Mathematical model for the in-host malaria dynamics subject to malaria vaccines

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Introduction

- P. *falciparum* malaria
- Parasite resistance to current anti-malarial drugs poses a serious threat to malaria control [3].
- To defeat the disease, many more tools with the potential to save lives today and in the future are needed [2].
- An efficacious, safe and affordable malaria vaccine would help to bridge the control gap left by other intervention measures .

Introduction

- A malaria vaccination strategy is performed to:
  - induce protective immune responses prior to malaria infection
  - provide protection in case of malaria attack [1].
- Current malaria vaccines have shown minimal efficacy: RTS,S/AS01 (36.3% VE)
- A more efficacious malaria vaccine is crucial if the 2030 goal of malaria eradication by WHO is to be accomplished [4].

Goal: To study the cell-parasite populations through a mathematical model and to numerically investigate the possible impacts of malaria vaccines on the severity of *P. falciparum* malaria infection.

Introduction

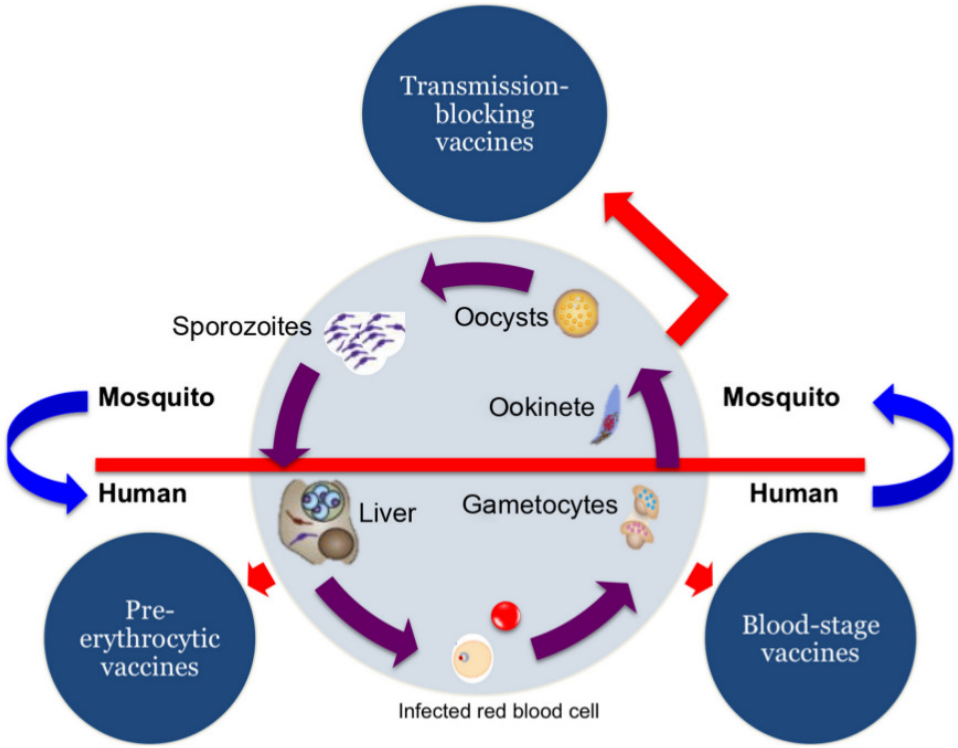


Figure: Target sites in the malaria life cycle that could be interrupted by: PEV, BSV and TBV. Source: [1]

Model

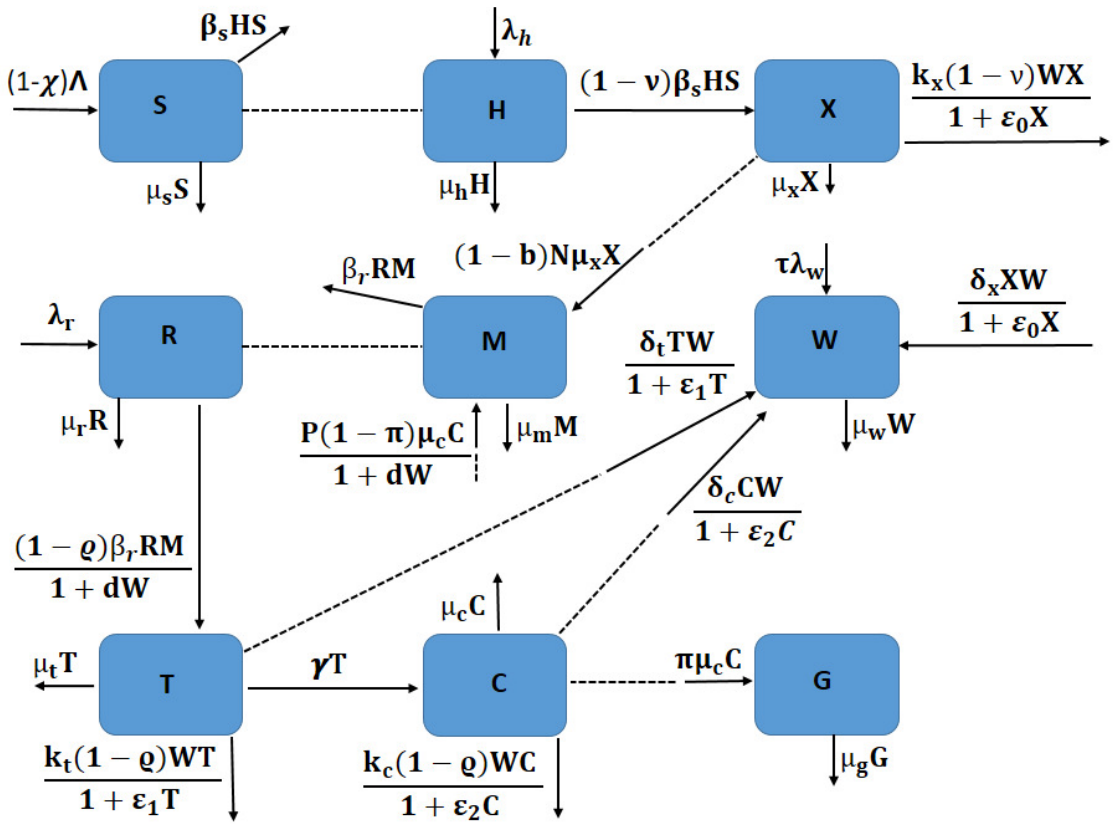


Figure: Schematic diagram for in-host malaria dynamics with vaccine therapy

Model

$$
\left.
\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= (1-\chi)\Lambda - \mu_s S - \beta_s HS, \\
\frac{\mathrm{d}H}{\mathrm{d}t} &= \lambda_h - \mu_h H - \beta_s(1-\nu)HS, \\
\frac{\mathrm{d}X}{\mathrm{d}t} &= \beta_s(1-\nu)SH - \mu_x X - \frac{k_x(1-\nu)WX}{1+\varepsilon_0 X}, \\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \lambda_r - \frac{(1-\varrho)\beta_r RM}{1+dW} - \mu_r R, \\
\frac{\mathrm{d}T}{\mathrm{d}t} &= \frac{(1-\varrho)\beta_r RM}{1+dW} - \mu_t T - \gamma T - \frac{k_t(1-\varrho)WT}{1+\varepsilon_1 T}, \\
\frac{\mathrm{d}C}{\mathrm{d}t} &= \gamma T - \mu_c C - \frac{k_c(1-\varrho)WC}{1+\varepsilon_2 C},
\end{aligned}
\right\}
$$

Model

$$\left.\begin{aligned}
\frac{\mathrm{d}M}{\mathrm{d}t} &= (1-b)N\mu_x X + \frac{P(1-\pi)(1-a)\mu_c C}{1+dW} - \mu_m M - \beta_r RM, \\
\frac{\mathrm{d}G}{\mathrm{d}t} &= \pi\mu_c C - \mu_g G, \\
\frac{\mathrm{d}W}{\mathrm{d}t} &= \tau\lambda_w + W\left(\frac{\delta_x X}{1+\varepsilon_0 X} + \frac{\delta_t T}{1+\varepsilon_1 T} + \frac{\delta_c C}{1+\varepsilon_2 C}\right) - \mu_w W.
\end{aligned}\right\}$$

Model Analysis

Well-posedness of the model

$$\Phi = \Bigg\{ (H, X, R, T, C, S, M, G, W) \in \mathbb{R}_+^9 : N_r(t) \leq \max\left\{ N_r(0), \frac{\lambda_r}{\mu_1} \right\},$$
$$N_h(t) \leq \max\left\{ N_h(0), \frac{\lambda_h}{\mu_2} \right\}, N_p(t) \leq \max\left\{ N_p(0), \frac{(1-\chi)\Lambda}{\mu_3} \right\},$$
$$W(t) \leq \max\left\{ W(0), \frac{\tau\lambda_w}{\mu_w} \right\} \Bigg\},$$

and $N_r(t) = R(t) + T(t) + C(t)$, $N_h(t) = H(t) + X(t)$.

Vaccine impacts and R_v

$$\mathrm{R}_v = \frac{P(1-\pi)(1-a)(1-\varrho)\gamma\beta_r\lambda_r\mu_c}{\mu_r\left(\frac{d\tau\lambda_w+\mu_w}{\mu_w}\right)^2\left(\mu_m+\frac{\beta_r\lambda_r}{\mu_r}\right)\left(\frac{(1-\varrho)\tau k_c\lambda_w}{\mu_w}+\mu_c\right)\mathcal{A}}.$$

where, $\mathcal{A} = \left(\frac{(1-\varrho)\tau k_t\lambda_w}{\mu_w}+\gamma+\mu_t\right)$

$$\mathrm{R}_m = \frac{P(1-\pi)\gamma\beta_r\lambda_r\mu_c}{\mu_r\left(\frac{d\lambda_w+\mu_w}{\mu_w}\right)^2\left(\frac{k_c\lambda_w}{\mu_w}+\mu_c\right)\left(\mu_m+\frac{\beta_r\lambda_r}{\mu_r}\right)\left(\gamma+\frac{k_t\lambda_w}{\mu_w}+\mu_t\right)}.$$

On comparing

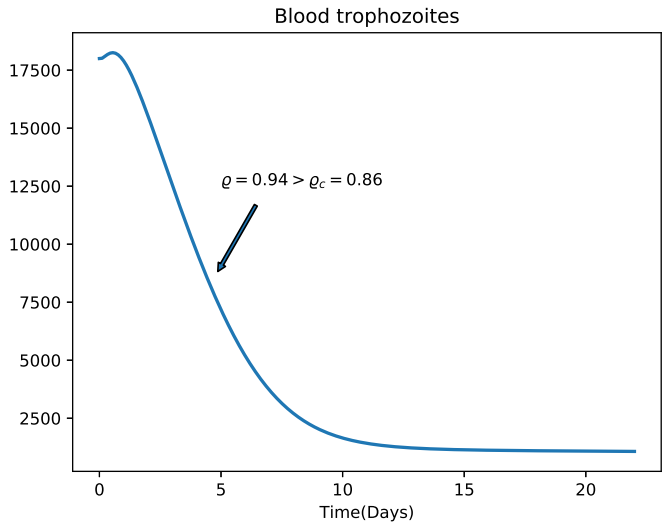
$$R_v = R_m \times \Theta^{**}, \quad (0 < \Theta^{**} < 1)$$

Sensitivity analysis

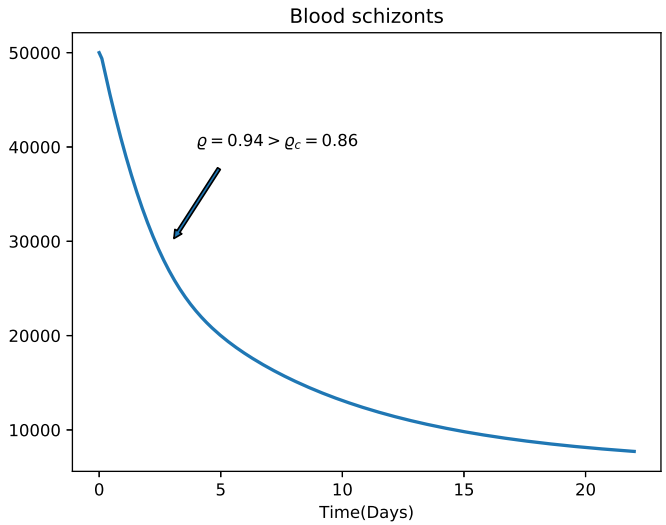
Table: The sensitivity indices of R_v with respect model parameters

Parameter	Sensitivity index	Parameter	Sensitivity index
P	+1	π	-0.25
a	-0.25	ϱ	-0.770486
γ	+0.293702	β_r	+0.0000663956
λ_r	+0.0000664	μ_c	+0.0000247494
μ_r	-0.000066396	d	-0.0222497
τ	-0.080544	λ_w	-0.080544
μ_w	+0.080	μ_m	-0.00006639
k_c	-0.0000247494	k_t	-0.0582696
μ_t	-0.235433		

Critical efficacy of Blood Stage Vaccine

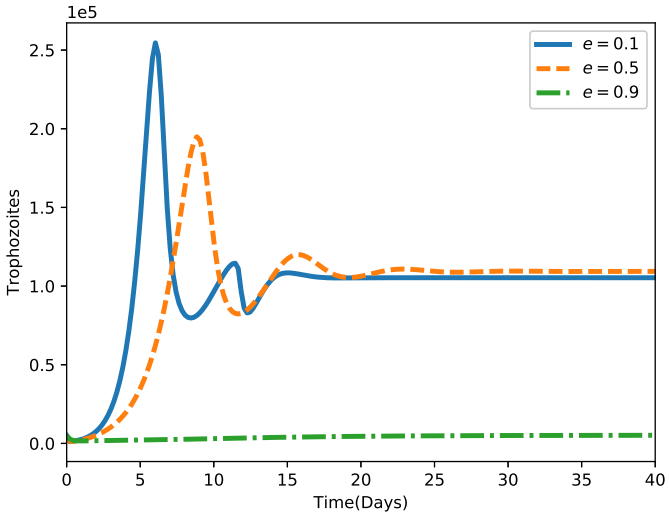


(a)

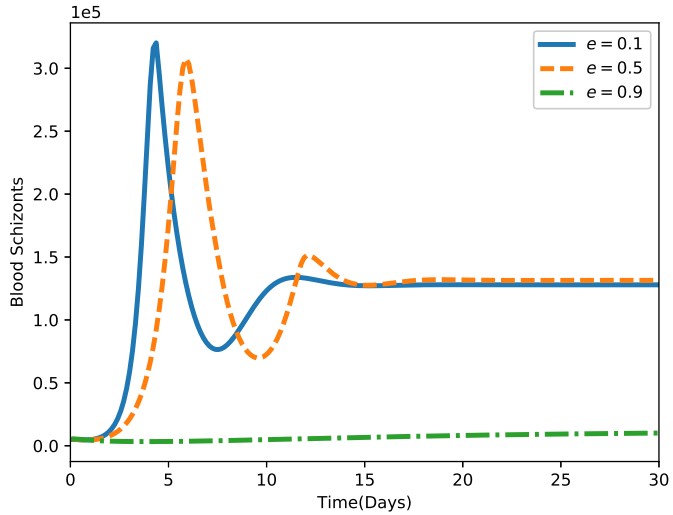


(b)

Figure: Graphs showing the density of (a) blood trophozoites $T(t)$ and (b) blood schizonts $C(t)$ when the blood stage vaccine efficacy, $\varrho = 0.94 > \varrho_c = 0.86$ and $R_v = 0.58 < 1$.



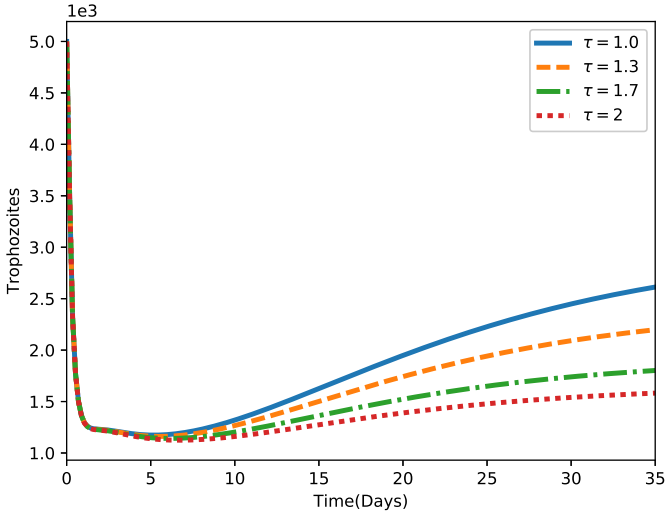
(a)



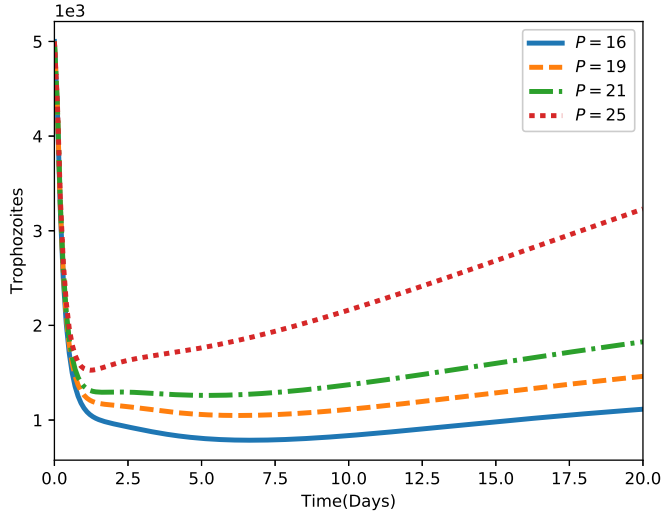
(b)

Figure: Simulations showing the effect varying the parameter ϱ on the density of infected red blood cells.

Note: Similar results are observed in the dynamics of gametocytes G.



(a)

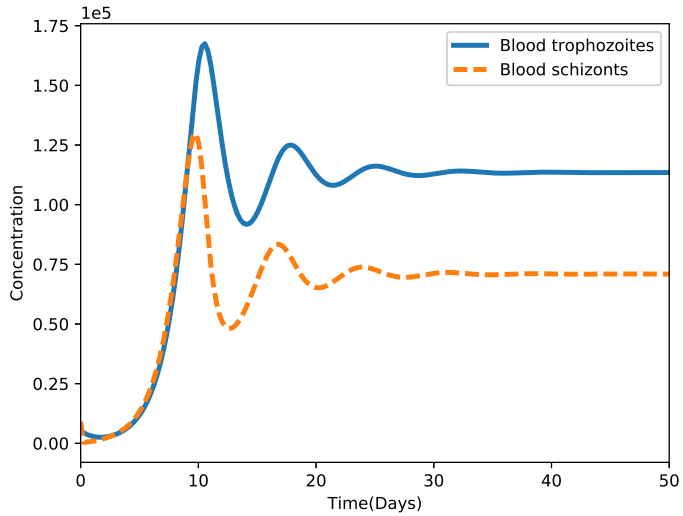


(b)

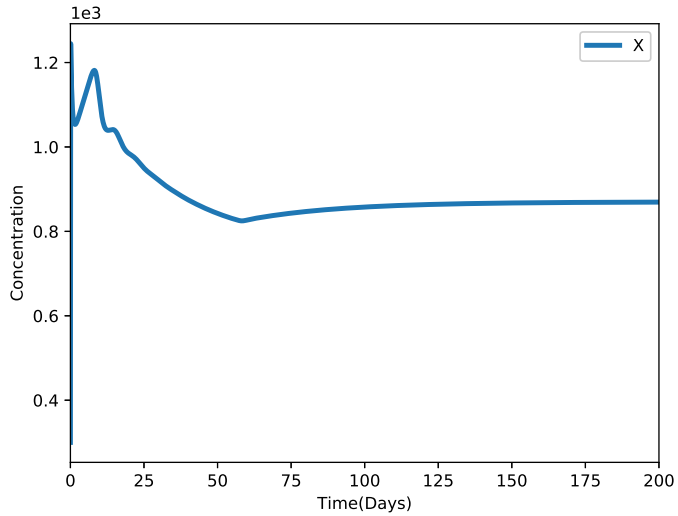
Figure: Simulation showing the the density of (a) blood trophozoites $T(t)$ and (b) blood schizonts $C(t)$ for varying values of blood stage vaccine-induced enhanced production parameter τ.

Note: Similar results are observed in the dynamics of blood schizonts C.

Threshold Analysis and Vaccine Impacts

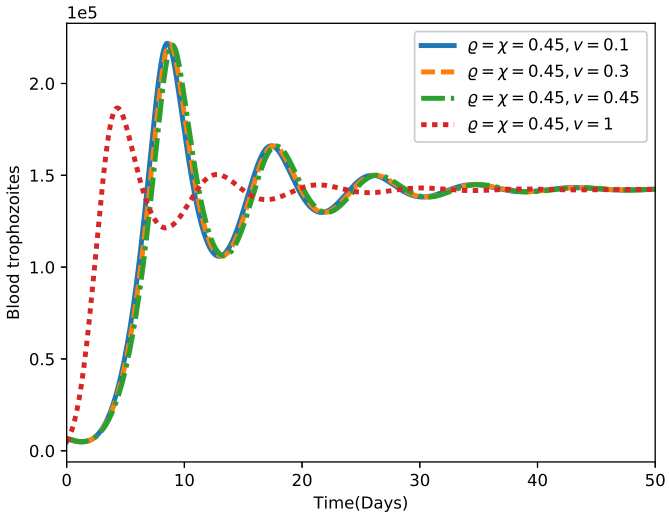


(a)

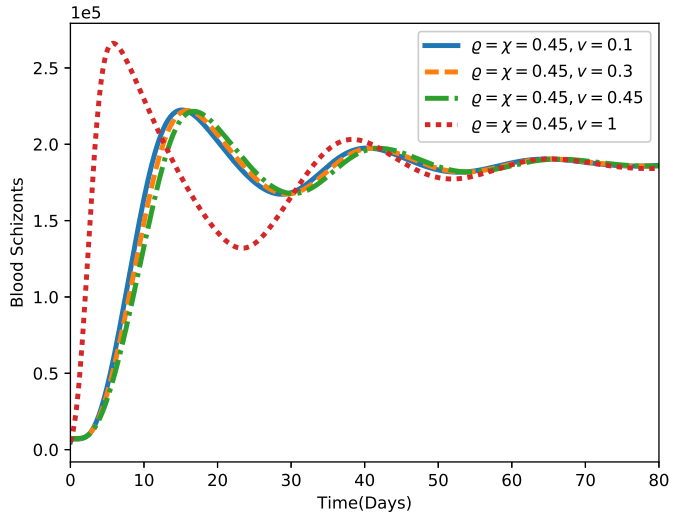


(b)

Figure: Time profile of the total concentration of infected red blood cells (a) and the concentration of infected liver hepatocytes (b) in the absence of malaria vaccines ($\varrho = \chi = \nu = 0$).

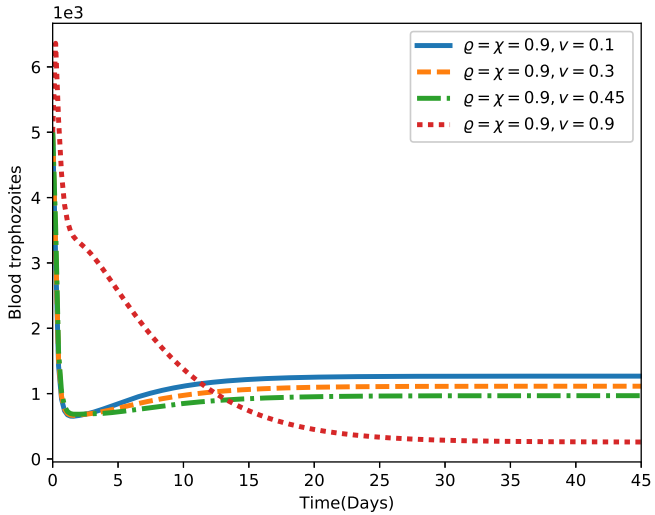


(a)

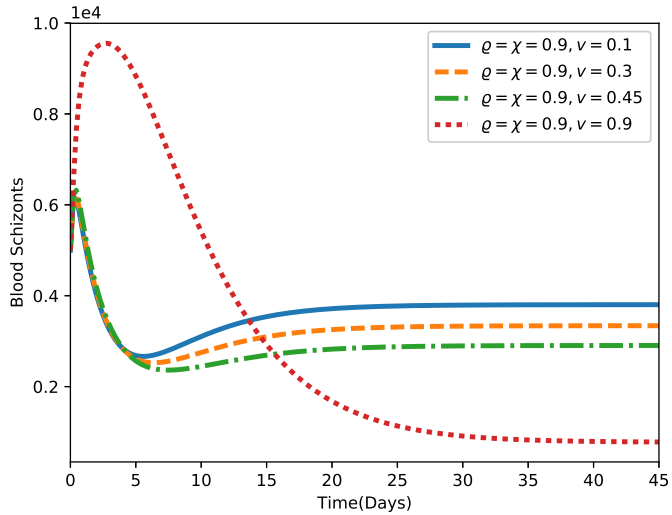


(b)

Figure: Time profile of the total concentration of (a) blood trophozoites and blood schizonts (b) for $\varrho = \chi = 0.45$ with varying efficacy of pre-erythrocytic vaccine ν.



(a)



(b)

Figure: Time profile of the total concentration of (a) blood trophozoites and blood schizonts (b) for $\varrho = \chi = 0.9$ with varying efficacy of pre-erythrocytic vaccine ν.

Discussion

- The activated $CD8^{+}$T-cells and malaria vaccines have a considerable effects on malaria control. Vaccination reduces the basic reproduction number by a constant factor.
- A highly efficacious BSV (at least 90%) is shown to be very effective in controlling in-host *P. falciparum* malaria.
- PEV minimize the total number of merozoites released per bursting infected liver hepatocytes, reduces the concentrations of infected erythrocytes.
- Efficacious BSV grately reduces the burst size of the blood schizonts, so that less merozoites are released from the infected eythrocytes.

Discussion

- The higher the vaccine potential to activate $CD8^{+}$T-cells (immune cells), the lower the concentration of infected erythrocytes.
- Different vaccine combinations yield different results.
- In the absence of vaccine therapy, the concentration of infected erythrocytes are shown to increase and stabilize at the PPE.
- An imperfect pre-erythrocytic vaccine with an efficacy of at least 90% is also shown to guarantee the attainment of a PFE.

Conclusion

- The analyzed model provide useful insights in individual and combined vaccine impacts in reducing the severity of clinical malaria.
- The notion of critical vaccine efficacy is key in the development of malaria vaccines with the potential to eradicate *P. falciparum* malaria in infected individuals.
- In order to achieve a substantial reduction in malaria mortality and morbidity, the efficacy of the malaria vaccine should be higher than the corresponding critical vaccine efficacy.
- The combined administration of malaria vaccines and anti-malarial drugs is likely to provide the much needed therapeutic control against *P. falciparum* malaria.

References

[1] Arama, C. and Troye-Blomberg, M. (2014). The path of malaria vaccine development: challenges and perspectives. *Journal of internal medicine*, 275(5):456–466.

[2] Birkett, A. J. (2016). Status of vaccine research and development of vaccines for malaria. *Vaccine*, 34(26):2915–2920.

[3] Dondorp, A. M., Yeung, S., White, L., Nguon, C., Day, N. P., Socheat, D., and Von Seidlein, L. (2010). Artemisinin resistance: current status and scenarios for containment. *Nature reviews microbiology*, 8(4):272.

[4] malERA Consultative Group on Vaccines et al. (2011). A research agenda for malaria eradication: vaccines. *PLoS medicine*, 8(1):e1000398.

Thank You