

MALARIA REPLICATION CHARACTERISTICS

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- 1 Introduction
 - Malaria trends between periods
 - HIV trends between periods
- 2 The malaria life cycle
- 3 Analysis of the model
 - Mathematical analysis
 - Numerical simulation
- 4 Conclusion

Some statistics on malaria

- 40% of the world population lives in malaria endemic area.
- 300 to 500 million cases of clinical malaria are reported each year.
- 1 to 1.7 million deaths due to malaria are reported annually.
- 800,000 to 1 million deaths occur in the sub-Saharan region.

WHO-Malaria facts 2008 and WHO-Malaria(2010)

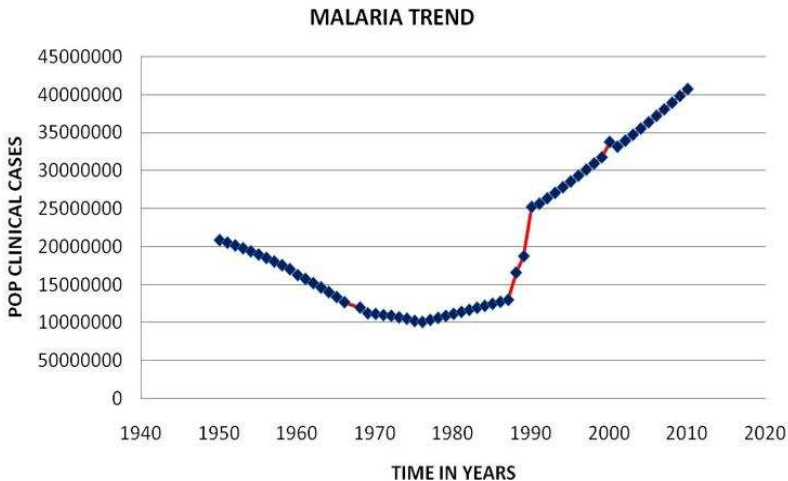
Malaria occurrence

In the Grip of Malaria in Africa



- In Sub-Saharan Africa malaria endemic areas, malaria has become the number killer of people living with AIDS.
- 50% of children deaths in Sub-Saharan Africa under the age of 5 are caused by malaria.

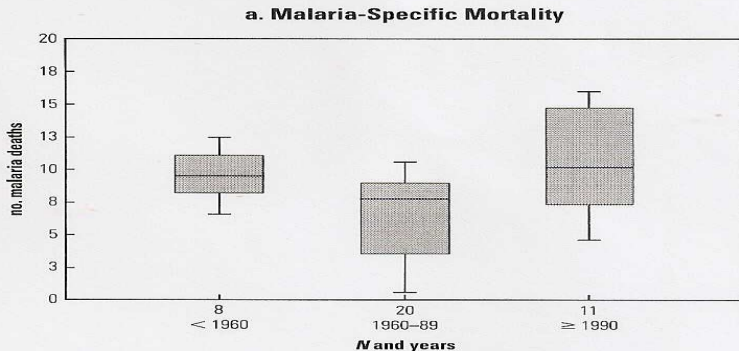
Clinical malaria trend 1950-2010



Malaria trends between periods

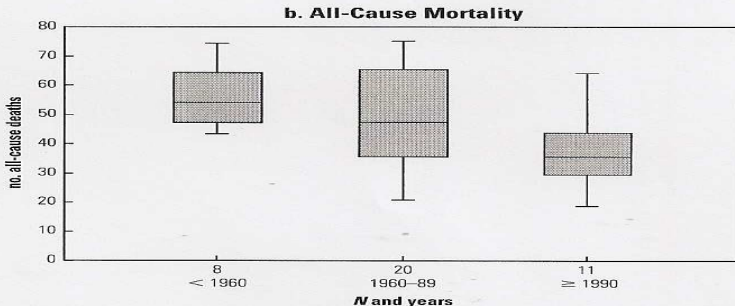
- Clinical malaria cases were in decline between 1950 and 1975.
- A combination of chloroquine and vector control (pesticide DDT) was responsible for declining clinical malaria cases between 1950 and 1975.
- During the same period vector control programs were very effective. The pesticide DDT was very effective at controlling mosquito populations.
- DDT was banned during the 1970s and no effective vector control pesticide has been found.
- After the 1970s malaria treatment drugs were available without a prescription.
- Malaria sufferers were treating themselves and some did not complete the medication.

Malaria deaths for children under five years old



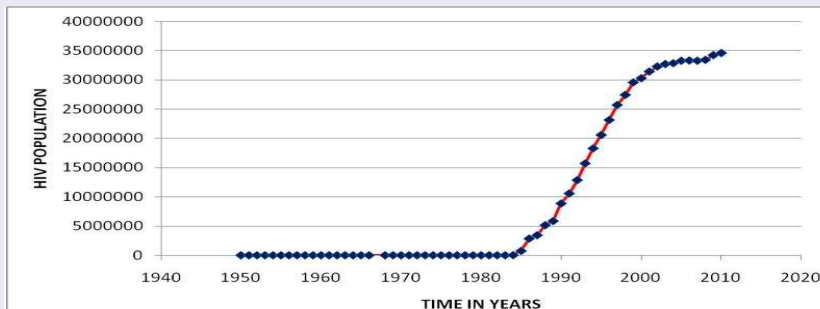
- The malaria trend in figure 1 is supported by the malaria-specific deaths over the period 1950 to 2010.
- The number of children deaths due to malaria has risen to 50% of the total children deaths in Sub-Sahara Africa.

All-causes deaths for children



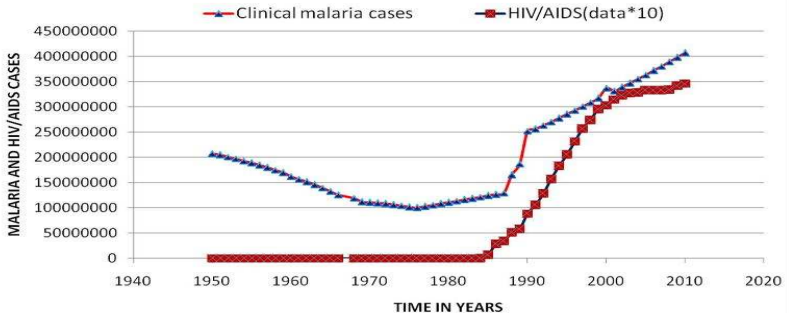
- While deaths for children under five years old have been declining, malaria-specific deaths have been rising.
- The rise in malaria-specific deaths increased rapidly before MCT programs.
- No study has been conducted to evaluate the impact of MCT programs on malaria-specific deaths for children.

HIV/AIDS facts



- Of the 33-35 million individuals infected with HIV/AIDS, 23 million live in resource-poor developing countries.
- HIV/AIDS started during the late 1980s and was acknowledged as an epidemic at the start of the 1990s.
- Treatment to control the spread of HIV/AIDS started after the year 2000.

Amplified relationship between HIV and malaria

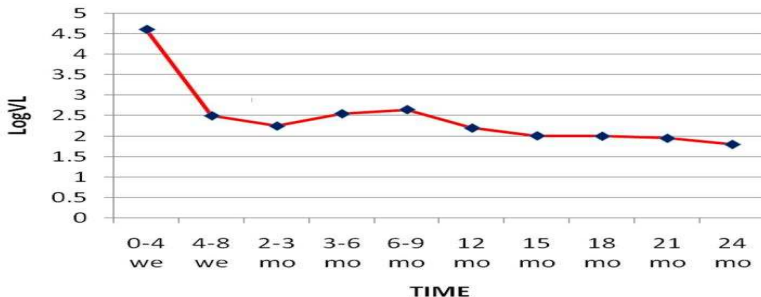


- There is a link between HIV/AIDS and TB, HIV/AIDS and Kaposi Sarcoma.
- Clinical malaria cases have increased rapidly during the period 1990 to 2010.
- There is no known (biological) link between HIV/AIDS and malaria.

Does malaria interfere with HIV treatment?

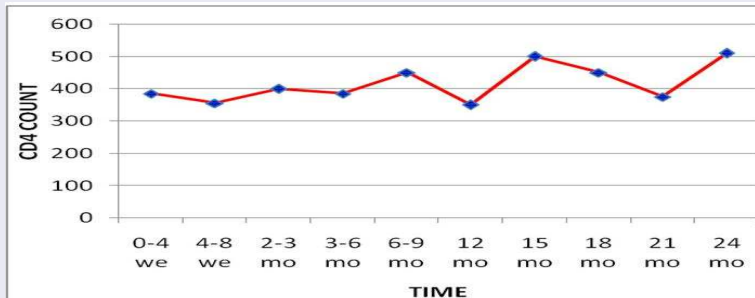
- We can rephrase the question to "Does malaria interfere with HIV treatment?"
- We give examples for two patients one of whom had a history malaria recurrence
- Both patients were on HIV/AIDS treatment. We compare their viral loads and CD4 count.
- The patients were in the treatment program for two years

Patient with no history of malaria- Viral Load



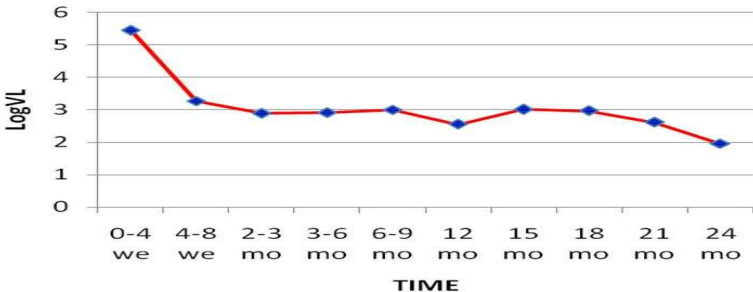
- The patient's entry viral load was $\log VL = 4.61$.
- For the first 3 months the patient's viral load was measured every month. From the third month the viral load was measured every three months.
- The patient's viral load dropped by 61% after 2 years.

Patient with no history of malaria- CD4 count



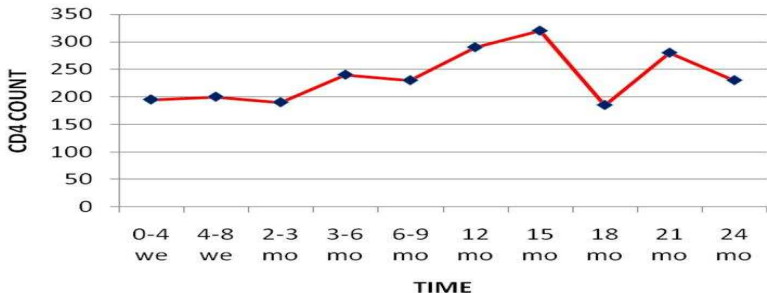
- The patient's entry CD4 count was 385 cells per μl of blood.
- The CD4 was measured at the same time as the viral load.
- The patient's CD4 count increased by over 32% to 510 cells per μl of blood after 2 years.
- This level of CD4 count is high to sustain an effective immune response against infections.

Patient with a history of malaria- Viral Load



- The patient's entry viral load was $\log VL = 5.46$.
- For the first 3 months the patient's viral load was measured every month. From the third month the viral load was measured every three months.
- The patient's viral load dropped by 64% after 2 years.

Patient with a history of malaria- CD4 count

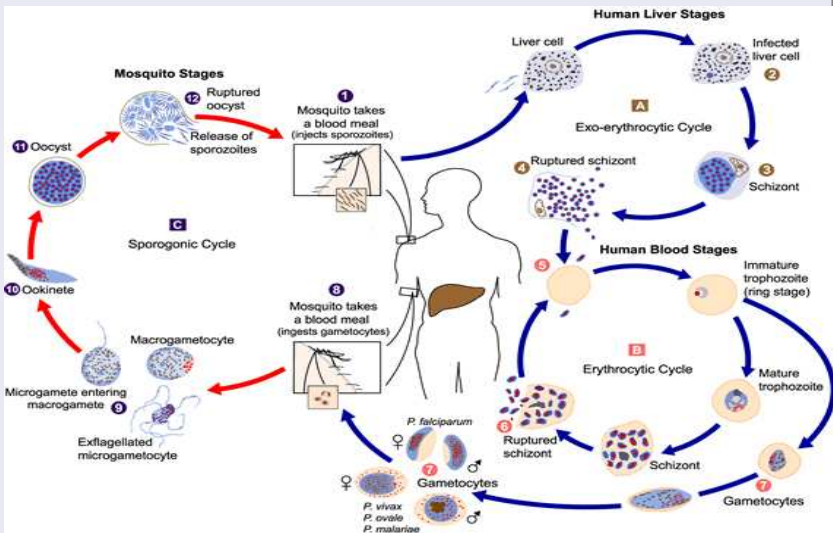


- The patient's entry CD4 count was 195 cells per μ l of blood.
- The CD4 was measured at the same time as the viral load.
- This patient had a relapse of malaria three times during the two year monitoring period.
- The patient's CD4 count increased by only 18% to 230 cells per μ l of blood after 2 years.

Comparing the two patients

- The viral load for the patient without malaria became indistinguishable after one year of treatment.
- The viral load for the patient with a history of clinical malaria was distinguishable even after 2 years of treatment.
- We must interpret these observations with care for the following reasons
- One patient had a much higher entry CD4 count than the other. The patient with lower CD4 count did not benefit from the therapy.
- Perhaps a revision of the CD4 count threshold for accessing anti-retroviral treatment is necessary.
- May be mono-therapy malaria treatment is not appropriate for individuals suffering from chronic illnesses such as HIV/AIDS, bilharzia etc.

Malaria life cycle, copied from Parasite Image Library



Malaria parasite cycle I

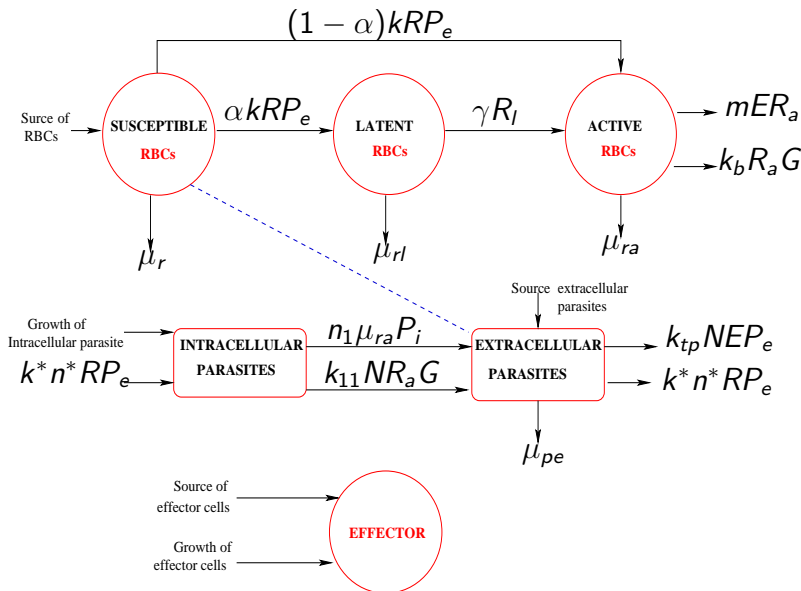
- The malaria parasite cycle involves three stages namely
 - 1 The sporogony cycle (The mosquito stage)
 - 2 The exo-erythrocytic schizogony cycle (The liver stage)
 - 3 The erythrocytic cycle (The red blood stage)
- Upon entering the human host, the sporozoites take up residence in the liver before initiating the red blood cell infection.
- In the liver, the sporozoites infect the hepatocytes.
- Within the hepatocytes, the sporozoites mature into schizonts which multiply and cause the infected hepatocyte to rupture and release merozoites.

- We consider the red blood stage
- Comparing HIV, TB bacteria, and malaria parasites, the malaria parasite replicates very fast and clinical symptoms may appear within six days.
- What replication strategy is the malaria parasite using?
- Our hypothesis is that the malaria parasite has a selective infection strategy which accelerates the replication process.
- This strategy differs from HIV and TB bacteria.

Models developed

- We have been developing models to investigate the following:
 - 1 What are the parasite production mechanism during the red blood stage?(Marijani and Lungu)
 - 2 Can treating malaria patients with a combination of drugs namely a generic drug of efficacy ε and a cytokine based drug, e.g., TNF_{α} , reduce the risk of drug resistance?(Friedman and Lungu)
 - 3 Can dual therapy for malaria target both human stages of the parasite? (Friedman and Lungu)

A diagrammatic representation of inhost malaria model



Model equations

Red blood cells (RBCs)

$$\dot{R} = S_r - \mu_r R - kRP_e.$$

$$\dot{R}_I = \alpha kRP_e - (\gamma + \mu_{rI})R_I.$$

$$\begin{aligned} \dot{R}_a = & (1 - \alpha)kRP_e + \gamma R_I - mER_a \\ & - k_b R_a \left(\frac{P_i^2}{P_i^2 + (NR_a)^2} \right) - \mu_{ra} R_a. \end{aligned}$$

Model equations

Parasites

$$\begin{aligned}\dot{P}_i = & k_{pi}P_i \left(1 - \frac{P_i^2}{P_i^2 + (NR_a)^2} \right) + k^* n^* R P_e \\ & - k_{11} NR_a \left(\frac{P_i^2}{P_i^2 + (NR_a)^2} \right) - n_1 \mu_{ra} P_i.\end{aligned}$$

$$\begin{aligned}\dot{P}_e = & S_{pe} + k_{11} NR_a \left(\frac{P_i^2}{P_i^2 + (NR_a)^2} \right) \\ & + n_1 \mu_{ra} P_i - k_{tp} N E P_e - k^* n^* R P_e - \mu_{pe} P_e.\end{aligned}$$

Effector cells

$$\dot{E} = \omega_e \left(1 - \frac{E}{r_e} \right) E.$$

Disease free equilibrium point(DFE) and reproduction number

Disease free equilibrium point

$$DFE = (R^*, R_L^*, R_a^*, P_i^*, P_e^*, E^*) = \left(\frac{S_R}{\mu_R}, 0, 0, 0, 0, r_E \right)$$

Reproduction number

$$R_0 = \sqrt{\left(\frac{n_1 \mu_{ra}}{(n_1 \mu_{ra} - k_{pi})} \right) \left(\frac{k^* n^* S_r}{(\mu_{pe} \mu_r + k^* n^* S_r + N k_{tp} r_e \mu_r)} \right)}$$

$$= \sqrt{R_0^*}, \quad \text{where}$$

$$R_0^* = R_{om} R_{op},$$

$$R_{om} = \left(\frac{n_1 \mu_{ra}}{(n_1 \mu_{ra} - k_{pi})} \right) > 1, \quad R_{op} = \left(\frac{k^* n^* S_r}{(\mu_{pe} \mu_r + k^* n^* S_r + N r_e k_{tp} \mu_r)} \right) < 1.$$

Analysis of the reproduction number

- Clinical malaria is caused by the failure of the immune system to control the red blood cell replication given by $R_{om} > 1$.
- A very important question is for what values of n_1 is $R_0 < 1$? and for what values of n_1 is $R_0 > 1$?
- The parameter n_1 denotes the average number of merozoites released from an infected red blood cell that dies naturally.

Stability of DFE

Theorem

The disease free equilibrium of the system is locally stable if $R_0^ < 1$.*

Is the disease free equilibrium point globally stable?

Perturbation technique

In the neighborhood of the DFE

As $t \implies \infty$, the perturbations decay, that is $\varepsilon(t) \implies 0$.

Far from the DFE

As $t \implies \infty$, the perturbations grow, that is, $\frac{1}{\varepsilon(t)} \implies \infty$.

Theorem

The disease free equilibrium is not globally stable.

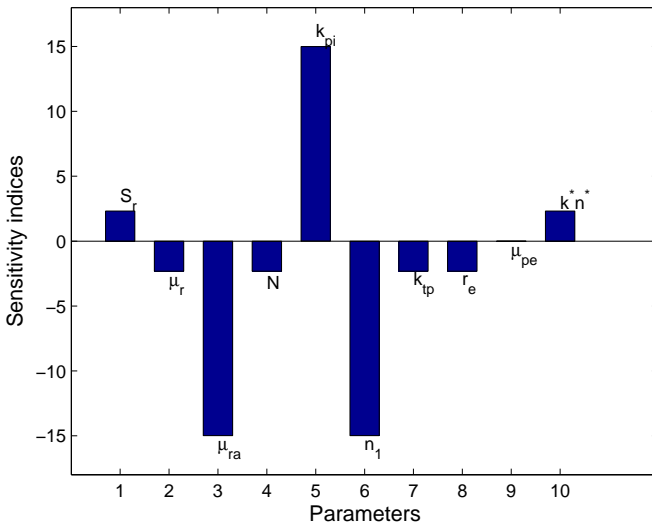


Figure: A sensitivity of various parameters on the R_0

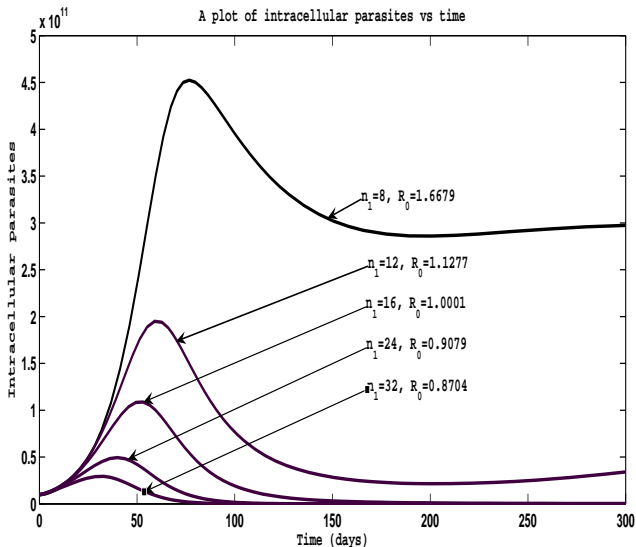


Figure: A diagram showing the population of intracellular parasites

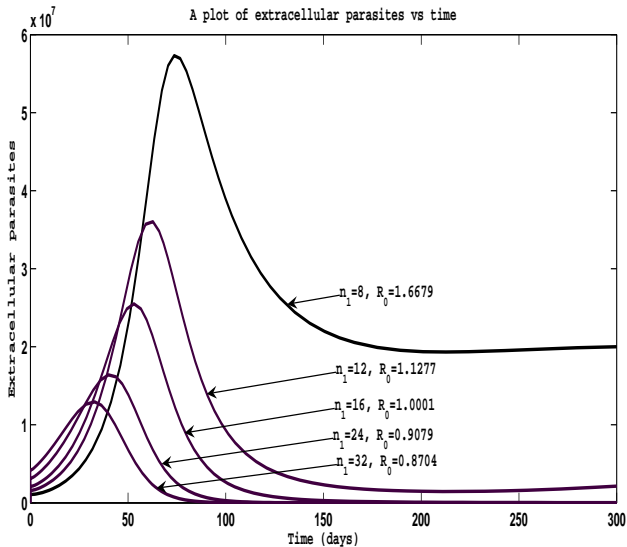


Figure: A diagram showing the population of extracellular parasites

Interpretation of the results I

- The parasite will establish itself for $n_1 < 16$ but will be cleared by the immune system for $n_1 \geq 16$.
- The life expectance of a healthy red blood cell is 120 days. The parasite has a strategy of infecting older red blood cells to evade the immune system.
- When treatment is administered, some of the infected red blood cells die before the chemodynamic effects of the drug is completed.
- This may be one of the reasons that lead to the development of resistant strains.

Interpretation of the results I

- The equation for extracellular parasites shows that there are two source terms from intracellular parasites namely

- 1 Bursting of infected red blood cells

$$k_{11}NR_a \left(\frac{P_i^2}{P_i^2 (NR_a)^2} \right).$$

- 2 Natural death of infected red blood cells

$$n_1\mu_{ra}P_i$$

- Of the two replication mechanisms, the reproduction from naturally dying infected red blood cells is far more significant than that from bursting of infected red blood cells.

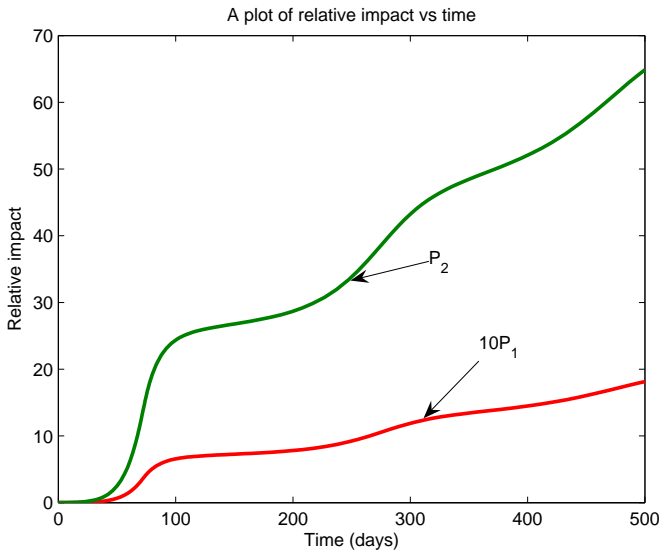


Figure: A relative impact of the two merozoites

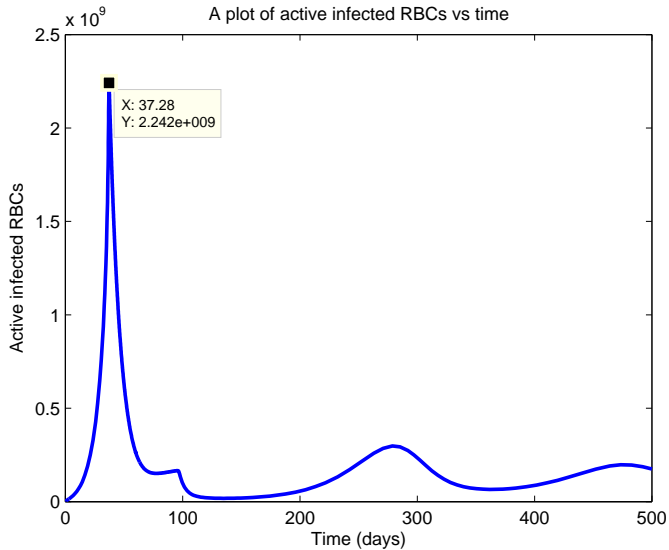


Figure: Diagrams showing the evolution of active RBCs with time

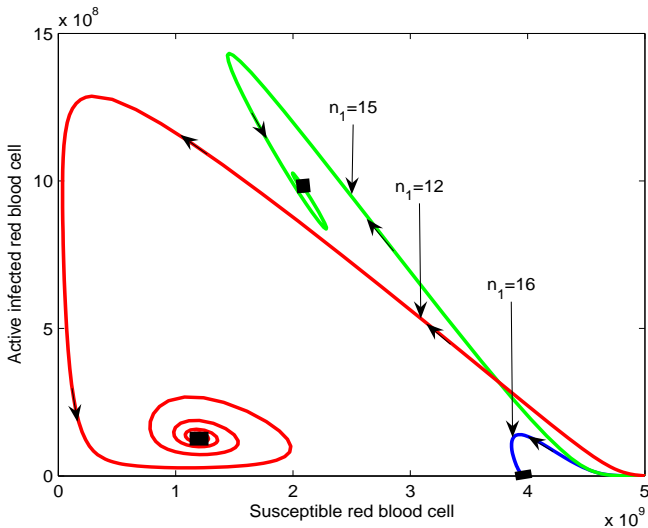


Figure: Contour plots represents for $n_1 = 12$, $n_1 = 15$ and $n_1 = 16$

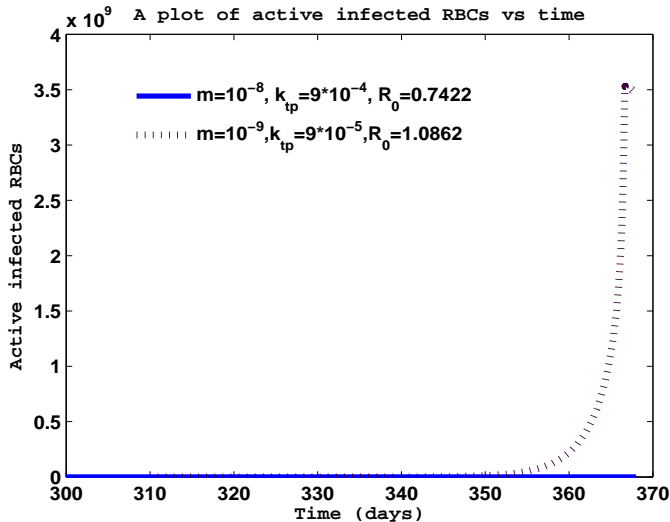


Figure: A diagrams of RBCs with varying values of m and k_{tp}

Conclusion

The sporogony cycle **is not the key process in the development of clinical malaria** even though it is the process that initiates the malaria life cycle.

Analysis of the model reproduction number suggests that **better treatment regimens would be more effective control measure than eradication programmes of the mosquito.**

We recommend that individuals with feverish symptoms who report at a healthy center should be tested by for chronic infection and if found to be suffering from any chronic infection, they should be treated for those diseases in order to make the current and future malaria treatment effective.

THANK YOU

- UNIVERSITY OF BOTSWANA,
- UNIVERSITY OF BUEA,
- SACEMA,
- TWOWS,
- AND ALL OF YOU

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