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Influence of Climate on Malaria in China

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Abstract

Malaria is the fifth leading cause of death from infectious diseases worldwide, after respiratory infections, HIV/AIDS, diarrheal diseases, and tuberculosis. With half the world's population living in areas at risk of malaria transmission, it remains a public health issue in many countries, including China. To understand the epidemiology of the disease, it is important to study the climate and environmental factors such as temperature, precipitation, relative humidity, and altitude, because these factors influence the life cycles and development of both the malaria parasite and mosquito vector. Global warming and climate change can increase the areas at risk of malaria incidence and affect transmission rates. As temperatures get warmer, incubation periods for the parasite and mosquito development can shorten, and malaria transmission can occur at higher elevations, infecting populations that have not been exposed to the disease. While control measures and efforts have been undertaken to eliminate malaria in China, the disease still exists in concentrated areas. Changes in temperatures and rainfall could reverse control efforts if the disease spreads from the seven provinces in which it has been concentrated.

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Abstract

Malaria is the fifth leading cause of death from infectious diseases worldwide, after respiratory infections, HIV/AIDS, diarrheal diseases, and tuberculosis. With half the world's population living in areas at risk of malaria transmission, it remains a public health issue in many countries, including China. To understand the epidemiology of the disease, it is important to study the climate and environmental factors such as temperature, precipitation, relative humidity, and altitude, because these factors influence the life cycles and development of both the malaria parasite and mosquito vector. Global warming and climate change can increase the areas at risk of malaria incidence and affect transmission rates. As temperatures get warmer, incubation periods for the parasite and mosquito development can shorten, and malaria transmission can occur at higher elevations, infecting populations that have not been exposed to the disease. While control measures and efforts have been undertaken to eliminate malaria in China, the disease still exists in concentrated areas. Changes in temperatures and rainfall could reverse control efforts if the disease spreads from the seven provinces in which it has been concentrated.

Literature shows that there are relationships between climate and malaria incidence all around the world. Malaria incidence and transmission risk change in accordance with climatic factors. Among the factors studied, temperature and precipitation have the strongest relationships with malaria incidence. Temperature and altitude as a proxy for temperature are easy to predict and analyze. Minimum threshold temperatures for parasite development of *Plasmodium falciparum* and *P. vivax* are 18°C and 15°C, respectively. Studies of diurnal temperature fluctuations show that fluctuations around low temperatures increased malaria risk while fluctuations around high temperatures decreased the risk. A study of malaria transmission and mosquito nets in relation to three altitude transects in Tanzania showed that while there were no parasites in the highlands, there was an 18.8% parasite prevalence in

the intermediate zone and 62.6% prevalence in the lowlands. Precipitation does not have a linear relationship with malaria incidence and risk. Rather, the relationship is quite complex because vector larvae can be flushed out of water basins during episodes of heavy rainfall. Land use change can also affect malaria transmission by modifying local temperatures and the availability of mosquito breeding sites and vegetation. A study on the Normalized Difference Vegetation Index (NDVI) in relation to malaria in Paraguay showed a direct correlation with malaria case rates in areas that underwent land use change from forest to non-forest.

Studies of climate and malaria in China produced similar results. In Shuchen County, temperatures lower than 16°C and higher than 30°C showed a negative impact on both mosquito vectors and the extrinsic incubation period of the malaria parasites. Several studies show that correlations between temperatures and malaria cases have a lag effect of one or two months. One study on social aspects of malaria in Heping Town in the Hainan Province showed that high temperatures affected human behavior in ways that put more people at risk of malaria transmission. Actual bed net use was lower than reported use, and some people explained that they did not use the net because it was too stuffy inside. In addition, more people than reported have bamboo-slat houses or thatched roofs, which keep temperatures cooler inside but also allow easy access for infected mosquitoes. A study of NDVI in the Yunnan Province concluded that while NDVI is sensitively related to malaria incidence in two townships, other variables must also be incorporated, such as temperature and dry and wet season data. Humidity, on the other hand, does not have a statistically significant correlation with malaria incidence. In addition, fog is shown to be a predictor of malaria incidence on the year-long scale; however, the results are questionable because a relationship exists only for one seven-month interval.

Models using climate variables can predict malaria risk and transmission. Following such models and research on climate change can help lay the groundwork for malaria prevention and control in China. To prevent reintroduction of malaria in non-endemic areas and reach its goals for malaria eradication, China must keep tight surveillance of malaria incidence, particularly in areas bordering endemic provinces, maintain communication of global climate data, and prepare for malaria treatment and control. In order to control and prevent malaria cases in China, further research is needed to learn more about the influence of climate on malaria. Additional research can be done on rainfall events and larvae losses in China, the effects of different types of hydrology and geology on the *Anopheles* life cycle, and how climate change may decrease malaria transmission in some areas of China.

Introduction

Malaria, the fifth leading cause of death from infectious diseases in low-income countries, is a global public health problem in many developing countries [7]. People show symptoms of malaria between one to two weeks after being bitten by an infected mosquito, or even months afterward, depending on the parasite species. Symptoms include fever, headache, and vomiting; if left untreated, malaria can become life-threatening, as it disrupts the blood supply to vital organs [14]. According to the World Health Organization and the Global Malaria Action Plan, 3.3 billion people live in areas at risk of malaria transmission [7]. The World Health Organization reported an estimated 243 million cases of malaria worldwide in 2008, and an estimated 863,000 deaths due to malaria [27].

This public health burden is a mosquito-borne infectious disease caused by the parasite *Plasmodium*. Though an estimated 156 named species of *Plasmodium* infect vertebrates, just five types cause human malaria: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale*, and *Plasmodium knowlesi* [1]. *P. falciparum* and *P. vivax* are the most common, and *P. falciparum* is the most deadly. Because there are different species of malaria as well as different species of mosquitoes, it is important to note their unique life strategies and ecology.

In order to complete its life cycle, the *Plasmodium* parasite needs two hosts: a female *Anopheles* mosquito and a human, or another vertebrate. As a result, the epidemiology of malaria is dependent on the mosquito vector, human host, and the parasite itself. In order to infect a human, the malaria parasite must first fully develop in the mosquito, during a phase called the extrinsic incubation period (EIP). The length of this period depends on several factors such as climate, the parasite species, and whether the mosquito survives long enough to allow the *Plasmodium* to complete its cycle, which lasts from 10 to 21 days [2].

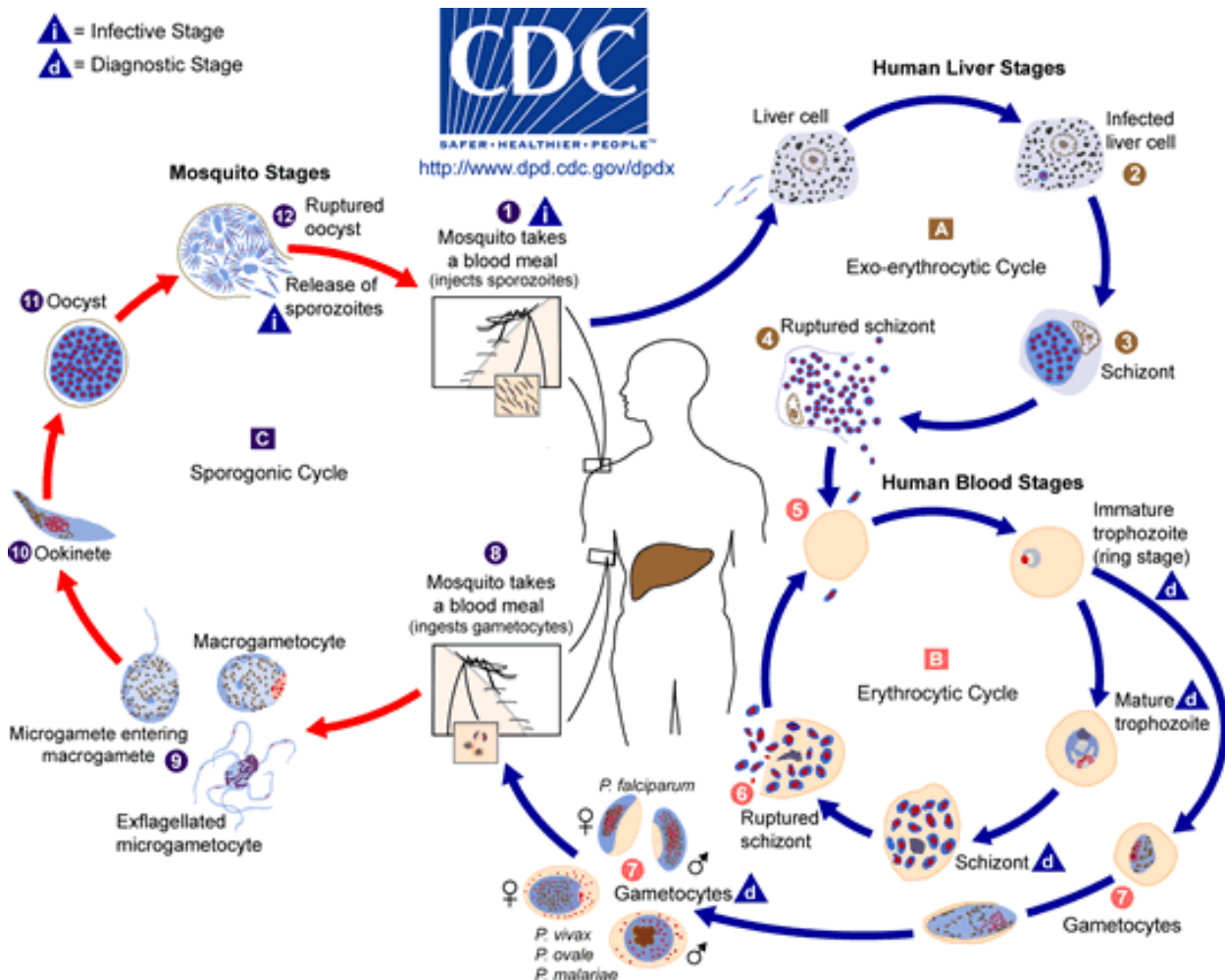
The mosquito vector is crucial in understanding malaria. Of the approximately 430 *Anopheles* species, about 30 to 40 act as malaria vectors. Mosquitoes have four stages in their life cycle: egg, larva, pupa, and adult. The first three stages are aquatic and develop over the course of five to fourteen days, depending on the species and the ambient temperature. The female adult stage acts as a vector as the *Anopheles* feeds on human blood. The females can live up to a month or even longer in captivity, but most survive for about one or two weeks in nature [2].

The 30 to 40 *Anopheles* species that act as vectors display various types of behavior, which can influence how and when humans get bitten and infected with malaria. Endophagic mosquito species feed indoors, while exophagic species feed outdoors. Endophilic species prefer to inhabit and rest indoors,

allowing for easier prevention methods such as residual insecticides on the house walls. Exophilic species, on the other hand, like to inhabit and rest outdoors, and can be more challenging to control [16].

A malaria-infected mosquito infects a human when feeding on the human's blood. Sporozoites in the mosquito's saliva enter the human host. Within the human host cycle, there are two main stages: the liver stage and the red blood cell stage. The sporozoites first infect the liver cells, in which they mature into schizonts. Depending on the parasite species, these either rupture and release merozoites, or lay dormant as hypnozoites and cause relapses by entering the bloodstream weeks or years later. After the parasites leave the liver, they undergo asexual multiplication in red blood cells, developing into trophozoites and then schizonts again. These then rupture, releasing merozoites. This stage of the malaria parasite's life cycle causes the main symptoms [1] (Figure 1).

Figure 1. Malaria life cycle. (Source: Centers for Disease Control and Prevention, <http://www.cdc.gov/malaria/about/biology/index.html>.)



The epidemiology and life cycle of malaria, the *Anopheles* mosquito, and human behavior are critical in linking climate change and malaria. The factors that will be examined here are temperature, altitude, precipitation, and vegetation as reflected by the Normalized Difference Vegetation Index (NDVI), with a focus on China.

Malaria used to be a serious health problem in China. In the 1940s, there were at least 30 million malaria cases, with a mortality rate of about 1% annually [11]. Furthermore, during the 1960s and the 1970s, widespread epidemics resulted in over 24 million cases of malaria [15]. As a result, a national malaria control program started in 1955 with participation from research institutes, antimalarial stations, the Ministry of Health and other ministries, and the Chinese government [11]. In 2008, there were 16,650 confirmed malaria cases, of which 1,222 were caused by *P. falciparum*. There were 23 reported deaths and a 0.01 incidence rate of confirmed malaria cases per 1,000 [17]. By 2009, there were no more than 15,000 confirmed cases of malaria [15]. However, the actual number of cases may be underreported, especially from rural or mountainous areas. While many areas of China are free of the malaria burden because of eradication programs, the disease is still present in densely populated areas (Figure 2). Presently, malaria occurs in just seven provinces: Anhui (Figure 3), Yunnan (Figure 4), Henan, Guizhou, Hubei, Hainan (Figure 5), and Jiangsu. Of these, the Yunnan and Hainan provinces have the highest number of malaria cases [15].

Figure 2. Incidence rate of confirmed malaria cases by province in China in 2003. (Source: World Health Organization, http://www.wpro.who.int/sites/mvp/epidemiology/malaria/chn_maps.htm.)

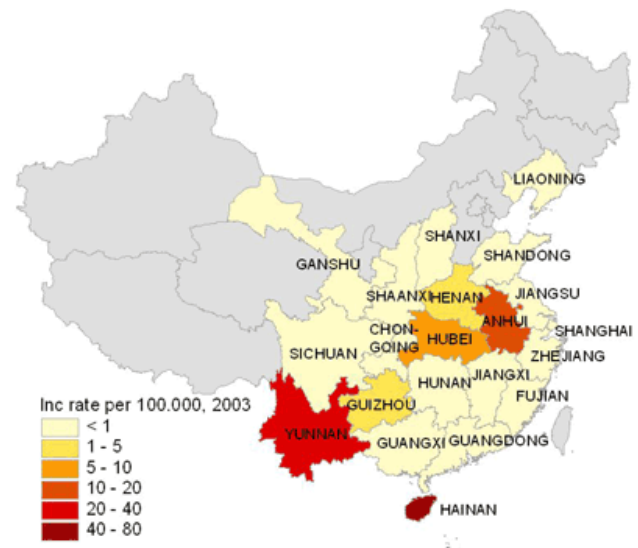


Figure 3 (left). Annualized average incidence of malaria in the Anhui Province from 2000 to 2006. (Source: Zhang, W., Wang, L., Fang, L., et al. "Spatial analysis of malaria in Anhui province, China." *Malaria Journal* 2008 7:206, <http://malariajournal.com/content/7/1/206/figure/F1.>)

Figure 4 (right). Raw standardized morbidity ratios for incidence cases of *P. vivax* (A) and *P. falciparum* (B) in the Yunnan Province from 1991 to 2006. (Source: Clements, Archie C.A.; Barnett, Adrian G.; Cheng, Zhang Wei, et al. "Space-time variation of malaria incidence in Yunnan Province, China." *Malaria Journal* 8.180 [2009]).

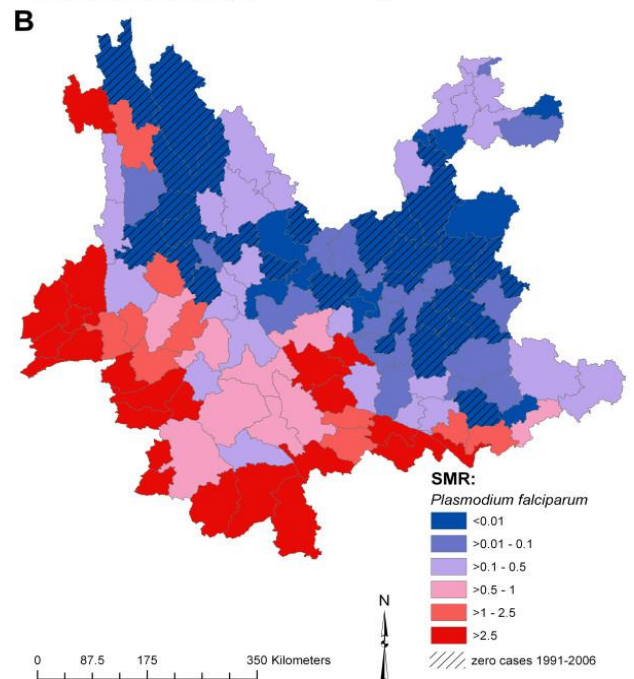
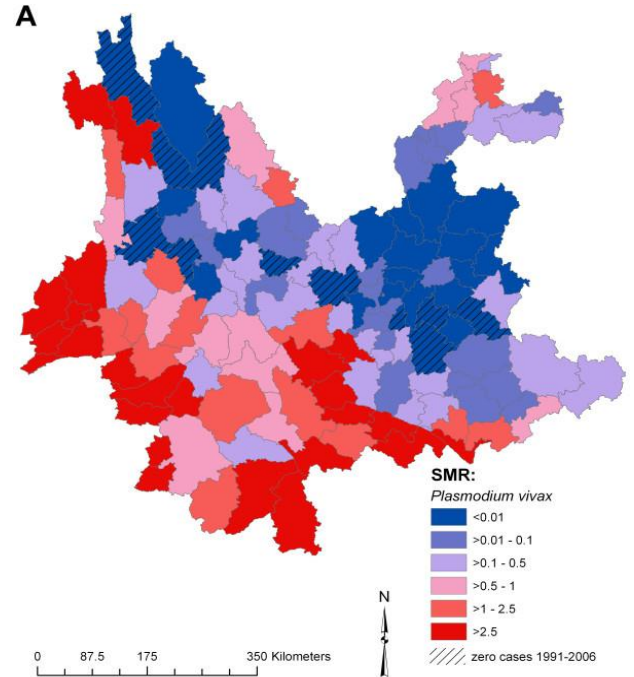
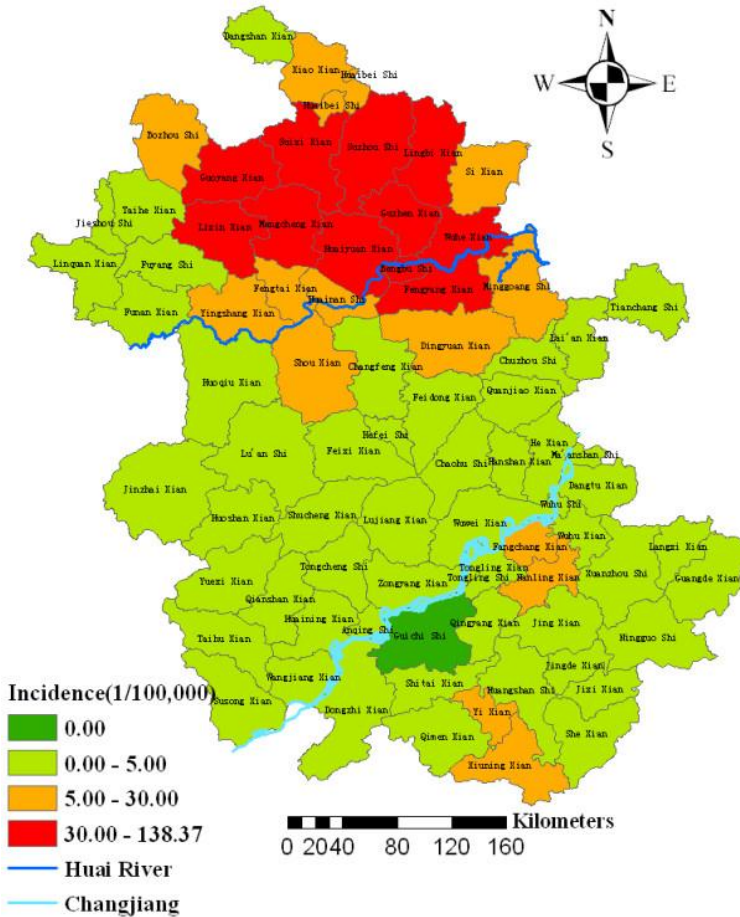
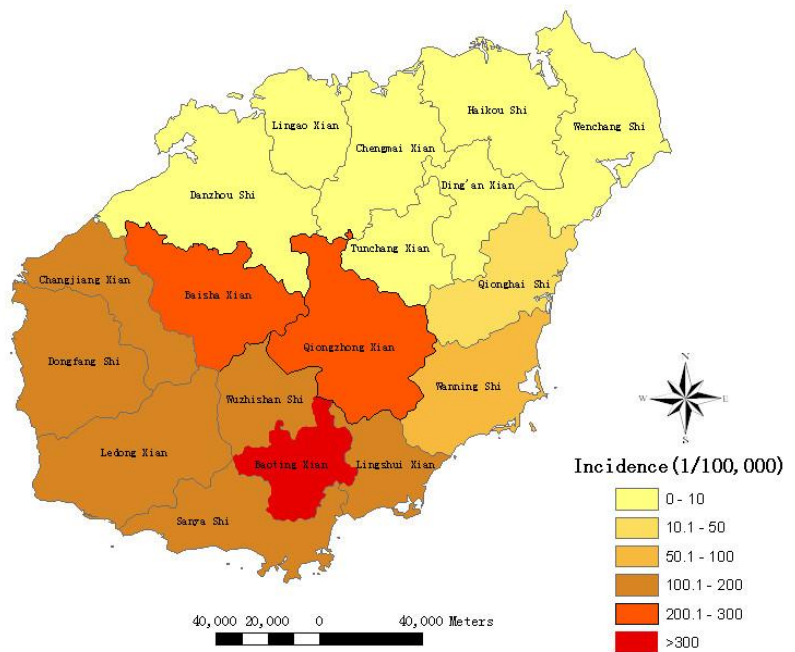


Figure 5 (left). Cumulative malaria incidence at the county level in the Hainan Province from 1995 to 2008. (Source: Xiao, Dan; Long, Yong; Wang, Shanqing, et al. “Spatiotemporal distribution of malaria and the association between its epidemic and climate factors in Hainan, China.” *Malaria Journal* 9 [2010]: 185-195).



In China, over 80% of all malaria cases are caused by *P. vivax* [15]. Seven mosquito vectors are found in different parts of China. *Anopheles sinensis*, an exophagic and exophilic species, is found in the Northern region at latitudes above 33°N, in the Central region at latitudes of 25°N and 33°N, and in the Southern region at latitudes below 25°N. It acts as the primary vector in re-emergent *P. vivax* regions. *A. anthropophagus*, an endophagic and endophilic species, is found in the Central and Southern regions. *A. minimus*, an endophagic and endophilic species, and *A. dirus*, an exophilic and exophagic species, are both found in the Southern region. Finally, most of the mosquito vectors found in the Western region are non-endemic and are a result of infected mosquitoes travelling to and from bordering countries with malaria. *A. messeae* and *A. sacharovi* are the principal malaria vectors in Xinjiang but have low vectorial capacity. In Tibet, *A. pseudowilmori*, both an indoor and outdoor species, is thought to be the principal mosquito vector [15].

Climate and Malaria

Temperature plays a role in malaria transmission by influencing the *Anopheles* vector and the *Plasmodium* parasite life cycles. This relationship has been well studied. An increase of just 0.5°C in temperature trend can increase mosquito abundance by 30–100%, showing “biological amplification” of temperature effects [23]. In addition, the minimum temperatures required for parasite development of *P. falciparum* and *P. vivax* are 18°C and 15°C, respectively. While the absolute temperatures for the two species vary, the EIP temperature curves are parallel (Figure 6). The EIP shortens to less than 10 days at higher temperatures, allowing for increased malaria transmission [23]. A mathematical model using

rainfall and temperature data as well as mosquito population dynamics, malaria invasion, and impact of seasonality on transmission in Tanzania shows that the optimal temperature for endemic transmission and spread into disease-free regions is around 32–33°C for both *P. vivax* and *P. falciparum* [22] (Figure 7). Higher maximum and mean temperatures also speed up vector development by increasing larval development and pupation rates [23].

Figure 6. Extrinsic incubation period (EIP), or the relationship between temperature and *P. falciparum* and *P. vivax* development time inside the mosquito. EIP shortens at higher temperatures, so mosquitoes become infectious sooner. There are relative threshold limits for malaria parasite development (18°C for *P. falciparum* and 15°C for *P. vivax*). (Source: Patz, Jonathan A.; Olson, Sarah H.. “Malaria risk and temperature: Influences from global climate change and local land use practices.” *Proceedings of the National Academy of Sciences* 103.15 [2006]: 5635-5636. © 2006 by The National Academy of Sciences of the USA).

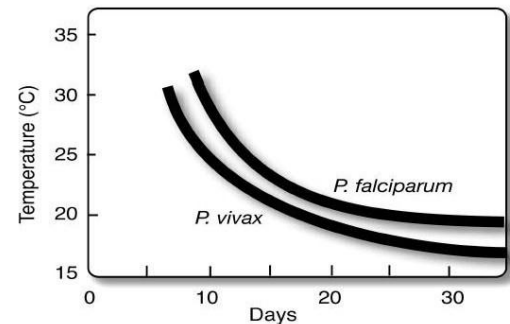
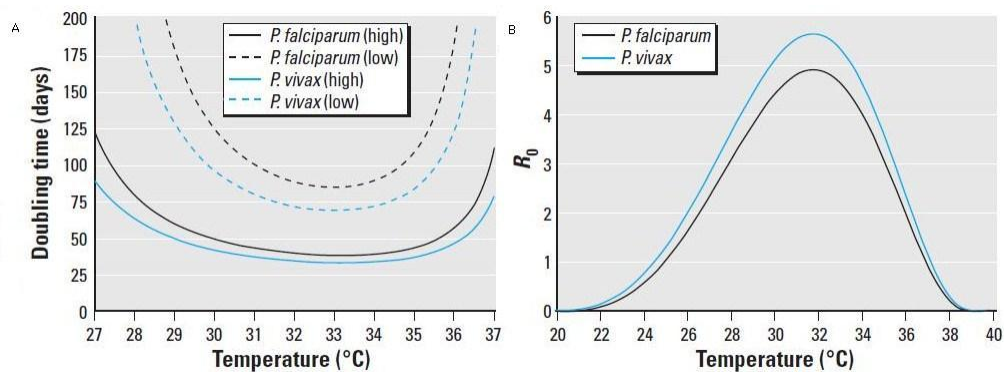


Figure 7. Graph A shows the number of days required to double the rates of parasite species in relation to temperature. High and low refer to vector density values: the number of mosquitoes per humans ($M=N$). Graph B shows the dependence of R_0 , a static measure of disease severity quantifying the expected number of secondary cases generated per infectious human introduced into a population, on temperature. (Source: Parham, Paul Edward; Michael, Edwin. “Modeling the Effects of Weather and Climate Change on Malaria Transmission.” *Environmental Health Perspectives* 118.5 [2010]: 620-626.)

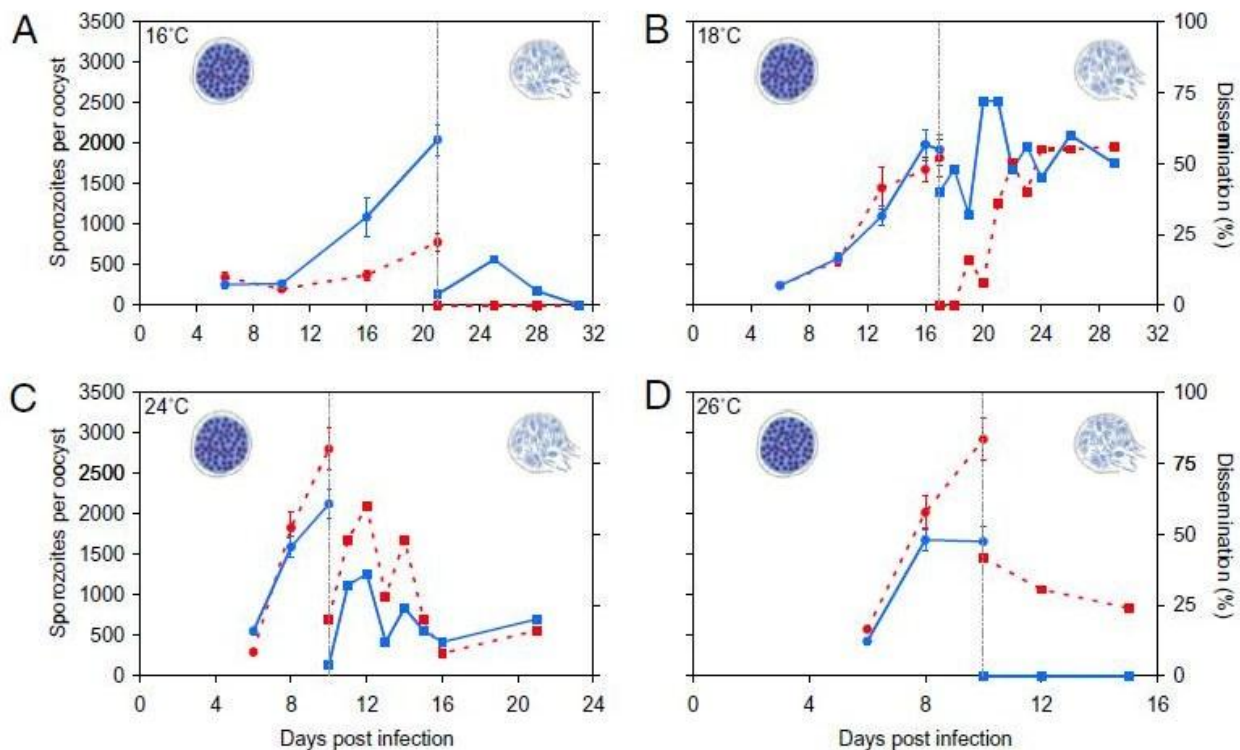


Paaijmans et al. performed two similar studies that investigate diurnal temperature fluctuations, arguing that mosquitoes and the malaria parasites are exposed to temperatures that fluctuate throughout the day, not average temperatures [19, 20]. In both highland and lowland environments in Africa, diurnal temperature variations (DTRs, the difference between the minimum and maximum temperature)

of 5°C to >20°C are common [19]. Using data from the Kenyan highlands, the authors show that models that do not account for diurnal variation actually overestimate malaria risk in warmer environments and underestimate risk in cooler environments. Inaccurate estimates occur because diurnal temperature fluctuation around average temperatures greater than 21°C slow parasite development compared with constant temperatures. On the other hand, fluctuations around average temperatures less than 21°C speed the parasite development because exposure to warmer temperatures for part of the day acts as a “rescue effect,” allowing parasites to develop at average temperatures below the assumed minimum threshold temperature [20]. This phenomenon, where biological processes appear to be faster under fluctuating low temperatures and slower under fluctuating high temperatures, is called the Kaufmann effect. EIP is very sensitive to temperature fluctuation [20].

Because diurnal temperatures can range from 5 to >20°C across many malarious areas in Africa, malaria transmission is possible at lower mean temperatures than currently predicted, and transmission can potentially be hindered at higher mean temperatures by disturbing *Plasmodium* development [19]. Using a temperature-development model of *P. falciparum* and a rodent-malaria model of *P. chabaudi* and *A. stephensi*, Paaijmans et al. (2010) show that temperature fluctuation in relation to both the kinetics of the development of malaria parasites and all the essential mosquito and parasite parameters that determine R_0 (the number of cases of malaria that arise from just one malaria case introduced into a population) differs when compared to equivalent, constant mean temperatures. Paaijmans et al. used two low baseline temperatures (16°C and 18°C) and two higher temperatures (24°C and 26°C) to study the development of malaria parasites within mosquitoes. With each baseline temperature, they kept the temperature constant (DTR = 0°C) and also fluctuated the temperature ($\pm 6^\circ\text{C}$, DTR=12°C). The experiment showed that fluctuating temperatures around 16°C resulted in an increase in parasite growth rate, with more sporozoites per oocyst, at the point of sporozoites release ($P < 0.001$). Fluctuating temperatures also led to a significant increase in the dissemination rate of sporozoites liberated from the gut into the salivary glands of the mosquito ($P = 0.02$). On the other hand, fluctuating temperatures around 26°C reduced the mean number of sporozoites per oocyst ($P = 0.03$) and actually reduced the dissemination rate to zero ($P < 0.001$). Trials at 18°C and 24°C showed similar but less intense results. Sporozoites per oocyst numbers were not significant, but the number of mosquitoes with disseminated sporozoites increased with fluctuating temperatures around 18°C ($P < 0.001$) and decreased around 24°C ($P = 0.01$) [19] (Figure 8).

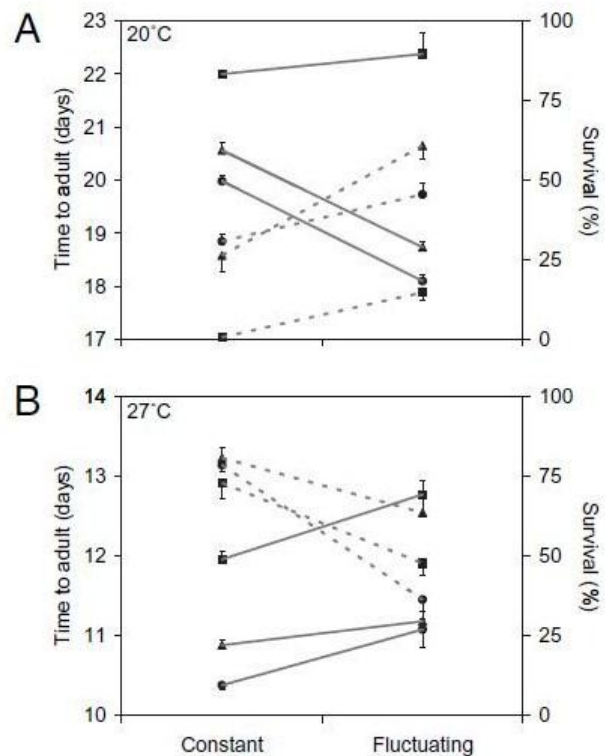
Figure 8. The four graphs show the growth and dissemination rates of *P. chabaudi* malaria in *A. stephensi* mosquitoes under constant and fluctuating temperature regimens. Mosquitoes were kept at either constant temperatures (red dashed lines) or temperatures with a diurnal fluctuation of $\pm 6^{\circ}\text{C}$ (DTR= 12°C ; blue lines). The four graphs represent baseline mean temperatures of 16°C , 18°C , 24°C , and 26°C . The left circles describe the number of sporozoites per oocyst, or the parasite growth kinetics up to the point of sporozoites release. The right circles describe dissemination, or the percentage of mosquitoes that were observed with mature sporozoites in the hemocoel. Error bars equal the standard error of the mean (SEM). Source: Paaajmans, Krijn P.; Blanford, Simon; Bell, Andrew S., et al. "Influence of climate on malaria transmission depends on daily temperature variation." *Proceedings of the National Academy of Sciences* 107.34 [2010]: 15135-15139. © 2010 by The National Academy of Sciences of the USA).



Fluctuation around cooler temperatures also sped up mosquito development when compared to constant temperatures ($P < 0.001$), and fluctuation around warmer temperatures had the opposite effect ($P < 0.001$). Temperatures fluctuating around 20°C increased the relative survival rate of *Anopheles* ($P < 0.001$), while those around 27°C reduced the relative survival rate ($P < 0.001$) [19] (Figure 9). Daily temperature dynamics also affect the length of the gonotrophic cycle, or the time between a blood meal and oviposition. Similar to the previous results, fluctuations around cool temperatures resulted in a shorter mean length of the first gonotrophic cycle from 7.4 to 6.7 days ($P < 0.01$), while fluctuations

around warm temperatures increased the cycle from 4.1 to 4.5 days ($P=0.02$) [19]. The results of this study show that temperature patterns and fluctuations influence malaria risk and transmission.

Figure 9. Both graphs A and B show the relationship between development time and survival of the immature stages of *A. stephensi* under constant temperatures and fluctuating temperatures. Again, the fluctuating regimen used temperatures with a diurnal fluctuation of $\pm 6^\circ\text{C}$ (DTR= 12°C). Development time is represented by the solid lines in days, and survival is represented by dashed lines in percentage. Three different larval densities were used ($\blacksquare=0.5$, $\blacktriangle=1$, $\bullet=2$ larvae/ cm^2). Error bars equal the SEM. (Source: Paaijmans, Krijn P.; Blanford, Simon; Bell, Andrew S., et al. "Influence of climate on malaria transmission depends on daily temperature variation." *Proceedings of the National Academy of Sciences* 107.34 [2010]: 15135-15139. © 2010 by The National Academy of Sciences of the USA.)



Altitude can be seen as a proxy for temperature because temperatures decrease as altitude increases. Generally, temperatures decrease on average by 6°C for every 1,000 meters of elevation gained [4]. Mboera et al. (2008) studied the transmission of malaria and mosquito net coverage in relation to altitude in six villages in Tanzania, three of which had healthcare facilities and three of which did not. The villages were located in three altitude transects: Idodi (965 m) and Makifu (985 m), which constituted the lowlands; Tosamaganga (1561 m) and Mangalali (1520 m), which constituted the intermediate elevations; and Lulanzi (1917 m) and Kilolo (2075 m), which constituted the highlands. The lowlands are hot and dry, with a mean annual rainfall of 500–600 mm and a mean annual temperature of $20\text{--}30^\circ\text{C}$. The intermediate zone receives a mean annual rainfall of 600–1,000 mm, and mean temperatures range from 15°C to 20°C . Finally, the highlands have the highest mean annual rainfall of 1,300 mm and the lowest average temperature of 15°C . While bed net use and the presence of a healthcare facility affected malaria transmission and incidence, the highlands had a parasite prevalence of 0%. In comparison, parasite prevalence was 18.8% in the intermediate zone and 62.6% in the lowlands. Children living in the intermediate transect were 16% less likely to contract malaria than those living in the lowlands (95% CI: 10–24%, $P<0.01$). In addition, the geometric means of parasite density

(GMPD) for *P. falciparum* in the lowlands and intermediate transects were 499.8 and 231.5/ μ l of blood, respectively. The GMPD was 2.4/ μ l higher in children living in the low transect than those in the intermediate transect ($P < 0.01$), and the gametocyte rate, which was observed in 0.73% of all the children, was higher in the low transect (1.5%) than in the intermediate transect (0.6%) ($P < 0.0001$) [18].

In addition to temperature, rainfall is a determinant of malaria incidence and risk. Temperature is related to precipitation because warmer air holds more moisture and encourages mosquito survival [8]. The intensity of malaria transmission is related to rainy seasons because precipitation provides vector breeding sites and prolongs the vector life span by increasing water availability. However, the lack of rainfall does not imply a reduction of larval populations, nor does prolonged and intense rainfall imply an abundance of larval populations. Lack of rainfall can create new habitats such as pools and puddles, thereby increasing larval populations, and possibly proving disadvantageous to predators, while intense and prolonged rainfall may flush away larval habitats [9].

Kiang et al. (2006) used neural network methods to model the dependency of malaria transmission on precipitation, temperature, relative humidity, and vegetation index, obtained from both climate time-series and satellite measurements in Thailand from 1994 to 2001, specifically from the Kanchanaburi, Mae Hong Song, and Tak provinces. In Thailand, *P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale* are all present. The first two, however, make up about 99% of all malaria cases. The major malaria vectors are *A. dirus*, *A. minimus*, and *A. maculates*. Monthly, provincial malaria data was gathered from the Epidemiology Division of the Department of Disease Control within the Thai Ministry of Public Health. Meteorological and environmental data was compiled from the Seasonal-to-Interannual Earth Science Information Partner data set, Moderate Resolution Imaging Spectroradiometer data set, Tropical Rainfall Measuring Missions, National Centers for Environmental Prediction's Reanalysis Monthly Means and Other Derived Variables data set, and the Normalized Difference Vegetation Index from NASA's Goddard Earth Sciences Data and Information Services Center, at a resolution of 8 km. Kiang et al. developed four configurations to model, which included different combinations of the input variables: time (t), average temperature (T), precipitation amount (P), precipitation amount in the previous month (P_{-1}), relative humidity (H), and vegetation index (V). The six years of data were divided into six groups, each consisting of five years of data for training and one year of data for testing [8].

Results showed that the training accuracy was higher than the testing accuracy; this is normal in classification techniques. Configurations 1 (inputs: t, T, P, P_{-1} , H, V) and 2 (inputs: t, P, P_{-1} , H, V) had relatively higher training and testing accuracies than Configurations 3 and 4. Both Configurations 1 and

2 had one hidden layer imbedded with one hidden node. Configuration 1 shows relatively high training accuracies ($75\pm 9\%$ in Kanchanaburi, $71\pm 10\%$ in Mae Hong Son, and $72\pm 10\%$ in Tak) and testing accuracies ($67\pm 10\%$ in Kanchanaburi, $57\pm 11\%$ in Mae Hong Son, and $64\pm 6\%$ in Tak). Similarly, Configuration 2 results in relatively high training accuracies ($74\pm 9\%$ in Kanchanaburi, $69\pm 11\%$ in Mae Hong Son, and $70\pm 11\%$ in Tak) and testing accuracies ($62\pm 12\%$ in Kanchanaburi, $56\pm 6\%$ in Mae Hong Son, and $63\pm 8\%$ in Tak). While Configurations 3 and 4 had relatively higher training accuracies (in the high 70s and 80s, respectively) than Configurations 1 and 2, their testing accuracies were extremely low (in the 50s and even dropping to 10% in Mae Hong Son with Configuration 4). The models show that while meteorological and environmental inputs are not solely reliable as malaria transmission predictors, they do make an impact. The inputs account for 60% to 70% of predicting malaria transmittance [8].

Indeed, while $0.9\pm 0.3\%$ of the first instar (L1) and $0.1\pm 0.1\%$ of the fourth instar (L4) were flushed out of the basins during nights without rainfall, Paaijmans et al. (2007) performed a study that showed that excessive rainfall can significantly affect different stages of larval mosquito populations, particularly larvae of *A. gambiae*, by flushing them out of their aquatic habitats and killing them. Young larvae were influenced the most by rainfall events, while the oldest larvae were able to better withstand the flushing ($P < 0.001$); 23% and 9% of the larvae were lost during one night of rainfall, respectively. L1 larvae flushing out on nights without rainfall is correlated with average wind speed ($\rho = 0.13$, $P < 0.05$). Significantly more L1 and L4 larvae were washed out during nights with rainfall compared to nights without precipitation ($P < 0.001$) [21].

Paaijmans et al. also noticed that some mosquito larvae survived even after being flushed out of their habitats because they are able to move actively over moist soil; L4 larvae were able to survive better than L1 larvae ($P < 0.001$). If they could reach a new body of water or return to the same one, they would have a chance at completing their development into adult mosquitoes [21]. Ultimately, the availability, persistence, and dimensions of mosquito larval habitats depend on the frequency, duration, and intensity of precipitation. Still, while rainfall patterns can influence vector abundance and thereby affect malaria endemicity, invasion, and extinction, precipitation is less predictable and more difficult to quantify than temperature.

Land use change can also affect malaria transmission because it modifies the presence or absence of predators, availability of breeding sites, hydrology and topography of an area, vegetation, and, consequently, temperatures. In a highland area of Uganda, Lindblade et al. (2000) studied *A. gambiae* and *P. falciparum* in eight villages located along natural papyrus swamps and eight villages located along swamps that had been drained and cultivated between December 1997 and July 1998. Land use

change from natural papyrus swamps to drained and cultivated swamps led to increase in both maximum and minimum temperatures by approximately 0.9°C among sites within the same valley (t , $P < 0.0001$) [10].

The NDVI is correlated to vector-borne diseases because it acts, among other things, as a surrogate for precipitation and surface temperatures, which, as stated above, are related to vector and parasite dynamics [26]. Wayant et al. (2010) investigated the NDVI in relation to malaria in the Atlantic Forest biome in eastern Paraguay for over 260 months. Malaria cases in the Canindeyú and Alto Paraná departments of Paraguay are due to *P. vivax*, and the main vectors are *A. darlingi*, *A. strodei*, and *A. albicans* [26]. The two areas underwent much land cover change, especially deforestation, during the study period. Therefore, the study analyzed the correlation of malaria rates with monthly NDVI time-series, and the correlation of individual pixel time-series (which can be translated to local conditions) with the case numbers [26]. Remote sensing data were collected from the Global Inventory Modeling and Mapping data set, at a resolution of 8 km. Malaria data were obtained from the Servicio Nacional de Eradicación y Control de Vectores, Asunción, Paraguay, and the raw data were transformed using a moving window approach varying from 3 to 7 years, in which the number of cases within each window was determined and then divided by the average number of cases for that window. With respect to the areas that underwent anthropogenic land cover change from forest to non-forest, there was a direct correlation with malaria case rates [26]. However, over the relatively long time-series scale of 260 months, the strength and duration of the association between NDVI and malaria case rates varied widely. The best correlations were found when the NDVI time-series lagged the disease series, showing that disease responds to environmental drivers, or “trigger events.”

Sainz-Elipse et al. (2010) also developed models of transmission risk for *P. falciparum* and *P. vivax* in relation to climate diagrams, including minimum temperature, number of potential *Plasmodium* generations via a Gradient Model Risk (GMR) Index, remote sensing images with the Eurasia Land Cover characteristics database and the monthly evolution of NDVI, and *A. atroparvus* population dynamics. Unlike previous studies, this study models risk in the Ebro Delta of Spain, a historically endemic area with rice fields. The last autochthonous malaria case in Spain was registered in May 1961, and Spain was declared malaria-free in 1964 [24]. However, imported cases of malaria occur as a result of the many immigrants who come from endemic countries and tourists who pass through the Delta. Both immigrants and natives who travel to countries with the disease pose a risk of malaria resurgence, especially because vectors are still present. Using climate data from 1961 to 1986 collected from a weather station in Tortosa, 72 10-day composite images from the 1 km Advanced Very High Resolution

Radiometer sensor, and bimonthly entomological surveys using CDC-light traps, Sainz-Elipse et al. analyzed the minimum temperature required for the development of the *Plasmodium* species and calculated the GMR index applied to predict malaria transmission risk. Climatic features included mean maximum temperature, mean minimum temperature, mean environmental temperature, precipitation, relative humidity, potential evapotranspiration, wind speed, vapor pressure, and global radiation [24].

The GMR of 116 (or higher) shows a transmission risk for one *Plasmodium* generation. As seen in Patz's paper, minimum temperatures of 15°C and 18°C are required for the development of *P. vivax* and *P. falciparum*, respectively [22]. Because models were used to project malaria transmission risk, no statistics were used. The many rice fields and irrigation farming in the area provide an ideal environment for vector development; in addition, the rice cultivation periods coincide with temperatures that permit the completion of the vector cycle. Vectors would be able to reach maximum abundance in June, July, and August, the season of maximum growth in the rice fields as a result of favorable climatic conditions. Favorable temperature conditions for both the vector and *P. falciparum* occur between May and September, while favorable conditions for the vector and *P. vivax* last from April until October. The models align with old observations in which 99% of all new malaria cases in the Delta occurred at the end of the summer [24]. The models provide a way to compare future projections to the times when malaria was present in the Ebro Delta.

Climate and Malaria in China

Several researchers in China have studied the relationships between climate and malaria incidence, showing that climate variables such as temperature can indirectly affect malaria transmission. Furthermore, high temperatures can alter human behavior, resulting in lower rates of bed net use and thereby allowing certain mosquito vectors easy access to feeding.

Bi et al. (2003) conducted a 12-year data analysis of malaria and monthly climate variables, mean minimum temperature, maximum temperature, relative humidity, and precipitation in Shuchen County, China. Most of the parasites found in the county are *P. vivax*, and the main mosquito vectors are *A. sinensis* and *A. anthropophagus*. Temperatures between 20°C and 30°C and humidity of 60% or more are optimal for *Anopheles* survival [3]. The EIP of *P. vivax* is about 11–25 days at temperatures of 20°C to 27°C [3]. Temperatures lower than 16°C and higher than 30°C show a negative impact on the mosquitoes and the EIP of the parasite in the vector. The data show that there is seasonal variability in the frequency of malaria cases, with the highest incidence in the summer and autumn, even though malaria remained endemic throughout the year. Using Spearman correlation analyses with a one-month

lag effect and cross-correlations, Bi et al. show that monthly mean minimum temperature ($\rho=0.467$, $P<0.0001$) and total monthly rainfall ($\rho=0.347$, $P<0.0001$) are positively correlated with monthly incidence of malaria [3].

Hui et al. (2009), Clements et al. (2009), and Xiao et al. (2010) also show that there is a lag effect of climate variables. Hui et al. and Xiao et al. both look at spatiotemporal distribution of malaria in the Yunnan and Hainan provinces. Using data from 1995–2000, Hui et al. show that while there were usually three to five times more *P. vivax* malaria cases than *P. falciparum* cases, the annual incidence trends were consistent with each other, with seasonal peaks in the summer and autumn, when farmers usually work and sleep in the open. However, the incidence peak of *P. falciparum* usually occurred one month earlier than the peak of *P. vivax*. The two climate variables that showed the best correlation with malaria incidence were monthly average temperature with a one-month lag (AT_1) and monthly average minimum temperature with a one-month lag ($MinT_1$). The Spearman correlation results of total malaria incidence and AT_1 were $\rho=0.826$, $P<0.001$, and with $MinT_1$ were $\rho=0.818$, $P<0.001$. The results were different for *P. vivax* (AT_1 : $\rho=0.824$, $P<0.001$ and $MinT_1$: $\rho=0.806$, $P<0.001$) and *P. falciparum* (AT_1 : $\rho=0.426$, $P<0.001$ and $MinT_1$: $\rho=0.397$, $P<0.001$) malaria incidence when they were considered separately [6]. Malaria incidence in the Yunnan Province had not changed much in the 11-year period of the study, even though there have been intervention programs. The study showed that malaria transmission is not random; there are areas with a high risk of malaria transmission such as those bordering Myanmar and Laos, and in the Yuanjiang River Basin [6].

Similarly, Clements et al. (2009) studied the space-time variation of *P. vivax* and *P. falciparum* malaria incidence in 128 counties within the Yunnan Province between 1991 and 2006. During this observation period, there were 250,070 cases of *P. vivax*, representing 3.12 cases per 100,000 people at risk per year, and 44,465 cases of *P. falciparum*, representing about 0.55 cases per 100,000 [5]. Spatiotemporal models showed that incidence of both types of malaria in January–February was correlated to incidence in the following June–September. County-level Bayesian Poisson regression models of incidence showed that there are strong associations between malaria incidence and rainfall and maximum temperature. When the authors controlled for provincial average temporal trend, regression slope of June–September on January–February, spatial random effect, spatially smoothed county-level temporal trend, and seasonal effect, results showed that the relative risk of malaria for monthly rainfall in 10-ml intervals is 1.045 with a 95% credible interval of (1.044, 1.046) for *P. vivax* and 1.037 (1.034, 1.040) for *P. falciparum*. The relative risk of the disease for monthly maximum

temperature in Celsius is 1.047 (1.045, 1.050) for *P. vivax* and 1.053 (1.047, 1.060) for *P. falciparum* [5].

Xiao et al. (2010) studied each county in the Hainan Province using data from 1995 through 2008. Like the Yunnan Province, the Hainan Province has high rates of malaria. Between 1995 and 2008, there were 64,478 reported malaria cases, with the highest malaria incidence in the central-south counties of the province. The highest annual malaria incidence in the province occurred in 2004, with 116.39 cases per 100,000 people, and the lowest incidence occurred in 2008, with 22.06 cases per 100,000. Approximately 70% of all annual malaria cases were reported between May and October [28]. Malaria case records were obtained from the Hainan Center for Disease Control and Prevention. Multivariate time-series analysis was used to predict malaria incidence by means of the climate variables collected from the China Meteorological Data Sharing Service System: mean temperature, mean maximum temperature, mean minimum temperature, accumulative rainfall, and mean relative humidity. The analysis showed a positive correlation or trend ($F=85.06$, $P<0.05$, $R^2=0.81$), but not causation. Accumulative rainfall was shown to be correlated with malaria incidence but was not used in the model as a predictor of malaria epidemics because this result was inconsistent with previous findings from field studies¹ in China, and accumulative rainfall showed co-linearity with other factors, which were incorporated in the model. Mean relative humidity showed no relationship with malaria incidence in Hainan. Some variables were closely correlated with other variables, shown by variance inflation factors (VIF) for individual variables. Monthly temperature had a $VIF=51.02$ and monthly temperature with a two-month lag had a $VIF=47.61$ [28], indicating that mean temperatures of the previous month and of the previous two months can be used to fit and predict malaria epidemics in the Hainan Province. This information can lay the groundwork for malaria surveillance and targeted control in the area.

Because the amount of vegetation affects local temperatures and hydrology, it is important to study the relationship of NDVI to malaria incidence in China as well. Liu et al. (2006) studied the relationship of NDVI and vector density and malaria incidence rate using monthly average, maximum, and minimum temperatures, rainfall, and insolation amount, *Anopheles* density, malaria incidence rate, and remote sensing NDVI data for the wet and dry seasons from 27 townships in 10 counties in the Yunnan Province from 1984 to 1993. The vectors studied were *A. minimus* and *A. sinensis*, and the three

¹ Xiao et al. (2010) refer to three field studies. Two of them, Clements et al. (2009) and Bi et al. (2003), also show a correlation between rainfall and malaria incidence. The third reference is to Wang, L.; Fang, L.; Xu, X., et al. "Study on the determinants regarding malaria epidemics in Anhui province during 2004-2006." *Zhong Hua Liu Xing Bing Xue Za Zhi*. 2009, 30:38-41. It is assumed, then, that Xiao et al. did not omit accumulative rainfall from the model because the previous field studies showed no correlation at all, but that the relationships found were different. Moreover, the researchers claim that rainfall is indirectly accounted for within the model because of the other factors that were incorporated into it.

evaluation indicators were remote sensing NDVI group, climate indicator group including temperature and sunshine indexes, and rainfall. The correlation matrix showed that the wet and dry season NDVI were highly correlated with *Anopheles* density in just four townships, while correlations of density in the other counties were not clear. Grey correlation analysis showed that while NDVI is sensitively related to malaria incidence and *A. minimus* density in the two townships of Mangguoshu and Mengpeng ($r=0.619$, $P<0.05$) [12], multiple indexes need to be used, such as temperature and differences between the dry season and the wet season.

Fog is a factor that may influence malaria transmission because fog precipitation acts as a water input in many mountainous and coastal environments [25]. Tian et al. (2008) conducted the first study that investigates annual fog day frequency as a weather predictor of the annual incidence of malaria in a time scale of years by investigating the effects of fog, temperature, rainfall, and humidity on malaria transmission in the rain forest area of Mengla County of Southwestern China for the 1971–1999 period using overall malaria incidence data from Yunnan Province’s Center for Disease Control and Prevention and weather data from the Yunnan Bureau of Meteorology. Mengla County has one of the highest annual malaria incidence rates in China, ranking sixth among the nation’s 2,353 counties. During 1994–1998, the annual malaria incidence rate in this county was 400.4 per 100,000 people. When the data are divided into three seasons — rainy (May–October), dry–cool (November–February), and dry–hot (March–April), auto-regressive integrated moving average models (ARIMA) show that seasonal variation is apparent in malaria incidence, particularly with the two weather variables, rainfall and the frequency of fog days. A fog day is defined as “a day when visibility is 1,000 m or less for more than 15 minutes” [25].

While they found no apparent association with humidity, Tian et al. showed that the cross-correlation between malaria and maximum temperature at a lag of four months is particularly strong in April and June ($\rho=0.410$, $P=0.034$; $\rho=0.429$, $P=0.023$), and the maximum temperature in the cool months is positively associated with malaria incidence after a four-month lag. Major incidence peaks were observed in the rainy season, and minor peaks were observed in the dry–cool season. Fog day frequency was the only variable associated with annual malaria incidence with a lag time of seven months, particularly with fog frequency in October and malaria incidence in May of the following year ($\rho=0.470$, $P=0.013$) [25]. The effect that fog would have on malaria incidence after seven months is questionable, however. The ARIMA regression of the logarithmic monthly malaria incidence showed that minimum temperature with a one-month lag had the relationship $\beta=0.032$, $P=0.002$, minimum

temperature with a two-month lag was $\beta=0.027$, $P=0.008$, and fog frequency with a seven-month lag was $\beta=0.004$, $P=0.020$ [25].

This study also confirms that there is an inconsistent relationship between rainfall and malaria incidence. The association between malaria incidence and rainfall is not linear, possibly because of the saturating effect of rainfall. An increase in precipitation does not necessarily produce additional malaria cases when breeding sites are not limited to begin with, and heavy rains and storms can destroy breeding sites, interrupt the development of mosquito eggs and larvae, or flush them out of the pools [25]. On the contrary, fog precipitation may actually provide water input and maintain aquatic breeding sites for mosquitoes when there is little rainfall, such as during the six-month dry season, resulting in a positive effect on malaria transmission [25].

Not only do climate variables influence *Anopheles* and *Plasmodium* species, they also influence *Homo sapiens*. Studies on prevention methods and social behavior show that people can increase their malaria risk in response to changes in climate, especially temperature. For instance, Linhua et al. (1995) studied the social, cultural, and behavioral data associated with malaria in Heping Town, Qiongzong County, and Hainan Province. Social aspects studied were the use of treated bed nets and the effectiveness of having the nets, health-seeking behavior, and mountain stays. In Heping, residential and agricultural land is separate; villages are located at lower altitudes than the rice fields, and farmers stay in mountain huts when maintaining land or planting or harvesting the rice. From these huts, the farmers also hunt and gather food from the high-altitude forests. Observing four study groups from 1991 to 1992, the study showed that between 64.4% and 81.5% of people used bed nets even when the ratio of nets to people was around 1:2.0 [11]. Actual bed net utilization was lower than reported use ($\chi^2=15.6$, $P<0.01$). People were sometimes reluctant to use bed nets because of the insecticide smell and the stuffiness of sleeping under a net. Of the 717 people who reported that they frequently use bed nets, 14% showed malaria antibody prevalence (IFA) ($P<0.001$). People who reported that they did not frequently sleep under bed nets had a prevalence of 34.2% ($P<0.001$). IFA rates were 25.8% for the 151 people who had stayed in the mountains overnight and just 15.6% for those who had not done so ($P<0.005$). Grey relational analysis shows that staying in the mountains ($r=0.869$) and reported bed net use ($r=0.827$) are strongly associated with malaria infection [11].

Liu et al. (1996) also showed that while bed nets were common in the surveyed area, they did not offer full protection because outdoor sleeping was widespread during the hot summer and autumn harvest season, especially among older males. Bed nets cannot offer protection if people are sleeping outside or staying up late during the hot season [13].

Furthermore, housing types can also influence malaria incidence. The open walls of bamboo-slat houses or thatched roofs are a particular problem with endophagic mosquitoes such as *A. anthropophagus*, *A. minimus*, and *A. pseudowilmori* because they can readily go indoors and feed on inhabitants. Only 26.2% of the households in Miao Village and 47.9% of the households in Li Village have cement or brick walls with tile-roofed houses; the rest have bamboo-slat houses or thatched roofs [11]. On the Li and Han farms, all households had tile-roofed houses. While income plays into types of housing, bamboo-slat houses keep temperatures inside cooler. On the contrary, mud-plastered and cement-rendered walls offer more protection against mosquitoes, but make the houses darker and hotter. In villages with mud houses, people occasionally build shelters on poles where children may rest and sleep outdoors where it is cooler. Putting all social factors together, malaria antibody prevalence in the Miao village was 24.2%; in the Li village, 20.1%; and in the Li and Han farms 10.2% and 2.1%, respectively [11]. The data show that mountain stays, housing, and bed net use are associated with climate, and in turn related to malaria incidence.

Discussion

As demonstrated above, climate influences malaria transmission and incidence. There are set temperature thresholds for mosquito and parasite survival. The optimal temperature range for the survival of *Anopheles* mosquitoes is between 20°C and 27°C. Temperatures lower than 16°C and higher than 30°C have a negative impact on the EIP of *Plasmodium* parasites. According to Bi et al. (2003), monthly mean temperature is positively correlated with monthly incidence of *P. vivax* malaria in Shuchen County. Hui et al. (2009) show that annual incidence trends of both *P. falciparum* and *P. vivax* cases in the Yunnan Province have seasonal peaks in the summer and autumn. The best correlations with malaria incidence were monthly average temperature with a one-month lag and monthly average minimum temperature with a one-month lag. Clements et al. (2009) also studied both types of malaria cases in the Yunnan Province and found a strong association between malaria incidence and maximum temperature. According to Xiao et al. (2010), monthly temperature and monthly temperature with a two-month lag are correlated to malaria incidence in the Hainan Province. Tian et al. (2008) illustrated that the cross-correlation between malaria and maximum temperature at a lag of four months is particularly strong in April and June, and the maximum temperature in the cool months is positively associated with malaria incidence after a four-month lag.

Certain human behaviors influenced by temperature can increase the risk of malaria transmission and incidence. Studies by Liu et al. (1996) and Linhua et al. (1995) reveal that bed nets did not offer full

protection because people did not use them frequently during the hot summer and autumn harvest seasons. Furthermore, actual bed net utilization was lower than reported use. Additionally, bamboo-slat houses and thatched roofs are more popular in the Miao and Li villages because they are cooler than mud-plastered and cement-rendered walls. Unfortunately, they pose a problem in areas with endophagic mosquitoes.

In addition to temperature, rainfall has strong associations with malaria incidence and risk. Both Bi et al. (2003) and Clements et al. (2009) demonstrate that precipitation is positively correlated with relative malaria risk. Data from Tian et al. (2008) show major incidence peaks during the rainy season and minor peaks during the dry-cool season. While this study also proves that the relationship between rainfall and malaria incidence is not linear, it does not address the complex relationship between rainfall and malaria transmission as Paaijmans et al. (2007) did in their work.

Normalized difference vegetation index acts as a surrogate for precipitation and local surface temperatures. Liu et al. (2006) studied NDVI, vector density, and malaria incidence rates in the Yunnan Province. Of the 27 townships analyzed, the correlation matrix showed that wet and dry season NDVI correlated with *Anopheles* density in just four townships.

Studies demonstrate that humidity does not play a role in malaria incidence in China. Xiao et al. (2010) showed that mean relative humidity has no relationship with malaria incidence in the Hainan Province. Similarly, results from the study by Tian et al. (2008) indicate no apparent association between incidence and humidity.

Tian et al. (2008) researched the relationship between fog and annual incidence of malaria in Mengla County and found that there is an association with a lag time of seven months. Moreover, the authors explain that precipitation from fog can provide water input and maintain aquatic breeding sites for the vectors during the dry season.

While there was no literature on the relationship between malaria incidence and altitude as a proxy for temperature in China, the results would probably be similar to those found by Bodker et al. (2003) and Mboera et al. (2008). Temperatures will decrease as altitude increases; then, malaria incidence will decrease because of the relationship between temperature and the *Plasmodium* parasite and *Anopheles* mosquito.

There are methodological limitations to the studies presented. In the study of fog by Tian et al. (2008), the results show that the overall association between malaria incidence and fog at a lag of seven months is driven by the cross-correlation in May only; in other words, the fog day frequency in October is positively associated with malaria incidence in May of the following year. However, the correlation in

other months was not statistically significant. As a result, the actual relationship between fog day frequency and malaria incidence is questionable.

Five of the studies on malaria and climate in China used passive malaria case records. Tian et al. (2008) and Xiao et al. (2010) obtained malaria incidence data from county Centers for Disease Control and Prevention. Clements et al. (2009) obtained malaria surveillance data from the Chinese Centre for Disease Control, and Bi et al. (2003) acquired data from the Department of Diseases Surveillance, Anhui Anti-Epidemic Station. Finally, Hui et al. (2009) obtained malaria data from the Yunnan Institute of Parasitic Diseases. These data may underestimate the actual prevalence of disease because they are based on passive detection of symptomatic malaria cases reported by hospitals and clinics. The data do not account for malaria cases among the migrant and displaced people who may not have sought or received treatment.

In conclusion, studies have shown that climate influences both *P. falciparum* and *P. vivax* in China. Even though thresholds may vary slightly between the two parasites, their responses to climate remain parallel. Studies consistently show that temperature has a strong positive correlation with malaria incidence because it influences mosquito and parasite development. However, the results of the studies disagree on which observed temperature relationship is strongest—average temperature, average minimum temperature, or average maximum temperature—and which lag time is strongest—one-month, two-month, or four-month. While rainfall is shown to have a relationship with malaria incidence, the studies do not completely explain the nonlinearity.

In order to control and prevent malaria cases in China, further research is needed to understand the influence of climate on malaria. One area of research could look into different *Anopheles* larvae losses resulting from rainfall events in China. While Paaijmans et al. (2007) studied *Anopheles gambiae* larvae in Kenya, the inconsistent terrain, hydrology, and mosquito vectors in China may show different results. In addition, there is a lack of field ecology and malaria risk research. The effects of precipitation and availability of breeding grounds can change with the development of dams, and local temperatures can increase with urbanization and land use change. New approaches could be used to study fog and humidity in China, and research should be done on how climate change may actually decrease malaria transmission and incidence in some areas of China.

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