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Modelling the effect of temperature change on the extrinsic incubation period and reproductive number of *Plasmodium falciparum* in Malaysia

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Abstract. According to the report of the Intergovernmental Panel on Climate Change (IPCC), Malaysia will experience an increase of 3–5°C in the future. As the development of the malaria parasite, *Plasmodium falciparum*, is sensitive to temperature, we investigated, using computer models, the effect of increase of 3º and 5ºC on the possible changes in the epidemiology of malaria transmission of *P. falciparum* in Malaysia. Four environmentally different locations were selected: Kuala Lumpur (KL), Cameron Highlands (CH), Kota Kinabalu (KK) and Kinabalu Park (KP). The extrinsic incubation period (EIP) was estimated using hourly temperatures and the mean daily temperatures. The EIP values estimated using the mean daily temperature were lower than those computed from hourly temperatures in warmer areas (KL, KK), but higher in the cooler areas (CH, KP). The computer simulations also indicated that the EIP will be decreased if the temperature was raised by 3º or 5ºC, with the effect more pronounced for the greater temperature increase, and for the cooler places. The vector cohort that is still alive at a time to transmit malaria (s^{EIP}) also increased when the temperature was raised, with the increase more pronounced in the cooler areas. This study indicates an increase in temperature will have more significant effect in shortening the EIP in a cooler place (eg CH, KP), resulting in a greater s^{EIP}, and consequently increasing the transmission intensity and malaria risk. A temperature increase arising from the global climate change will likely affect the epidemiology of malaria in Malaysia, especially in the cooler areas.

INTRODUCTION

It has been estimated that the rise in greenhouse gas emissions over the past few decades has already warmed the planet by 0.8ºC (Watson *et al.*, 1996). Furthermore, if greenhouse gas emissions continue to rise unchecked, the prediction is that global temperature could further rise by 1.0–4.0ºC by 2100.

Kiszewski *et al.* (2004) had demonstrated that climate interacts with the biological characteristics of vector mosquitoes (such as blood meals taken from human hosts, daily survival of the vector, and duration of the transmission season and of extrinsic incubation) and explains much of the regional variation in the intensity of malaria transmission. When temperature rises, precipitation patterns will change and affect malaria epidemiology. Teklehaimanot *et al.* (2004) had shown that in cold districts, rainfall and minimum temperature were associated with a delayed increase in malaria cases, while in hot districts, the association occurred at relatively shorter lags.

Although there is evidence that the climate change will affect insect-borne diseases (Githeko *et al.*, 2000; Kelly-Hope & Thomas, 2005; Pascual *et al.*, 2006; Barbazan *et al.*, 2010), the precise effects are yet to be worked out. The fraction of changes in vector-borne diseases attributable to climate change is still unknown, because of the slow rate of

change, and the possible adaptation of human populations to climate change which would minimize the impacts (Githeko *et al.*, 2000).

The exact relationship between climate change and malaria epidemics is however still debatable (Lindsay & Martens, 1998; Hay *et al.*, 2002, 2005; Zhou *et al.*, 2004; Pascual *et al.*, 2006). Nevertheless, we do know that in warmer weather, the mosquito would feed more often and digest the blood more quickly which would result in increasing the transmission rate of malaria if it has the parasites. Similarly, the parasite would complete its life cycle more quickly (Detinova, 1962), increasing its number in the mosquitoes. As global warming result in higher temperature in areas of higher altitudes and greater latitudes, the vectors will be able to spread and colonize new areas. It has been estimated that by 2080, up to 320 million more people could be affected by malaria because of these new transmission zones (Lindsay & Martens, 1998; Martens *et al.*, 1999).

Climate change has also been predicted to result in stronger cyclones and floods (Ali, 1999; Knutson *et al.*, 2010) which in turn could affect the spread of insect-borne diseases, such as malaria and dengue fever (Barbazan *et al.*, 2010) endemic in South-East Asia and other parts of the developing world. Fortunately these diseases are also the current focus of researchers, partly because the diseases are so prevalent but also because outbreaks seem linked to climate change.

Increased rainfall in normally dry areas, for example, can create stagnant pools of water where mosquitoes breed and consequently increase the size of vector population, and increase the vector survival rate due to increased humidity. Heavy rain can improve synchrony between vector host-seeking and virus transmission, but washing away breeding sites and destroying habitats (Jepson *et al.*, 1947; Reiter, 2001). On the other hand, decreased rainfall would increase in container-breeding mosquitoes because of more water storage, and higher numbers of vectors that breed in dried-up river beds.

Similarly, an increase in temperature can affect the vectors in various ways including increased population growth, decreased survival of some mosquito species, increased mosquito's feeding rate to combat dehydration (resulting in higher vector-human contact), expanded seasonal and spatial distribution, faster incubation in vector, extended transmission season and expanded distribution (Tsai & Liu, 2005; Tabachnick, 2010).

In Malaysia, four *Plasmodium* species are endemically present viz, *Plasmodium vivax*, *Plasmodium falciparum*, *Plasmodium malariae* and *Plasmodium knowlesi*. Here, we have launched several campaigns to eradicate malaria, with the first one started in 1961, and the latest (National Strategic Plan for Malaria Elimination) in 2010. This has resulted in the drop in number of cases from 243,000 cases in 1961 to about 7,000 cases since 2003. Similarly, the malaria incidence rate per 100,000 Malaysians has decreased from 26.7 in 2008 to 23.5 in 2010. Presently Malaysia is one of ten partners of Asia Pacific Malaria Elimination Network (APMEN) which was established in 2009.

The Intergovernmental Panel on Climate Change (IPCC) report has indicated Malaysian climate will experience an increase of 3–5ºC. As it is known that the growth rate of *P. falciparum* is temperature sensitive (MacDonald, 1957), we decided to investigate the effect of the predicted temperature increase on the growth rate of *P. falciparum* using computer models. Four environmentally different locations in Malaysia were chosen for the study viz Kuala Lumpur (KL) and Cameron Highlands (CH) in peninsular Malaysia, Kota Kinabalu city (KK) and Kinabalu Park (KP) in East Malaysia.

Specifically, we examined the effect of a 3º and 5ºC increase in temperature on the extrinsic incubation period (EIP) and the vector cohort that is still alive to transmit (ie. s^{EIP}, where s=vector survival) of *P. falciparum*.

MATERIALS AND METHODS

The four chosen sites for this study were Kuala Lumpur (KL) and Cameron Highlands (CH) in peninsular (West) Malaysia, Kota Kinabalu (KK) and Kinabalu Park (KP) in East Malaysia. These sites are of different altitudes and have different climates: KK is 8 m above sea level, KL 17 m, CH is 1,829 m and KP 4,095 m. KK and KL are cities, CH a highland resort as well as agricultural area, while KP situated at the base of Mount Kinabalu is a resort (Table 1).

The following four models were used in our investigation and all simulations were conducted using Excel 2007.

Air temperature model

The temperature model used was based on a sinusoidal submodel for daytime and a decreasing exponential submodel for the night (Parton & Logan, 1981).

For daytime where $t_{rise} \leq t < t_{set}$, the sinusoidal submodel is given by:

$$T_t = T_{min} + (T_{max} - T_{min}) \sin[\pi(t - 12 + \tfrac{1}{2}D) / (D + 2p)]$$

For night time where $t_{set} \leq t < t_{rise}$, the decaying exponential submodel is:

$$T_t = [T_{min} - T_{set} \exp(-N/\tau) + (T_{set} - T_{min}) \exp(-(t - t_{set})/\tau)] / [1 - \exp(-N/\tau)]$$ where

T_{min}, T_{max}: minimum and maximum daily air temperature

T_{set}: temperature at sunset

t_{rise}, t_{set} : time (hours) of sunrise, sunset

D, N: hours of day, night

τ: nocturnal night constant

p: time duration between solar noon and maximum air temperature

The values of various parameters for the four sites are given in Table 1.

The model was first tested by running it for Kuala Lumpur. The predicted temperatures were compared with temperatures recorded for Oct 26–6 Nov, 2011 (data from http://www.timeanddate.com/weather/malaysia/kuala-lumpur/historic), and the fit was found to be good (Fig. 1).

Extrinsic Incubation Period (EIP) Models

We used two models to calculate the extrinsic incubation period (EIP) of *P. falciparum* at the four sites.

The first model was thermodynamic and calculated the temperature-dependent growth. It used the hourly temperatures predicted by the temperature model to compute the hourly growth rate which was then summed successively until the value reached 1. This represents that the growth for the parasite has been completed. The rate of growth per hour is given by:

$$r_T = [0.0001127T(T - 15.384)\sqrt{(35 - T)}]/24$$ (Paaijmans *et al.*, 2009)

where T = the hourly air temperature.

Table 1. Details of the four sites and the parameters used in the models

Place	Co-ordinates	Environmental type, altitude	Sun-rise (hr)	Sun-set (hr)	Sun-set temp °C	Day length	Max temp °C	Min temp °C	τ	p
Kuala Lumpur (KL)	03°07'N 101°33'E	City, 17 m above sea level	0720	1920	27	12	30.0	22.9	3	3
Cameron Highlands (CH)	04°30'N 101°15'E	Highland, agricultural, 1,829 m asl	0730	1920	20	12	22.2	15.3	3	4
Kota Kinabalu (KK)	05°59'N 116°04'E	City, 8m asl	0625	1828	27.6	12	28.8	25.3	3	4
Kinabalu Park (KP)	6°4'N 116°34'E	Nature Park, 4,095 m asl	0625	1828	21.5	12	24.0	15.0	3	4

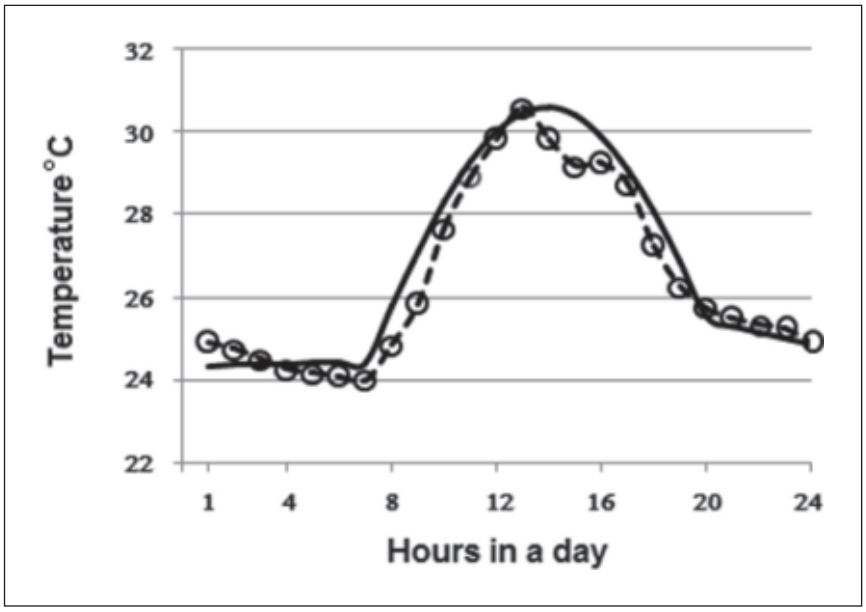

Figure 1. Comparison of predicted (thick line) and actual air temperatures (open circles) for Kuala Lumpur. The observed values are mean temperatures for the period 26 Oct – 6 Nov 2011, obtained from http://www.timeanddate.com/weather/malaysia/kuala-lumpur/historic

The second EIP model is "static" and used the Detinova equation (1962):

EIP = 111/(T-16) (also used by Kiszewski *et al.*, 2004), where T= mean temperature of the day.

Calculation of s^{EIP}

The vector cohort that is still alive to transmit malaria is given by s^{EIP}, where s=vector survivorship. The EIP values from the two models were used separately in the calculation of s^{EIP}, giving two sets of s^{EIP} values.

Loong *et al.* (1990) estimated the horizontal survivorship for the Malaysian strain of *Anopheles maculatus* Theobald to be 0.761 (calculated from the log regression of recaptures), and the vertical survivorship was 0.710 (calculated from the log regression of mosquitoes in each age-group (1-, 2-, 3-, 4- or 5-parous). Similary Chiang *et al.* (1991) also calculated the survival rates of *An. maculatus* to be 0.699-0.705.

In this paper, we used the value of 0.71 for the survivorship of *An. maculatus*.

The term s^{EIP} is part of the equation for estimating basic reproductive number (R_0), or the number of cases of a disease that arise from one case of the disease introduced into a population of susceptible hosts.

$R_0 = [ma^2bc / r(-\ln s)](s^{EIP})$ (rearranged from MacDonald's, 1957) where

s = median daily survival of mosquito = 0.71

r = recovery rate of hosts from infection

m = vector: host ratio

a = biting rate of the vector

b = transmission coefficient from vertebrate to vector

c = transmission coefficient from vector to vertebrate

Since m,a,b,c,r are all constants for a particular scenario, and s is fixed for *An. maculatus* in this model, it can be seen that R_0 is proportional to s^{EIP}. The value of s^{EIP} would enable us to compare the relative effect of temperature changes on malaria risk.

RESULTS

Effects of temperature change on EIP calculated from hourly temperatures

For all the sites, the EIP values predicted from the computer simulations using the current hourly temperatures show a decrease if the temperature was raised by 3º or 5ºC. The decrease is greater for the cooler and higher altitude sites (CH and KP) than for KL and KK. For example, in CH, the respective EIP values were 37.50 (current temperature), 20.38 (for 3ºC increase) and 15.21 (for 5ºC) days (Table 2), for KP in East Malaysia 31.67, 19.63 and 14.29 days. For the warmer areas: KL 11.88, 10.42 and 11.46 days, and for KK 10.33, 9.42, and 9.92 days.

Effects of temperature change on EIP calculated from daily mean temperatures

Using the daily mean temperatures and the Detinova equation, the EIP values estimated were lower than those computed from hourly temperatures in warmer areas (KL, KK), but higher in the cooler areas (CH, KP, and only at the current temperature). All EIP values decreased when the current temperature was raised by 3º and 5ºC. For KL, the EIP's were 11.73, 8.91 and 7.68 days respectively, for KK 10.48, 8.17 and 7.12 days, for CH 36.54, 18.88 and 14.09 days, and for KP 38.08, 18.78 and 14.03 respectively.

Effects of temperature change on s^{EIP}

The values of s^{EIP} show an increase if the temperature was raised, with a bigger increase for a higher temperature rise and for a cooler site (Table 3). For example, for KL the s^{EIP} only increased by 3 and 4 times for a 3º and 5ºC rise respectively and for KK 2 and 3 times. However for CH, the increase is 841 and 4340 times, and for KP 743 and 3780 times respectively.

DISCUSSION

The Detinova equation uses daily mean temperatures in estimating the EIP, and when compared to those based on hourly temperatures, gives lower values in warmer places and higher values in cooler places. This results in overestimating malaria risk for warmer areas and underestimating risk in cooler areas. As indicated by Paaijmans *et al.* (2009), under warmer conditions, diurnal fluctuation increases the EIP due to the nonlinear effects of short-term exposure to sub- and superoptimum temperatures.

The computer simulations have shown that any temperature increase will affect the EIP of the *Plamodium* parasite and subsequently the s^{EIP} (the vector cohort that is still alive to transmit malaria). The effect

Table 2. Effect of 3º and 5ºC rise on the extrinsic incubation period (EIP) of *P. falciparum* in four sites of Malaysia as predicted by the models. The EIP was calculated using the hourly temperature as well as the average daily temperature. Daily mean temperatures are given, with range within parentheses

Place		Current Temperature in Malaysia		Temperature increased by 3º		Temperature increased by 5º	
		EIP calculated using		EIP calculated using		EIP calculated using	
		hourly temp	average temp	hourly temp	average temp	hourly temp	average temp
Kuala Lumpur (KL)	Temp (°C)	25.46 (22.0-30.0)		28.46 (25.0-33.0)		30.46 (27.0-35.0)	
	EIP (days)	11.88	11.73	10.42	8.91	11.46	7.68
Cameron Highlands (CH)	Temp (°C)	18.88 (15.2-22.2)		21.88 (18.2-25.2)		23.88(20.2-27.2)	
	EIP (days)	37.50	38.54	20.38	18.88	15.21	14.09
Kota Kinabalu (KK)	Temp (°C)	26.59 (25.2-28.8)		29.59 (28.2-31.8)		31.59(29.2-32.8)	
	EIP (days)	10.33	10.48	9.42	8.17	9.92	7.12
Kinabalu Park (KP)	Temp (°C)	18.91 (14.8-24.0)		21.91 (17.8-27.0)		23.91(19.8-29.0)	
	EIP (days)	31.67	38.08	19.63	18.78	14.29	14.03

Table 3. Effect of 3º and 5ºC rise on the vector cohort that is still alive to transmit *P. falciparum* (s^{EIP}) in four sites of Malaysia as predicted by the models. Values in brackets indicate the number of times the increase in s^{EIP} as compared to the s^{EIP} at the current temperature

	Kuala Lumpur (KL)	Cameron Highlands (CH)	Kota Kinabalu (KK)	Kinabalu Park (KP)
	s^{EIP}	s^{EIP}	s^{EIP}	s^{EIP}
Current temp.	0.0180	0.000003	0.0276	0.000002
Incr. by 3°C	0.0473 (2.63X)	0.00156 (841X)	0.0610 (2.21X)	0.00161 (743X)
Incr. by 5°C	0.0721 (4.01X)	0.0080 (4340X)	0.0873 (3.16X)	0.0082 (3780X)

is greater if the range of daily temperature is big such as in CH (6.9ºC) and KP (9ºC), and the maximum is below 25ºC (Table 1). This is because temperature increase will reduce the EIP relatively more if the current temperature is lower, even though the range may stay the same. The drop in EIP is relatively less if the baseline temperature is already high ie above 25ºC (eg KL, KK). Lindsay & Martens (1998) had pointed out that effective malaria transmission can occur only in areas with a temperature higher than 20ºC, and transmission below 18ºC is unlikely because few adult mosquitoes survive the 56 days required for sporogony at that temperature (Craig *et al.*, 1999). This indicates the potential rise in malaria cases in places where the current temperatures are below 20ºC such as in CH and KP.

The highest temperature observed in the simulations was only 35ºC for KL (Table 2), which is high enough to reduce the survivorship of the adult mosquitoes. Rueda *et al.* (1990) had shown that below 15 and above 34, survival from egg eclosion to adult emergence dropped drastically. Thermal death for mosquitoes occurs around 40–42ºC and daily survival is zero at 40ºC (Jepson *et al.*, 1947). With temperature of more than 40ºC, malaria infection rate may drop. This has been observed in Senegal, where high temperature increase coupled with reduced precipitation has reduced malaria prevalence by more than 60 per cent in the past 30 years (Githeko *et al.*, 2000).

These results demonstrate how the interaction between temperature and its biological influence on mosquito and parasite life cycle can be an important factor in the association between temperature and malaria. Other workers (Teklehaimanot *et al.*, 2004; Parham & Michael, 2010) have also made similar conclusions.

Although higher temperature may result in an increase in the population of vectors, this does not necessarily translates into an increase in disease. Many factors are also important; these include ecological and societal factors (water storage and disposal systems, agricultural practices, deforestation, population density, living conditions, control programmes and health infrastructure) (Reiter, 2001), human behavior, human population's immunity and the parasite's levels of drug resistance. For example, it has been reported in East Africa, a drop in mosquito control and a rise in drug resistance appears to be confounding studies assessing whether malaria incidence has grown because of, or independently of, climate (Parry *et al.*, 2007).

Parham & Michael (2010), using a model of R_0 which is dependent on temperature and rainfall model found vector population extinction be more strongly dependent on rainfall than on temperature and identified a temperature window of around 32-33ºC where endemic transmission and the rate of spread in disease-free regions is optimized.

This study also indicates that modeling the effect of temperature change could help understand the transmission dynamics of malaria and prepare the country for an increase in malaria incidence rate. However for the purpose of forecasting disease outbreaks and acting as early warning systems, accurate rigorous models are needed and these would require more reliable

and detailed climate and disease data. The importance of high quality weather station data has also been highlighted by Hoshen & Morse (2004) in their weather-driven model of malaria transmission. Early warning systems have already been developed for operational use in other countries, eg in Eritrea (Ceccato *et al.*, 2008), and in Kenya and Uganda (The Highland Malaria Project - HIMAL, Abeku *et al.*, 2004).

Perhaps Asian countries should consider developing an early warning model to be ready for global climate change. Such models may consider including geographic information systems that can link data to specific locations and allow both spatial and temporal analyses of disease data, and non-climatic factors such as drug resistance which can influence epidemics.

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