slowdown in global warming.[17] However, to date, the longitudinal, population-level empirical data for studying the interplay between climate factors and spatial heterogeneity of malaria is often absent for China.

See Online for appendix

We address this subject by revealing the spatial heterogeneity of malaria and its response to climate change over 27 years (from January, 1984, to December, 2010) in Hainan, a tropical island province in southern China with 9 million residents in an area of 32 900 km². Hainan exhibited endemic malaria throughout the year under consistent surveillance criteria (eg, case definition). The region also has high environmental and altitudinal heterogeneity in a comparatively small area (appendix p 2) which was surveyed longitudinally with uniform standards (eg, data format). Therefore, confounding factors are easier to account for compared with studies from African countries. Furthermore, malaria incidence in Hainan increased monotonically from the low-altitude northern plain regions to the medium-altitude southern hilly regions and the high-altitude central highland regions (up to 1800 metres). For every 100-metre increase in altitude, the cumulative incidence increased by 166·2 per 10 000 residents, which contrasts with the pattern in other endemic regions (eg, malaria incidence decreases from low to high altitude in Ethiopia and Colombia[21]). Over the past 50 years, more than 2 million malaria cases were reported in Hainan. In 1955, total annual incidence reached 1036 per 10 000 people, and parasites were detected in more than 50% of residents in the island's south-central highland region.[22] Due to successful control efforts, *P falciparum* incidence has declined, and *P vivax* has been the dominant malaria parasite on Hainan since the 1980s. *Anopheles minimus* and *Anopheles dirus* were the main malaria vectors. In 2021, WHO declared China a malaria-free country after a 70-year effort. We use a temperature-dependent model of malaria transmission to investigate how temperature variability might have influenced the seasonal and geographical distribution of disease, and compare the differences between the wet and dry seasons. Our results highlight the importance of considering the sensitivity and non-linear response of malaria transmission to temperature when predicting future risk and malaria disease burden.

Methods

Data collection

For this longitudinal cohort study, individual malaria cases in Hainan, China, during Jan 1, 1984, to Dec 31, 2010, were obtained from the Hainan Provincial Center for Disease Control and Prevention. We collected the malaria cases from 2011 to 2015 for Hainan. In total, 63 cases were reported, 53 of which were imported cases. The sample size of local cases was too small to support the analysis. Therefore, 2010 was chosen as the last year for data collection. We collected data starting from 1984. Clinically diagnosed and laboratory-confirmed cases were identified according to a unified set of diagnostic criteria issued by the Chinese Ministry of Health (panel).[23] From 1984 to 2010, a total of 188 884 cases were reported from 18 cities and counties in Hainan. Among these cases, 55 170 (29·2%) cases were confirmed by clinical diagnosis, and 133 714 (70·8%) cases were confirmed by both laboratory (microscopy) and clinical diagnosis. In our dataset, clinically diagnosed cases were defined as a patient with malaria-like symptoms and having lived in or recently travelled to areas with known malaria transmission. Laboratory-confirmed cases were defined as patients clinically diagnosed with malaria parasites confirmed by microscopy. Because the recorded monthly number of cases does not distinguish between clinically diagnosed and laboratory-confirmed cases, we used the total number of cases in the subsequent analysis.

The total population size and gross domestic product (GDP) per capita from 1986 to 2010 were obtained from Hainan Province's statistical yearbook.[24] Temperature and rainfall were obtained from the seven local meteorological stations in Hainan from 1984 to 2010 (appendix p 2). The averages of the standard 19 bioclimatic variables across 1970–2000 were downloaded from WorldClim at 340 km² resolution.[25] The bioclimatic variables were used for hierarchical clustering. To process the WorldClim dataset, the average across a specific region was calculated with ArcGIS v10.3. Due to the seven meteorological stations in Hainan, the temperature data from WorldClim was also downloaded. Land use and land cover data in Hainan were derived from the annual European Space Agency Climate Change Initiative land cover maps with a 300-metre spatial resolution.[26]

Temperature-dependent R_0 models

Over the past century, most malaria models of predicting optimal transmission were developed under the assumption of constant or linear responses of mosquito and parasite life-history traits to temperature. However, these models often contradicted the field observation. With more realistic ecological assumptions, a well established temperature-dependent R_0 model[1] was used to evaluate the transmission dynamics of malaria. In this model, all mosquito and parasite parameters are temperature sensitive.[1,3,27,28]

Panel: Diagnostic criteria for defining the clinically diagnosed and laboratory-confirmed malaria cases

The diagnostic criteria of suspected malaria cases (meets criterion 1 and 2), clinical malaria cases (meets criterion 1, 2, and 3, or 1, 2, and 4), and confirmed malaria cases (meets criterion 1, 2, and 5) were identified according to the criteria issued by the Chinese Ministry of Health:

1. A person who had resided in malaria-endemic areas during the malaria transmission season, or had a history of transfusion
2. A person who had clinical symptoms of chills, fever, sweating, and other malaria clinical symptoms, occurring in periodic attacks; splenomegaly and anaemia might occur after multiple attacks for the malaria cases; patients with severe malaria might go into shock or have fatal collapse
3. Clinical improvement (eg, no fever and chills) has been observed after 3-day antimalarial medication (mainly including piperaquine, chloroquine, and primaquine)
4. Positive results of indirect fluorescent antibody test or enzyme-linked immunosorbent assay
5. Plasmodium species (including *Plasmodium vivax*, *Plasmodium falciparum*, *Plasmodium malariae*, or *Plasmodium ovale*) is found in blood smear

$$R_{0,it}=\left(\frac{a(T_{it})^2 bc(T_{it}) e^{-\mu(T_{it})/\mathrm{PDR}(T_{it})}\mathrm{EFD}(T_{it})p_{EA}(T_{it})\mathrm{MDR}(T_{it})}{N_i r\mu^3(T_{it})}\right)^{1/2}$$

where (T) denotes the established parameter response for temperature;[5] a is the per day per mosquito biting rate (ie, [days to oviposition]$^{-1}$); bc is vector competence, b represents the proportion of infectious bites that infect susceptible humans, and c represents the proportion of bites on infected humans that infect susceptible mosquitoes; μ is the adult mosquito mortality rate (adult mosquito lifespan=$1/\mu$ days); PDR is the parasite development rate (ie, [days to parasite development]$^{-1}$); EFD is the number of eggs laid per female per day; p_{EA} is the mosquito egg-to-adult survival probability, and MDR is the larval mosquito development rate (ie, [days to larval mosquito development]$^{-1}$); N is the human density and T is the temperature, where i is a given region and t is the time; and r is the human recovery rate (ie, [days to human recovery]$^{-1}$). For mosquito density at population equilibrium, $M(T)$, we used the formula developed by Parham and Michael[4] and Mordecai and colleagues[2,5] as follows: $M(T)=\mathrm{EFD}(T)\times p_{EA}(T)\times \mathrm{MDR}(T)/\mu(T)^2$. Finally, the model output is scaled between zero and one (ie, R_0 was divided by the maximum), which could reflect the thermal suitability for malaria transmission.

For more on **ArcGIS** see https://www.esri.com/en-us/home

Statistical analysis

To identify whether there are regions that share similar patterns of climate or malaria epidemics in Hainan, we applied hierarchical clustering to identify regional clusters, relying on the squared Euclidian pairwise difference between climate time series or malaria time series as the distance metric.

To evaluate the effect of temperature and other cofactors, we used negative binomial generalised linear models on monthly malaria incidence (Y) with temperature-dependent R_0, human population size, GDP, medication, and area of each land cover. Time series analysis was done with the R package MASS.

$$Y_{it} \sim \text{NegBin}(\mu_{it}, \theta)$$

$$\log(\mu_{it}) = \alpha + \beta R_{0,it} + \gamma_1 \text{Cropland}_{it} + \gamma_2 \text{Grass}_{it} + \delta \text{Medication}_{it} + \xi \log(\text{GDP}_{it}) + \phi \log(\text{Pop}_{it})$$

where i is a given region and t is the time; β, γ_1, γ_2, δ, ξ, and ϕ are regression coefficients; R_0 is the temperature-dependent R_0; Cropland and Grass denote the proportion of area of cropland and grassland, respectively; GDP is the gross domestic product per capita; and medication represents the proportion of the population using antimalarial drugs.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of and the decision to publish the report.

Results

During 1984–2010, more than 180 000 malaria cases were reported in Hainan, China, with annual incidence ranging from 0·09 to 29·65 cases per 10 000 inhabitants. Among laboratory-confirmed cases, *P vivax* accounted for 131 425 (70%) of 187 988 cases. Malaria epidemics in Hainan occured before the start of the rainy season, between April and October, regardless of the magnitude of the incidence (figure 1A). In addition to this seasonal pattern, the magnitude of malaria incidence differed significantly across the island and was positively correlated with altitude (r=0·67, p=0·0024; figure 1B). Altitude is greatest in the central highland regions, second highest in the southern hilly regions, and lowest in the northern plain regions. A strong negative correlation was observed between rainy season temperature and altitude (r=–0·97, p<0·0001; figure 1B), although temperature should be decreased with increasing altitude. The negative association was not significant between rainy season rainfall and altitude (r=–0·08, p=0·87).

Since malaria in Hainan is structured by geography and climate, we also sought to explore the variables that might be associated with the intensity of malaria transmission on the island. We applied clustering method to district-level time series of malaria incidence and identified three main geographical regions that share similar epidemiological characteristics: northern plain regions, central highland regions, and southern hilly regions (appendix p 3). We recovered a near-identical set of three main regions when this method was applied to bioclimatic variables from WorldClim for the same

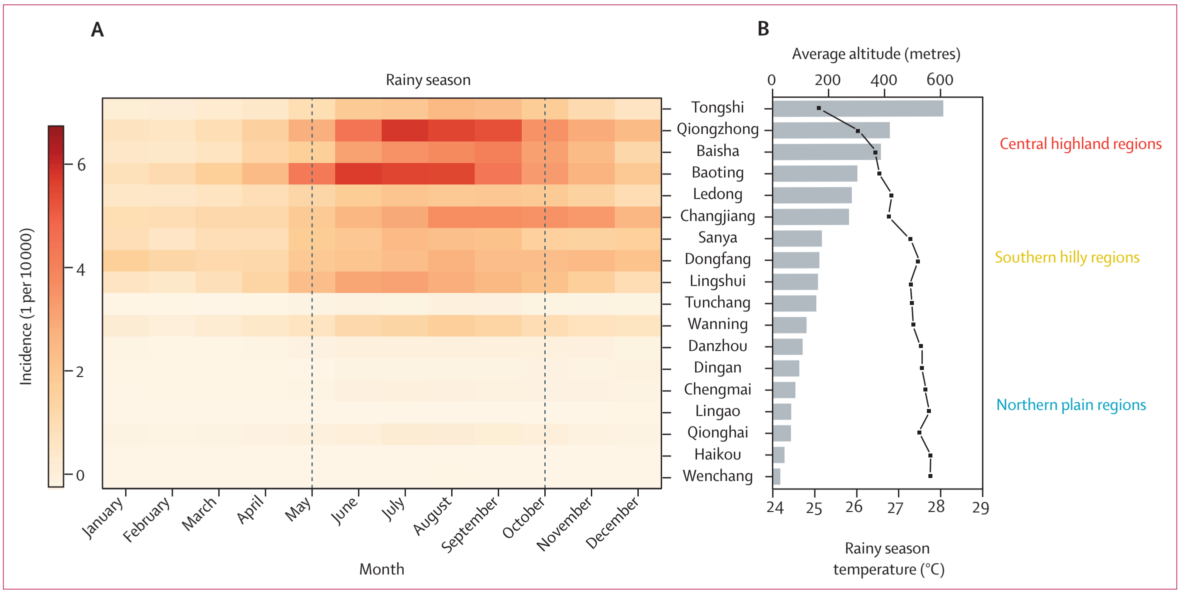

Figure 1: **Regions of distinct malaria epidemiology and climate in tropical Hainan, China**
(A) Average seasonal incidence of malaria for each district. Districts are ordered by altitude from low (top) to high (bottom). Malaria cases peak during the rainy season (May to October). (B) Mean altitude and rainy season temperature (black line) for each district in Hainan. Central highland regions include Tongshi, Qiongzhong, Baisha, Changjiang, and Dongfang. Southern hilly regions include Baoting, Ledong, Sanya, Lingshui, Wanning, and Qinghai. Northern plain regions include Tunchang, Danzhou, Dingan, Chengmai, Lingao, Haikou, and Wenchang.

districts (mutual information 0·58; appendix p 3), suggesting that climate and temperature contributes to the structure of malaria dynamics on the island. This result is robust to the number of climate variables per location used (appendix pp 4, 12). By comparing the epidemiological and climate clusters, we found that the temperature seems to be a key factor (appendix pp 2–3). The temperature is affected by the altitude, which affects the malaria transmission through the temperature-sensitive characteristics (eg, biting rate). Climatic factors explain the malaria incidence partly. Other factors (eg, farming in areas dense with mosquito populations) might also contribute to malaria incidence, which can cause inconsistency between epidemiological and climate clusters for some districts (ie, Dongfang, Tongshi, Qionghai, and Baoting).

The analysis found that climatic variables geographically matched the risk of malaria in Hainan. To understand this relationship and to quantify dynamics of malaria disease incidence in Hainan, we used a well established temperature-dependent R_0 model of malaria transmission that incorporates the effect of temperature on mosquito and parasite traits.[5] Following previous approaches,[5] these trait–temperature relationships were estimated by fitting experimental data (appendix p 13). All these relationships were unimodal and were used to predict the thermal response of malaria transmission. R_0 was maximised at about 25°C (figure 2B). The average temperatures of 25–26°C (covering the optimal temperature for R_0) in the rainy season for the highland regions of Hainan promote malaria transmission with the observed largest incidence. However, malaria incidence declines for the lower altitude districts were observed during the rainy season due to higher temperatures (exceeding 25°C) than the optimal one (figure 1A, B). The difference of daily temperatures from 1984 to 2010 is shown in the appendix (p 5) with a mean value of 7·51°C, and the daily mean temperature figure (appendix p 5) with a mean value of 24·23°C. The temperature also shows that Hainan is suitable for malaria transmission. In general, rainfall has effects on malaria transmission. However, rainfall is abundant across Hainan during the rainy season. Therefore, the effect of rainfall on malaria transmission should be very small (appendix pp 6, 15).

This model enabled us to predict the seasonal transmission potential of malaria in Hainan from monthly mean temperature data. During the dry season, the mean monthly temperature decreases from 22°C in November to 17°C in January, resulting in an annual minimum R_0 in winter (figure 2C). Temperatures and R_0 values rise between February and April, indicating increasing thermal suitability for transmission and R_0 remains high during the rainy season between May and October (figure 2C). Crucially, the model predicts differences in the magnitude of baseline transmission among epidemiological regions, particularly during the rainy season (figure 2C). Specifically, mean temperatures in the northern plain regions and southern hilly regions exceed the thermal optimum and thus relative R_0 values in those regions are depressed during the summer. In contrast, in the central highland regions, temperatures remain more suitable for transmission throughout the rainy season (figures 1B, 2C), although relative R_0 still drops during the summer months. These trends can explain the observed variation in malaria incidence among the three regions in Hainan (figure 2D): with the average seasonal incidence for each region (between 1984 and 2010), human malaria cases are highly correlated with temperature-dependent R_0 (r=0·75, p<0·0001). In addition, we estimated the R_0 of the three regions using the daily temperature curve; the result is consistent and can also explain the difference in the size of three different endemic areas (appendix p 7).

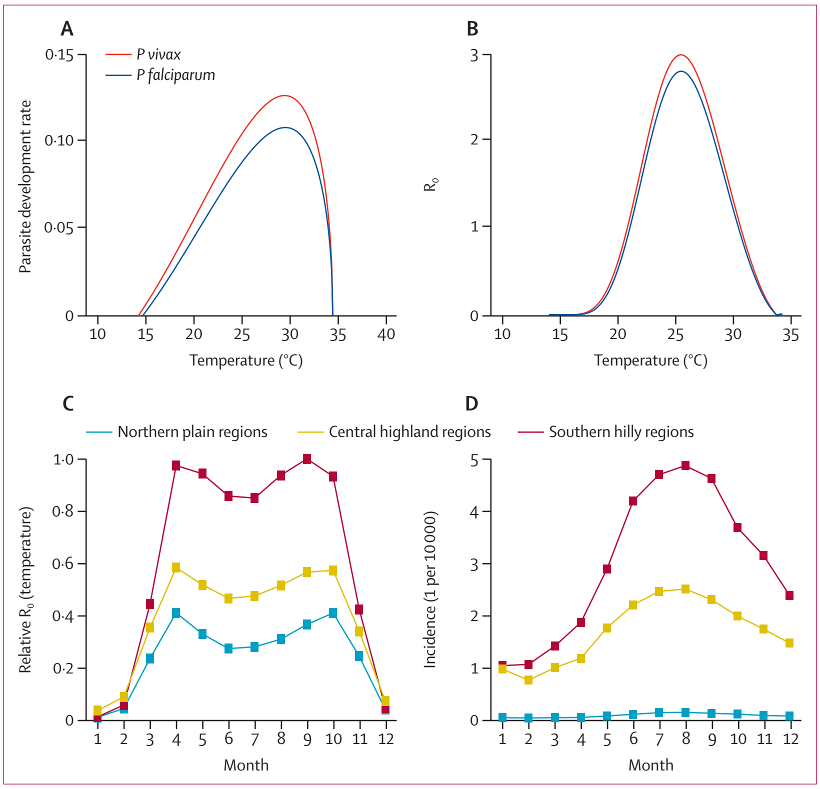

***Figure 2:* Effect of temperature on *Plasmodium* species dynamics and malaria transmission**
(A) Parasite development rate of *Plasmodium vivax* and *Plasmodium falciparum*. (B) Temperature-dependent R_0 for *P vivax* and *P falciparum*. (C) Seasonality of temperature-dependent relative R_0 values for the three epidemiological regions based on the WorldClim dataset. (D) Average seasonal incidence of malaria for the three epidemiological regions from 1984 to 2010.

In addition to the association between temperature and malaria incidence in Hainan, we found that the timing of the annual epidemic peak has changed with rising temperature. Mean temperatures in Hainan have increased by 1·5°C during the past 50 years and the minimum temperature has increased by 2°C (appendix p 8). Since 1984, when our malaria case data began, the timing of the peak in malaria transmission has changed

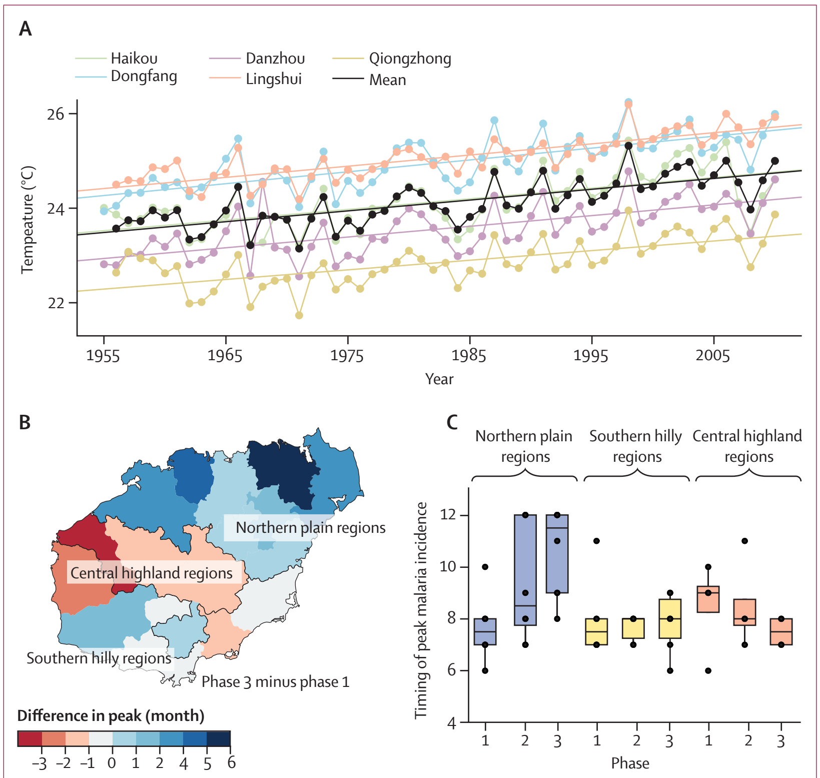

Figure 3: **Rising temperature and shift in timing of peak malaria incidence in Hainan, China, from 1984 to 2010**
(A) The change in mean annual temperature at weather stations in Hainan. (B) Change in the timing of the malaria seasonal peak among districts between phase 1 and phase 3. The magnitude of the time change in peak malaria is shown with a colour scale; red for earlier and blue for later. (C) Movement of malaria peak in each city over time in the northern plain regions, central highland regions, and southern hilly regions. Bar indicates median value and 95% CI. Phase 1=1984–92. Phase 2=1993–2001. Phase 3=2002–10.

with increasing temperature. The peak timing has significantly changed over time (northern plain regions, paired sample *t* test, p=0·020; central highland regions, p=0·00056; and southern hilly regions, p=0·11). The direction of change in epidemic peak time varies among locations. In the central highland regions, the epidemic peak has shifted to earlier in the year (from September to July) whereas in other regions it shifted to later in the year (from July to August or September; figure 3C). This change, when placed in the context of our temperature-dependent R_0 model (figure 2C), can be interpreted as a consequence of rising mean temperatures. As temperatures have risen, optimum conditions for transmission in the relatively cooler central highland regions have shifted earlier in the rainy season, whereas the same rise in low-altitude regions leads to greater depression of malaria transmission until the end of the rainy season. These patterns empirically show the consequences of the non-linear relationship between rising temperature and malaria transmission.

The predicted temperature-associated shift in malaria transmission across the year is shown in figure 4. A rising temperature might facilitate malaria during the dry season as conditions become more favourable for transmission but can also depress transmission in the rainy season because of temperatures exceeding the thermal optimum. Sensitivity analyses indicate that temperature is a key factor for malaria transmission potential in Hainan, especially in the low-altitude region (figure 4D). Correspondingly, the number of reported malaria cases during winter increased in more recent decades in some low-altitude northern plain regions (appendix p 9). To further investigate the effect of temperature, we used a negative binomial regression to analyse how malaria incidence in Hainan varies with temperature and other covariates. Malaria incidence among epidemiological regions is best explained by a model (chosen with the Akaike information criterion) that includes temperature-dependent R_0, GDP, antimalaria drug use, and landscape (including cropland and grassland). This model (table) indicates that temperature is an important determinant of malaria transmission heterogeneity. In the central highland regions, the model estimates that a 1°C increase in temperature corresponds to a change in cases of –6·5% (95% CI –5·2 to –7·7) in the rainy season to 11·9% (9·8 to 14·2%) in the dry season. In the southern hilly regions, the estimated change in cases ranged from –9·2% (–7·6 to –10·9) in the rainy season to 7·0% (6·0 to 8·0) in the dry season, and in the northern plain regions, it ranged from –5·6% (–4·5 to –6·6) in the rainy season to 4·6% (3·7 to 5·5) in the dry season. Estimates were obtained with all other covariates set to constant values. Malaria incidence in Hainan has decreased in recent decades because of socioeconomic development and large-scale interventions, such as mass drug administration and long-lasting insecticide-treated mosquito nets. These measures seem to reduce the general magnitude of malaria epidemics rather than the spatiotemporal patterns (figure 4E).

Discussion

Long-term trends in malaria incidence are affected by land-use change, malaria-control strategies, and drug resistance. The Hainan dataset with long time series and consistency provides an opportunity to control for confounding factors. Furthermore, this context allows us to examine the role of temperature in shaping malaria heterogeneity in a straightforward way. Our results show that long-term temperature rise is linked to, and is a likely cause of, changes in malaria incidence across a tropical island, with the implication that climate change has influenced the current malaria burden. Specifically, the seasonality and intensity of malaria in Hainan since the 1980s are consistent with the patterns we would expect from thermal-response transmission models. A previous study indicated the declining malaria disease burden in response to the rising temperature by the predictions.[10] Our study reveals a complex interplay between temperature and altitude on malaria epidemics in Hainan. This highlights the importance of incorporating appropriate non-linear interactions into mathematical models for prediction of malaria dynamics.

The model of temperature-dependent malaria transmission that we fitted to experimental data better explained the magnitude and seasonal activity of malaria across all three altitudinal regions of Hainan. Whether the predicted dip in relative R_0 during the middle of the year induces the decrease of malaria incidence is unclear and warrants future investigation. A possible explanation is that if the highest temperature exceeds the estimated optimum of 25°C,[5] malaria transmission would be restrained. Alternatively, actual temperatures for mosquitoes in their natural habitats in Hainan, such as forests, livestock sheds, and human residences, might be lower than the ambient temperature recorded by meteorological stations.

The effect of rising temperature on the spatiotemporal distribution of malaria in the central highland regions has been documented previously for Ethiopia and Colombia.[21] By incorporating a model of the thermal responses of mosquitoes and parasites, our longitudinal data from Hainan yield further insights into malaria epidemiology. First, malaria incidence on the island is higher in the central highland regions and lower in the northern plain regions (for every 100-metre increase in altitude, the cumulative incidence increased by 166·2 per 10 000 residents; appendix p 2), most likely because highland temperatures are closer to the optimum for transmission than those in the northern plain regions. Second, patterns of incidence have changed along with rising temperature—ie, transmission is lower in the rainy season but higher in the dry season in Hainan. And the annual peak incidence appeared earlier in the year in the central highland regions but later in the northern plain regions. Therefore, our study indicates that temperature is an important driver of disease patterns, although other socioeconomic factors also influence malaria transmission. Similar geographical distribution of GDP and population size were observed, and they were mainly distributed in low altitude areas (appendix p 2), supporting the association.

We also collected malaria cases from 2011 to 2015 for Hainan. In total, 63 cases were reported and 53 cases were imported. The sample size of local cases was too small to support the analysis. Therefore, 2010 was chosen as the end of study period. In 2021, WHO declared China a malaria-free country after a 70-year effort.[29] Key factors for success include usage of preventive antimalarial medicines, specific treatment, an effort to reduce mosquito breeding, the use of insecticide spraying, and insecticide-treated nets. Additionally, the 1-3-7 strategy was employed, which facilitates fast case reports (within 1 day), confirming and determining the risk of spread (within 3 days), and implementing appropriate measures to prevent further spread (within 7 days). The 1-3-7 strategy should also be helpful for other vector-borne diseases in China.

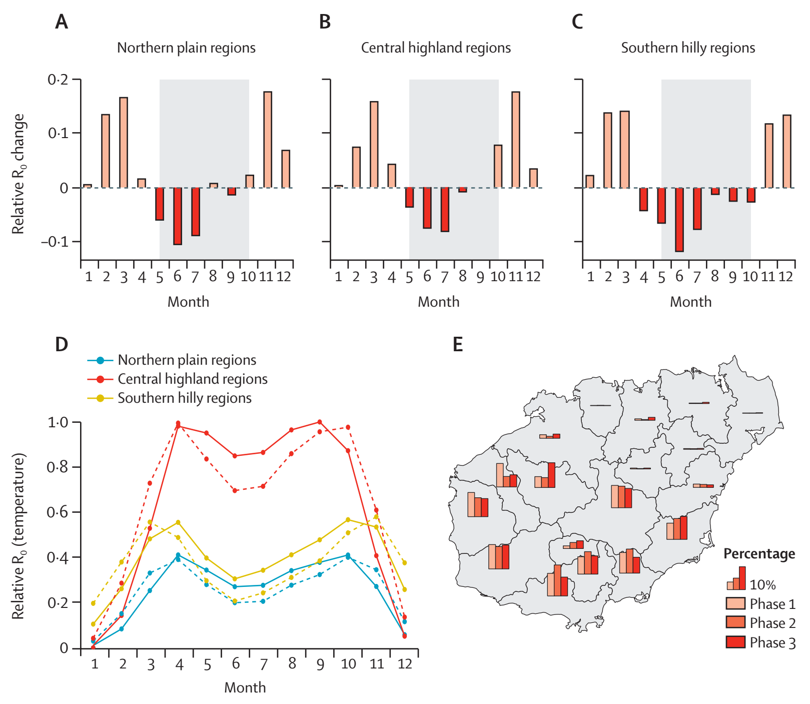

Figure 4: **Change in relative R_0 among regions over time and the robustness**
(A) Change in seasonal relative R_0 in northern plain regions over time. (B) Change in seasonal relative R_0 in central highland regions over time. (C) Change in seasonal relative R_0 in southern hilly regions over time. Relative R_0 in different months is generated from the corresponding monthly mean temperature. The grey shaded box indicates the rainy season. (D) Testing the robustness of the changing trend in transmission potential per region to a hypothetical temperature increase of 1°C in the future (as observed in the past). The solid lines represent the temperature-dependent R_0 in epidemiological regions during 2002–10. The dotted lines represent the scenario in which the temperature increases by 1°C. (E) Percentage of malaria cases in each district for phases 1, 2, and 3. Phase 1=1984–92. Phase 2=1993–2001. Phase 3=2002–10.

	Coefficient (SE)	p value
Intercept	–7·01 (9·22)	0·45
Population	1·48 (0·75)	0·050
Gross domestic product per capita	–0·91 (0·08)	<0·0001
Proportion of cropland by area	–0·17 (0·04)	<0·0001
Proportion of grassland by area	1·49 (0·20)	<0·0001
Proportion of the population using antimalarial drugs	–0·00 (0·00)	0·11
Temperature-dependent R_0	0·16 (0·02)	<0·0001

Table: **Parameter estimates for the negative binomial regression model**

There are a few limitations to our study. We assume control measures reduce the general magnitude of malaria epidemics rather than the spatiotemporal patterns. No significant spatial autocorrelation for malaria incidence was detected (Moran's I=0·17, p=0·27). Although we assume that the effect of rainfall on malaria transmission should be very small (appendix p 6), it is possible that rainfall seasonality could, along with control measures, regulate malaria transmission patterns. However, the parameter estimates from the best model indicate that the temperature is significantly associated with malaria incidence (appendix pp 14–15), but not for rainfall in Hainan. We also checked the interaction between rainfall and medication. Although the interaction is significant, the effect size is quite small in Hainan (appendix p 15). The sufficient rainfall might also weaken the effect of time lag on malaria transmission. The rainfall with a 1-month lag is not significantly related to the malaria incidence (appendix p 16). However, the temperature with a 1-month lag is still significantly associated with incidence. The interdependencies between climate factors and human and mosquito habitats might have an effect on malaria incidence. Further data are needed to determine the association. The current thermal responses we used were generated from *Anopheles* spp (mainly *A gambiae*, *A stephensi* and *Anopheles quadrimaculatus*; appendix p 13) and, to our knowledge, experimental thermal response data are scarce for *A minimus* and *A dirus*. However, the seasonal proportion of mosquitoes arrested (appendix p 11) and the average seasonal incidence of malaria follows the similar pattern of temperature-dependent R_0. A study in Yunnan, China, indicates the biting rate of *A minimus* is highest in August with an average temperature of 25·5°C.[30] This might indicate the optimal temperature of R_0 is similar for different *Anopheles* spp. However, experimental data are needed to validate this.

Our study shows that a deeper understanding of the interactions between climate change and malaria epidemiology are required to optimally inform malaria elimination and public health decisions. The findings of earlier annual peak incidence in central highland regions indicates an earlier response in these regions.

Contributors
HT contributed to the conceptualisation of the report. HT, OGP, NCS, YaL, and GW were responsible for the supervision of the research activity planning and execution. HT, YoL, JL, MK, QH, BC, LD, RW, and ZW were responsible for the methodology. YaL, GW, DG, YuL, WS, and DS were responsible for data curation. YoL, YiL, BC, and ZW were responsible for the software. HT, YoL, and YiL were responsible for the visualisation of data presentation. HT, OGP, and ZW were responsible for the writing of the manuscript. YaL, GW, DG, YuL, WS, DS, and RW verified the underlying data. HT, NCS, and GW had full access to all the data in the study and all authors had final responsibility for the decision to submit for publication. The corresponding author confirmed that all authors have seen and approved of the final text.

Declaration of interests
We declare no competing interests.

Data sharing
All data used in this study are provided in the Article or appendix, and from the authors on request. The code is available at https://github.com/wangzengmiao/Malaria-Hainan.

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