Modelling Malaria Transmission using an SIS-SEI model, in the context of global warming

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Introduction:

Malaria remains a significant global health challenge, particularly in tropical and subtropical regions. The disease is caused by *Plasmodium* parasites transmitted by infected female *Anopheles* mosquitoes. Hence, understanding malaria transmission dynamics is crucial for developing effective control strategies.

Mathematical modeling of malaria transmission has evolved significantly since the early 20th century, providing insights to guide public health interventions. Ronald Ross's 1908 model[1] established the framework for understanding the host-vector dynamics, demonstrating the necessity of considering the mosquito population. George Macdonald's 1950s model[2] introduced detailed aspects such as mosquito life expectancy, parasite development within the mosquito, and the basic reproduction number R_0, crucial for assessing outbreak potential.

Recent models have increased in complexity, incorporating factors like human immunity, age-structured populations, spatial dynamics, climate variables, and intervention effects. For this project, we have chosen the Macdonald model as our base, motivated by its historical significance and ability to effectively incorporate key epidemiological parameters. Considering the modern context of global warming, we have altered the model to reflect the temperature dependency of its parameters, providing a solid foundation for understanding the basic dynamics of malaria transmission through the relationship between mosquito density and malaria spread.

The Macdonald Model:

In the classic SIR model, the disease transmission dynamics are captured through three compartments:

Figure 1: Standard SIR model

[1] *Ross, Ronald. "An application of the theory of probabilities to the study of a priori pathometry.—Part I." Proceedings of the Royal Society of London. Series A, Containing papers of a mathematical and physical character 92.638 (1916): 204-230.*

[2] *Macdonald, G. "1957The epidemiology and control of malaria." London: Oxford University PressMacdonaldThe epidemiology and control of malaria1957.*

$$\frac{dS}{dT} = \quad - \beta SI$$
$$\frac{dI}{dT} = \beta SI - \gamma I$$
$$\frac{dR}{dT} = \gamma I$$

where β = infection rate

γ = recovery rate

However, the Macdonald model differentiates from the traditional SIR model in two ways. Firstly, by considering two populations: humans and mosquitoes. Secondly, humans follow an SIS pattern:

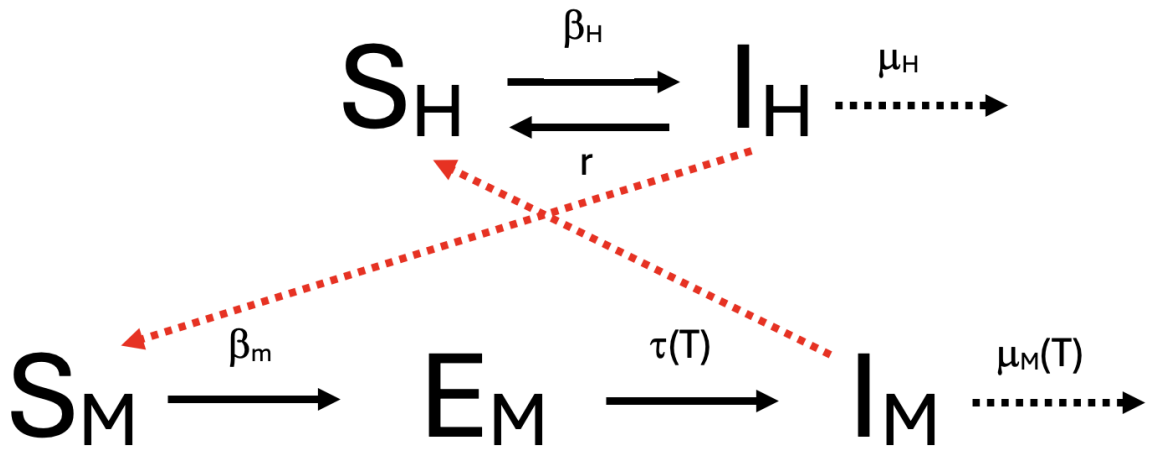


Figure 2: Macdonald model

The SIS model fits malaria as immunity is short-lived due to antigenic variation and immune evasion by *Plasmodium falciparum*, enabling reinfection. Reinfection is possible and prevalent, which is why the SIS model, without a distinct Recovered compartment, is particularly suitable for modeling malaria transmission dynamics. This model choice emphasizes the need for ongoing interventions and highlights the persistent vulnerability of populations to malaria, even among those who have previously recovered[3].

[3] *Mandal, Sandip et al. "Mathematical models of malaria--a review." Malaria journal vol. 10 202. 21 Jul. 2011, doi:10.1186/1475-2875-10-202*

Human dynamics equations:

$$\frac{dS_H}{dT} = -\beta_H S_H I_M + rI_H$$

$$\frac{dI_H}{dT} = \beta_H S_H I_M - rI_H - \mu_H$$

where β_H = infection rate of humans = Mosquito biting rate (a(T)) X Proportion of bites that produce infection in human (b) X Ratio of number of female mosquitoes to that of humans (m)

r = recovery rate

and μ_H = death rate due to malaria

Mosquito dynamics equations:

$$\frac{dS_M}{dT} = -\beta_M S_M I_H$$

$$\frac{dE_M}{dT} = \beta_M S_M I_H - \beta_M I_H(t-\tau_M)[1 - E_M(t-\tau_M) - I_M(t-\tau_M)]e^{-\mu_M \tau_M} - \mu_M E_M$$

$$\frac{dI_M}{dT} = \beta_M I_H(t-\tau_M)[1 - E_M(t-\tau_M) - I_M(t-\tau_M)]e^{-\mu_M \tau_M} - \mu_M I_M$$

where β_M = infection rate of mosquitos = Mosquito biting rate (a(T)) X Proportion of bites by which one susceptible mosquito becomes infected (c)

τ_M = Latent period of mosquito

and μ_M = Death rate of mosquitos

$R_0 = \frac{ma^2bc}{r\mu_M}e^{-\mu_M \tau_M}$ as given by MacDonald.

In the equations above, τ_M is the time delay or incubation period that accounts for the time it takes for an infection to progress within the mosquito. After a mosquito bites an infected human, the parasites undergo an incubation period inside the mosquito before the mosquito becomes infectious. τ_M represents this time lag in the model and is used to calculate the state of the system at a previous time $(t - \tau_M)$.

Additionally, the exponential function in these equations, expressed as $e^{-\mu_M \tau_M}$, represents the survival rate of the mosquitoes over the incubation period. The term $e^{\mu_M \tau_M}$ models the proportion of mosquitoes that survive over this period since the natural death rate of the mosquitoes reduces their numbers exponentially over time.

Methodology:

In the original Macdonald model, τ_M is considered as a constant with values ranging from 5 to 15 days. The reason for a difference in latency period can be significantly attributed to the variations in environmental temperature, a factor that has become increasingly important in the context of global warming. As global temperatures rise, they can alter the latency period of the malaria parasite within the mosquito. Consequently, we modeled τ_M, the latency period, to be a function of temperature, to capture these climate-driven changes($\tau_M(T)$). This was done by performing regression analysis on empirical data which compared temperature and the earliest day plasmodium sporozoites were found in mosquito salivary glands[4] (meaning it can now infect humans, hence E_M to I_M) (Figure 3)

[4] *Vanderberg, Jerome P., and Meir Yoeli. "Effects of Temperature on Sporogonic Development of Plasmodium Berghei." The Journal of Parasitology, vol. 52, no. 3, 1966, pp. 559–64. JSTOR, https://doi.org/10.2307/3276326. Accessed 21 Apr. 2024.*

Tempera-ture	Earliest day for sporozoites in salivary glands	*Sporo-zoites per mosquito	Infec-tivity
14 C	**	**	**
16 C	21		+
18 C	17	5,500	+
18–21 C	11	25,000	+
21 C	9	32,000	+
24 C	8	7,500	+

* (Mean number of recovered sporozoites)/(mosquito) at peak number for each temperature.
** High mosquito mortality at this temperature.

Figure 3: Data on temperature and the earliest day plasmodium sporozites were found in female *Anopheles* salivary glands

The regression plot was found to be as follows:

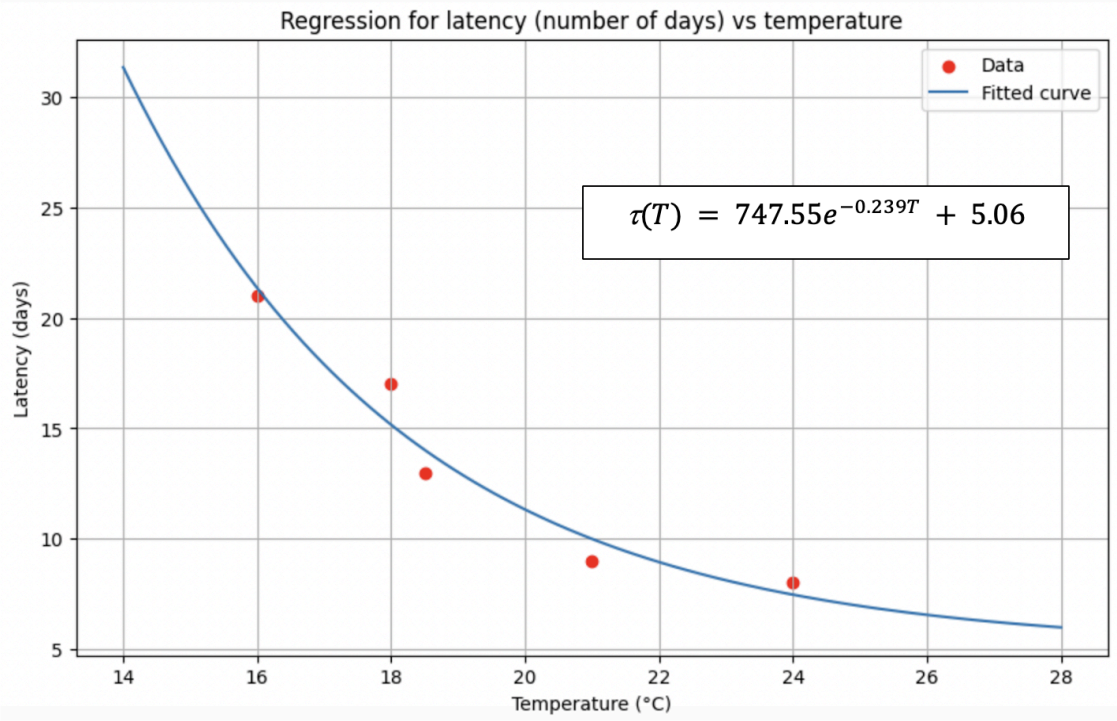


Figure 4: Regression analysis of temperature vs latency (days)

This regression function captures that an increase in temperature leads to an exponential decrease in the latency period.

Alongside the latency period, warmer temperatures have been shown to increase mosquito biting rates, reflected by the parameter *a.* This is attributed to elevated metabolic rates in mosquitoes that necessitate more frequent blood meals for egg production. Recognizing the role of rising global temperatures, we felt we should reflect the role of temperature in determining *a*. To find an equation for it, we found a dataset and performed regression analysis. Here is the data and the regression plot[5]:

Temperature	Infectious Mosquito Days	Biting Rate	Predicted Bites
21˚C	493.4	**0.193** (0.171–0.215)	**95.2** (84.4–106.1)
24˚C	695.9	**0.246** (0.222–0.270)	**171.2** (154.5–187.9)
27˚C	630.4	**0.296** (0.261–0.331)	**186.6** (164.5–208.7)
30˚C	257.3	**0.337** (0.288–0.386)	**86.7** (74.1–99.3)
32˚C	196.8	**0.377** (0.324–0.430)	**74.2** (63.7–84.6)
34˚C	133.0	**0.421** (0.352–0.49)	**56.0** (46.8–65.17)

Mean (and standard deviation) number of infectious bites predicted for a cohort of 100 females over a period of 50 days. Values calculated by using the relative force of infection model that takes into account the dynamic distribution of both mortality and infection and daily biting rate.

https://doi.org/10.1371/journal.pbio.2003489.t002

Figure 5: Data on temperature and biting rate

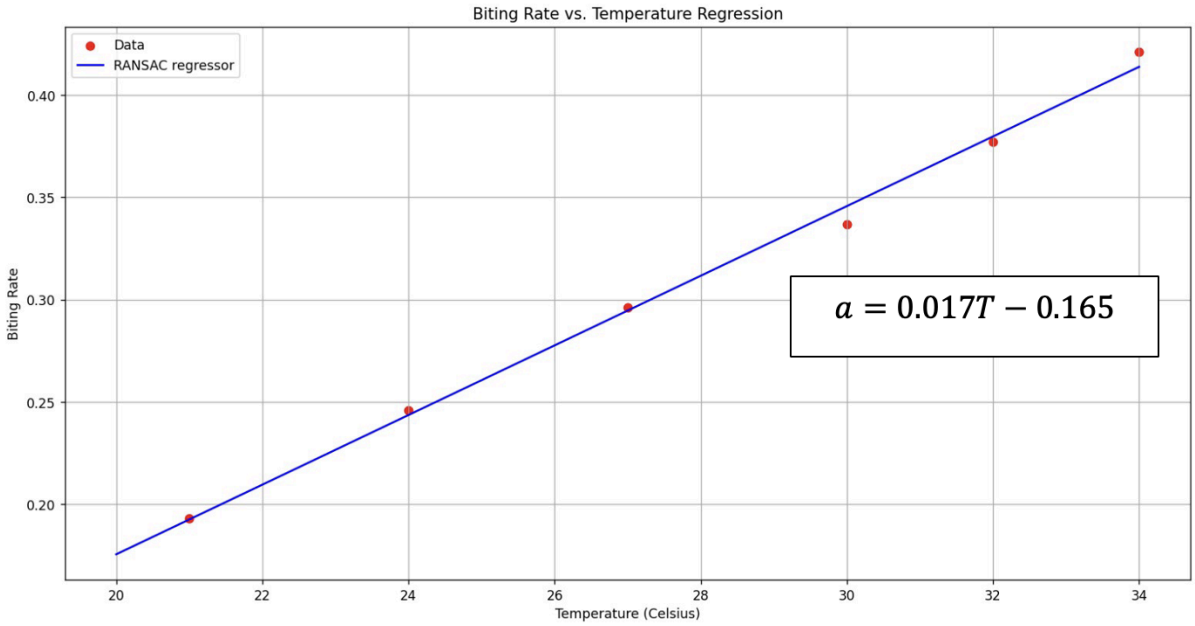


Figure 6: Regression analysis of temperature vs biting rate

[5] *Shapiro, Lillian L M et al. "Quantifying the effects of temperature on mosquito and parasite traits that determine the transmission potential of human malaria." PLoS biology vol. 15,10 e2003489. 16 Oct. 2017, doi:10.1371/journal.pbio.2003489*

Finally, mosquito mortality rate varies significantly with temperature as well. Research led us to an equation that had been determined from a study by Ngarakana-Gwasira et al.[6]:

$$\mu_M(T) = \frac{1}{-0.03T^2 + 1.31T - 4.4}$$

The inclusion of temperature in our model has resulted in a more robust model that is pertinent in the context of global warming. It acknowledges temperature's multifaceted influence on malaria transmission, affecting the parasite's latency period and mosquito biting rates. Here is table of the final parameters we are considering and their range of values:

Table 1: Parameters and their range of values

Parameter	**Range of values[7]**
a: Man Biting Rate	a(T) = 0.017T- 0.165
b: Proportion of bites that produce infection in human	0.2-0.5
c: Proportion of bites by which one susceptible mosquito becomes infected	0.5
m : Ratio of number of female mosquitoes to that of humans	0.5-40
r : Average recovery rate of human	0.005-0.05 per day
μ_H: human mortality rate from malaria	0.0001 - 0.004 per day
μ_M: Per capita rate of mosquito mortality	$\mu_M(T) = \frac{1}{-0.03T^2 + 1.31T - 4.4}$
τ_m: Latent period of mosquito	$\tau_m(T) = 747.55e^{-0.239T} + 5.06$
T: Temperature	14 - 40°C

[6] *Ngarakana-Gwasira, E T et al. "Assessing the Role of Climate Change in Malaria Transmission in Africa." Malaria research and treatment vol. 2016 (2016): 7104291. doi:10.1155/2016/7104291*

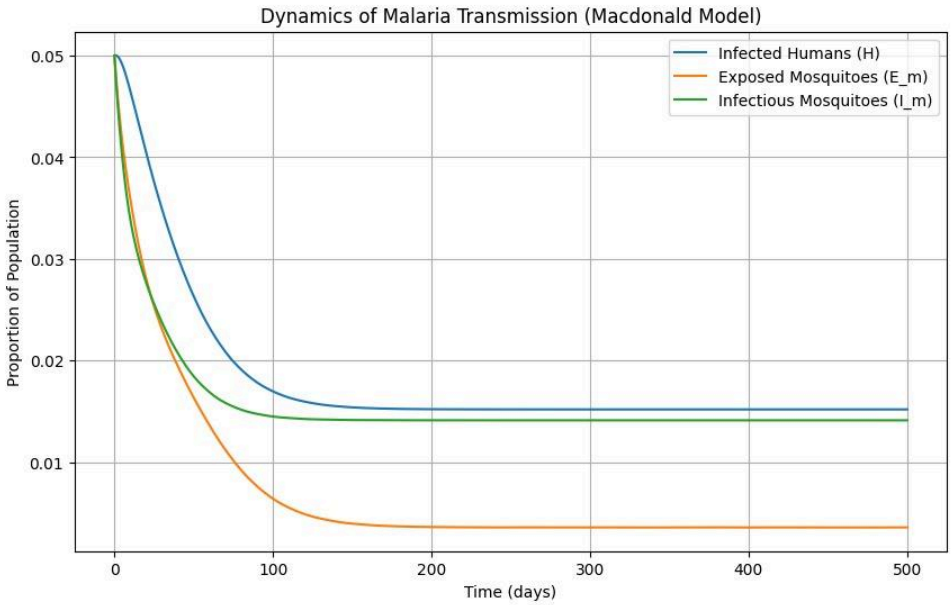
[7] *Mandal, Sandip et al. "Mathematical models of malaria--a review." Malaria journal vol. 10 202. 21 Jul. 2011, doi:10.1186/1475-2875-10-202*

To analyse the results of our model, we graphed the peak of the infection, the day it is reached and R_0 value. The range of temperatures chosen was 14°C to 40°C to include mean temperatures typically seen around the world.

Results and analysis:

Initial values for I_H, E_M, I_M: [0.05, 0.05, 0.05]

Dynamics when R0 < 1:



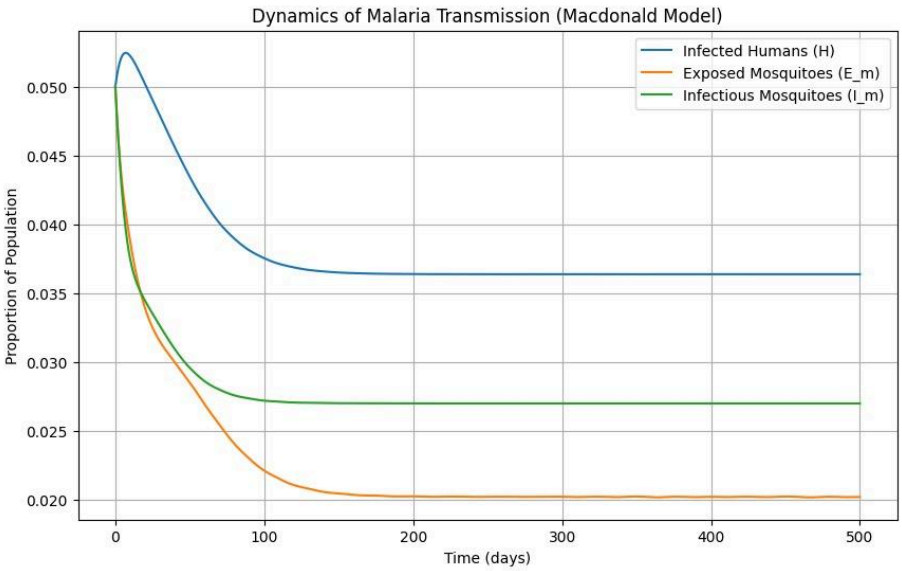
Graph 1: Dynamics of Malaria Transmission when $R_0 < 1$

Basic reproduction number: 0.626

Peak infected human proportion: 0.050 on day 1 (both rounded to 3 decimal places)

As expected, when R_0 is below 1, the infection fails to spread.

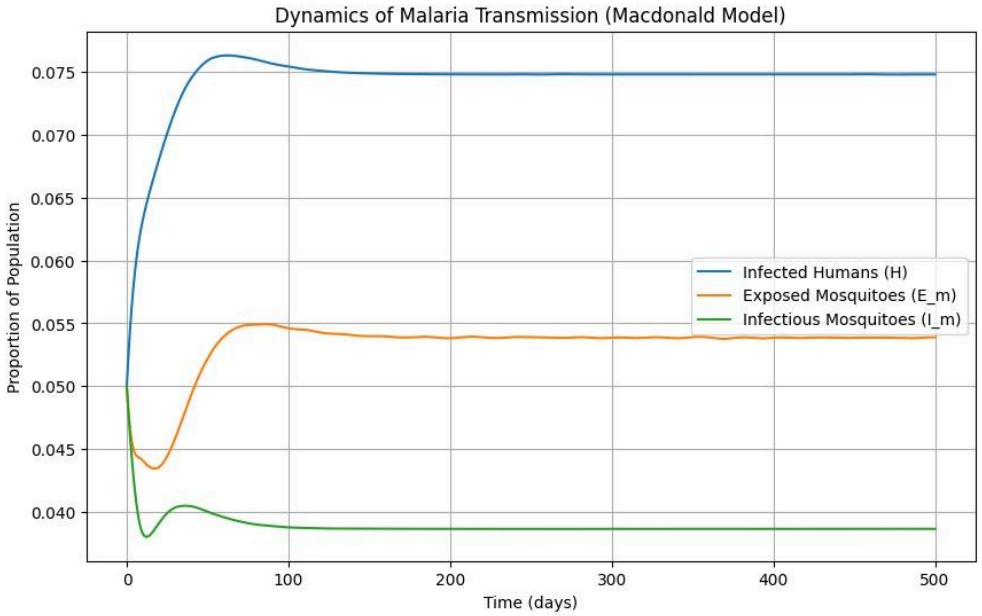
Dynamics when R0 = 1:



Graph 2: Dynamics of Malaria Transmission when $R_0 = 1$

Basic reproduction number: 1.000
Peak infected human proportion: 0.052 on day 7
When $R_0 = 1$, the infection sees a slight spread but soon dips and remains at a low equilibrium point.

<u>Dynamics when R0 > 1:</u>



Graph 3: Dynamics of Malaria Transmission when $R_0 > 1$

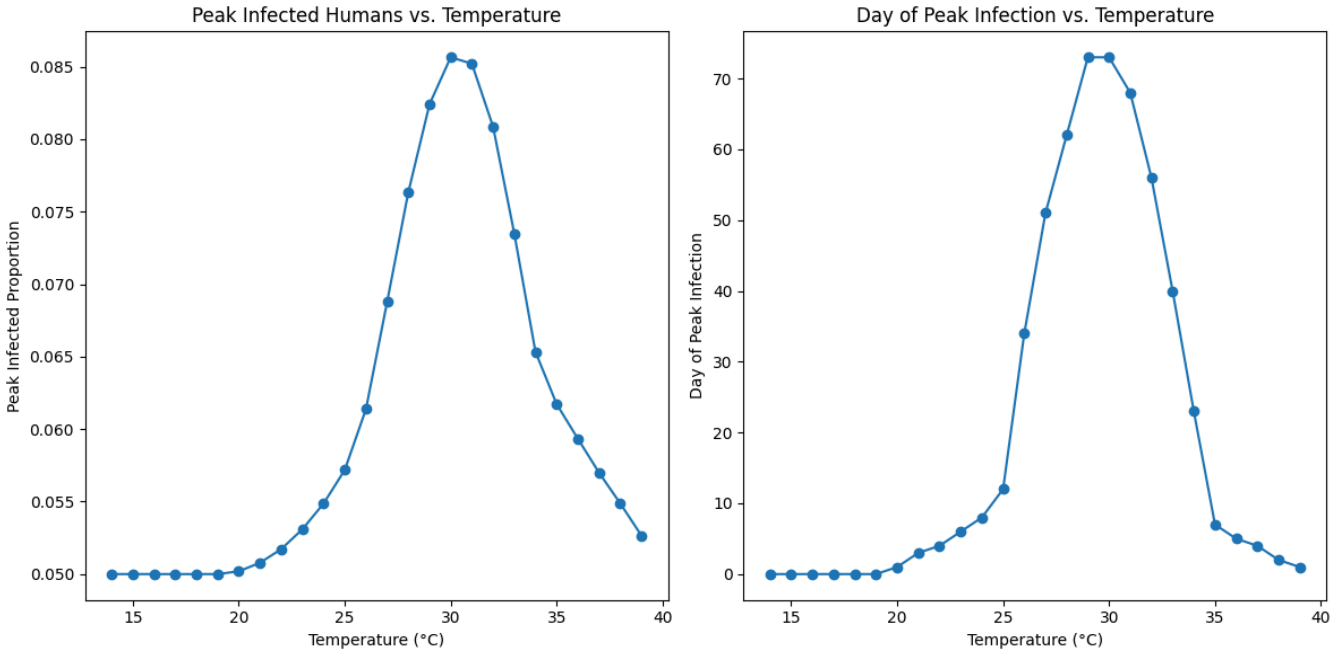
Basic reproduction number: 1.495

Peak infected human proportion: 0.076 on day 62
A value of R_0 > 1 shows the expected behaviour of an epidemic.

Notably, in all scenarios, the proportion of infected humans decreases over time but does not reach zero. This is indicative of a persistent, low-level transmission and possibly a reservoir of infection, as indicated by the proportion of exposed and infected mosquitos at equilibrium, that could flare up under favourable temperatures.

<u>Specifications of the following analysis</u>
Initial values for I_H, E_M, I_M: [0.05, 0.05, 0.05]
Parameter values (median values were chosen in most cases):
b = 0.35
c = 0.5
m = 1
r = 0.05
μ_H = 0.002

<u>Effects of Temperature on time and ratio of Peak Infection:</u>



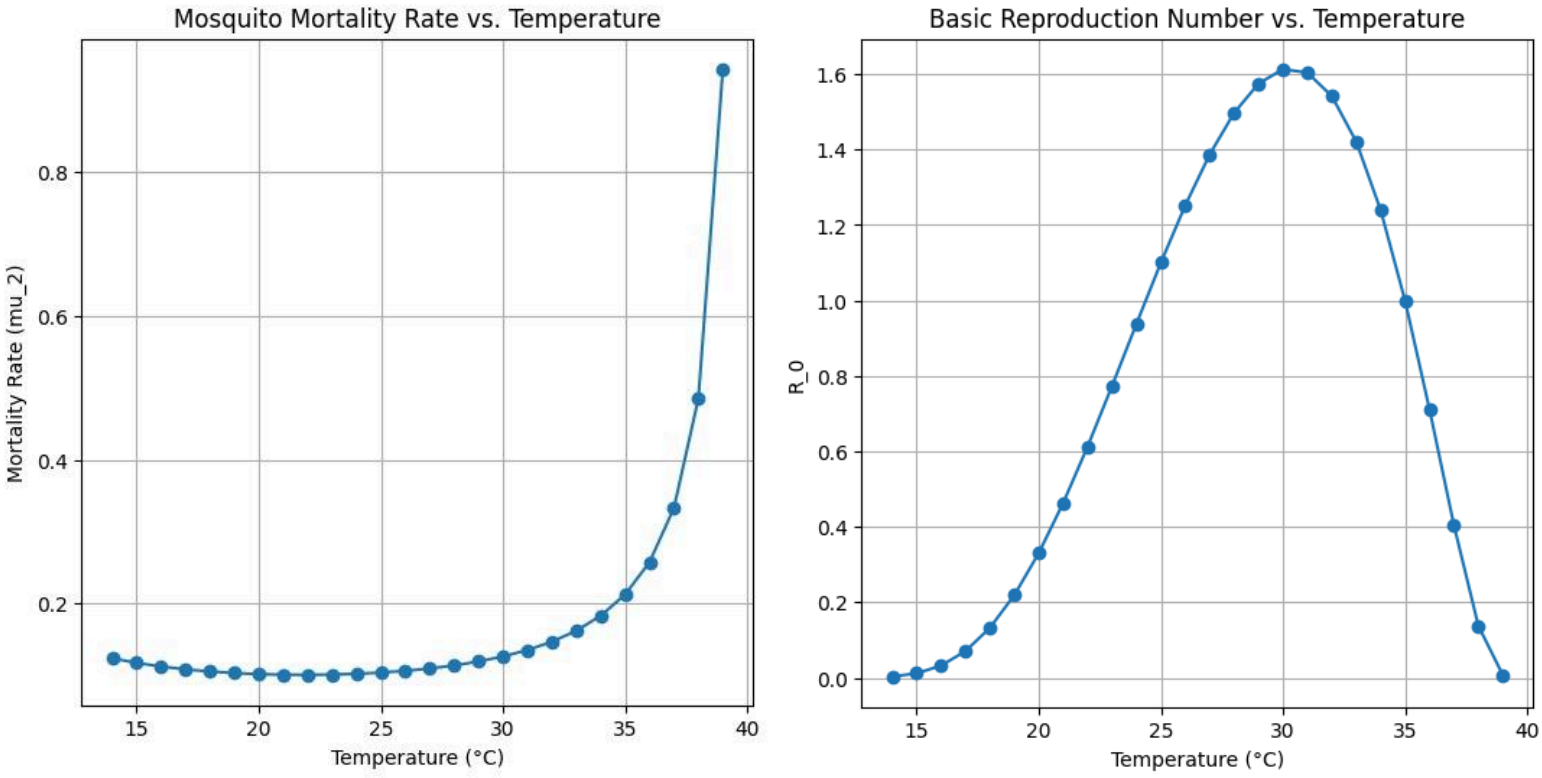
Graph 4: a) Peak infected proportion vs Temperature; b) Day of peak infection vs Temperature

Both the day of the peak and the proportion of the peak show a similar relationship with temperature; they increase steadily with temperature until their peak is reached, and then decrease at a similar rate as temperature increases further. Both attain their maximum value close to 30°C.

In the case of the proportion of the peak, we can attribute the increase to an increased biting rate and a reduction in the latent period, resulting in more infections and in infection developing quicker. While the mosquito mortality rate also increases, it is outweighed by these two combined factors. After the maxima, the increase in mortality rate becomes more significant and the reduction in latent period begins to taper off, resulting in a large number of deaths of exposed and infectious mosquitoes which reduces the spread of the disease.

When it comes to the day of the peak, we can essentially attribute the increase to an increase in R_0 (which will be further discussed below). Due to this, rather than the infection peaking and dying out early, it sustains for a longer period of time and attains a higher peak later. The decrease follows the same logic as above; temperatures increasing above a certain amount result in the mosquito mortality rate outweighing other factors which makes the infection die out much faster.

Effect of Temperature on μ_M and R_0:



Graph 5: a) Mortality rate of mosquitos vs Temperature; b) R_0 vs Temperature

As it can be seen from the graph of mortality rate (mosquitos) vs temperature from above, the mortality rate of mosquitoes increases dramatically after 33°C. This can be used to explain why the graph of R_0 reduces sharply after 33°C which in turn contributes to the change in the peak and the day of the peak. However, the lower values, and rates of change, of R_0 seen before 20°C are attributed to the high latency period of exposed mosquitoes and low biting rate of mosquitoes at lower temperatures.

It is worth noting that in the equation for R_0 as shown below:

$$R_0 = \frac{ma^2bc}{r\mu_M}e^{-\mu_M\tau_M}$$

μ_M is factored in twice: once in the calculation of the duration of infectiousness ($e^{-\mu_M\tau_M}$) and once in the denominator of the transmission rate ($\frac{ma^2bc}{r\mu_M}$). Thus, it is evident why mosquito mortality rate is such an impactful factor, and this is compounded by its high variability.

Most malaria models to date assume constant or linear responses of mosquito and parasite life-history traits to temperature, predicting optimal transmission at 31 °C. The peak of the graph of R_0 vs temperature is at approximately 30°C, consistent with predictions made by earlier mechanistic models[8]. Newer models[9] factor in more complex ecological assumptions about the thermal physiology of insects, and have estimated the peak to be lower at about 25°C (to be discussed in the next section):

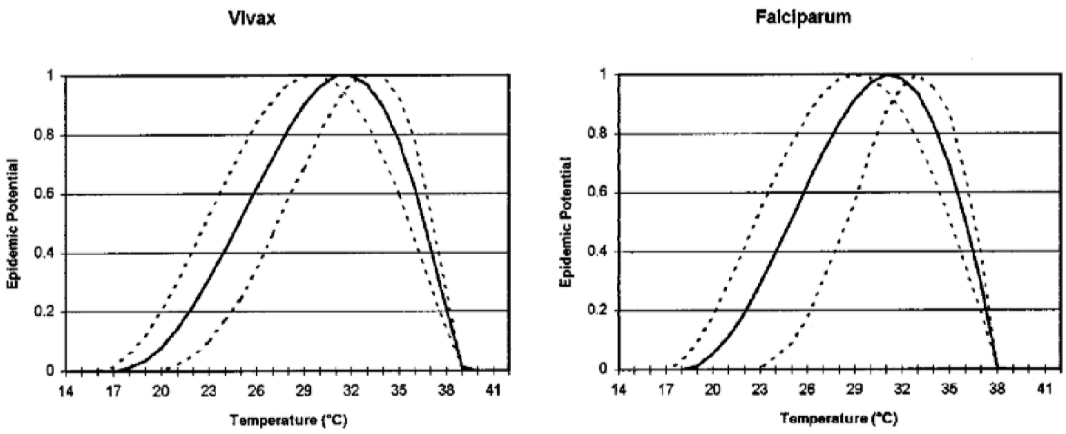


Figure 7: Graph from Mertens et. al showing peak of R_0 at a approximately 33°C

[8] *Martens, W.J.M., Jetten, T.H. & Focks, D.A. SENSITIVITY OF MALARIA, SCHISTOSOMIASIS AND DENGUE TO GLOBAL WARMING. Climatic Change* ***35****, 145–156 (1997).*

[9] *Mordecai, Erin A et al. "Optimal temperature for malaria transmission is dramatically lower than previously predicted." Ecology letters vol. 16,1 (2013): 22-30. doi:10.1111/ele.120*

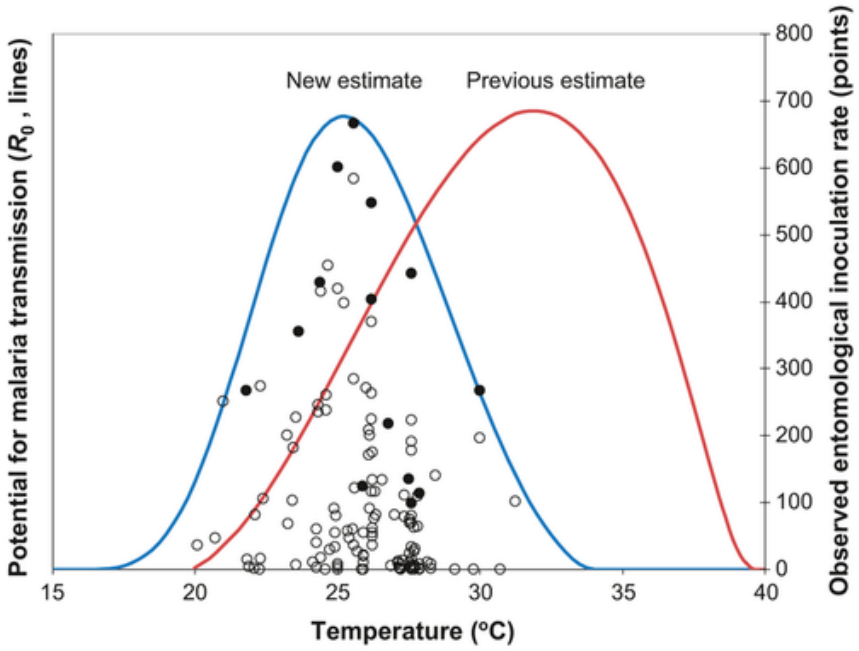


Figure 8: Graph from Mordecai et. al showing peak of R_0 at a approximately 25°C

Discussion:

Our model underscores the potential consequences of global warming on malaria transmission. By predicting a shift in the optimal temperature for malaria transmission to 30°C, we provide evidence that global warming could expand the geographical range of malaria into areas previously unsuitable for transmission due to cooler temperatures, including some temperate zones. Simultaneously, in the hottest regions, further temperature increases might surpass the upper survival limits for mosquitoes or parasites, reducing the viability of transmission. However, we realise that the model does not account for immunity and mosquito development.

While we chose an SIS model for malaria as immunity is not long-lasting, more complex models can incorporate aspects like waning immunity[10], partial protection from repeated exposures or vaccination[11], and age-structured populations with varying immunity

[10] Kelly-Hope, L.A., McKenzie, F.E. The multiplicity of malaria transmission: a review of entomological inoculation rate measurements and methods across sub-Saharan Africa. *Malar J* 8, 19 (2009). https://doi.org/10.1186/1475-2875-8-19

[11] Hamilton, A., Haghpanah, F., Hasso-Agopsowicz, M. *et al.* Modeling of malaria vaccine effectiveness on disease burden and drug resistance in 42 African countries. *Commun Med* 3, 144 (2023). https://doi.org/10.1038/s43856-023-00373-y

levels[12]. However, these often simplify mosquito dynamics by reducing them to a parameter.

Additionally, our model does not include the development cycle of a mosquito from an egg to an adult. This development is also significantly affected by temperature and is one of the key factors accounted for in the paper by Mordecai et al., which leads to the left-shifted peak of R_0. However, this model followed an entirely different system of equations that was outside the scope of this class.

Furthermore, for the temperature dependency of biting rate, our regression analysis showed a linear relationship. Though some papers use a linear model[13], some other papers suggest a significant drop after around 41°C[14], but the range of areas with such high temperatures is very low, and more importantly, we could not find data on biting rates at these temperatures to factor in.

As temperatures increase due to global warming, it becomes crucial to implement strategies to combat malaria transmission. It is important to increase the distribution of insecticide-treated mosquito nets and use repellents, especially in areas where temperatures are approaching the critical threshold. This would reduce the mosquito biting rate[15] (a(T)). Environmental management, such as the removal of standing water bodies, disrupts mosquito breeding grounds, reducing the ratio of mosquitoes to humans[16] (m). Combatting global warming by reducing emissions would reduce multiple parameters influencing the spread of malaria by decreasing temperature, but would require a concentrated and coordinated effort by governments. The effectiveness of current interventions may be impacted by climate change, requiring ongoing monitoring and adaptation.

Our current model thus represents a foundational step, focusing on the most directly measurable temperature effects, with the understanding that future work could develop

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[12] Paul, R.E., Bonnet, S., Boudin, C. et al. Age-structured gametocyte allocation links immunity to epidemiology in malaria parasites. Malar J 6, 123 (2007). https://doi.org/10.1186/1475-2875-6-123

[13] MARTENS, WILLEM J., et al. “SENSITIVITY OF MALARIA, SCHISTOSOMIASIS AND DENGUE TO GLOBAL WARMING.” *Climatic Change*, vol. 35, no. 2, 1997, pp. 145–156, https://doi.org/10.1023/a:1005365413932.

[14] *Mordecai, Erin A et al. “Optimal temperature for malaria transmission is dramatically lower than previously predicted.” Ecology letters vol. 16,1 (2013): 22-30. doi:10.1111/ele.120*

[15] Nalinya, S., Musoke, D. & Deane, K. Malaria prevention interventions beyond long-lasting insecticidal nets and indoor residual spraying in low- and middle-income countries: a scoping review. *Malar J* 21, 31 (2022). https://doi.org/10.1186/s12936-022-04052-6

[16] Nabatanzi, Maureen et al. “Malaria outbreak facilitated by increased mosquito breeding sites near houses and cessation of indoor residual spraying, Kole district, Uganda, January-June 2019.” *BMC public health* vol. 22,1 1898. 12 Oct. 2022, doi:10.1186/s12889-022-14245-y

a more comprehensive model accounting for additional temperature dependencies in the context of global warming.

Author contributions:

All of us contributed equally to the research, modelling, coding and report, with us having slightly different emphasis on different aspects.

Aaryan Shah: Research, derivation of equations, code, writeup. Contributed more to incorporating the delay in the script for solving differential equations.

Aman Ali: Research, derivation of equations, code, writeup. Contributed more to the parameters and plotting for the temperature aspect as well as bug fixing.

Aryan Mohanani: Research, derivation of equations, code, writeup. Contributed more to ideation and development of the model.