Analysis of Stability in a Delay Differential Equation Model for Malaria Infection With Treatment

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Abstract: In this paper, we introduce a biological model employing delay differential equations to explore the evolution of malaria within a host undergoing drug treatment. Our analysis focuses on the stability of equilibrium points, leveraging the critical case theorem, an extension of the Lyapunov-Malkin theorem, which is particularly useful for scenarios involving zero roots in the characteristic equation. By determining equilibrium points and assessing their stability through the eigenvalues of the linearized system, we ensure the applicability of the theorem via translations to zero. The results highlight the significant influence of treatment-induced delays on the stability of malaria dynamics, offering valuable insights for optimizing control strategies and improving disease management.

Key-Words: Malaria Infection, Erythropoietin (EPO), Merozoites, Gametocytes, Loss during cell cycle, Drug concentration, Equilibrium points, Critical Case, Stability Analysis.

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1 Introduction

Malaria, a potentially deadly disease caused by the *Plasmodium* parasite, is transmitted through the bites of Anopheles mosquitoes, which primarily feed on humans. Infected individuals often experience severe symptoms such as high fever, chills, cough, fatigue, and flu-like illness, typically manifesting 10-15 days post-infection. The mild initial symptoms make malaria difficult to diagnose, and without prompt treatment, the disease can escalate rapidly, potentially becoming fatal within 24 hours, [1].

For those residing in or traveling to high-risk regions -such as Africa, Central and South America, the Caribbean, Eastern Europe, South Asia, and Southeast Asia- it is crucial to seek medical attention at the onset of symptoms, particularly fever. Severe cases demand immediate emergency care.

Malaria remains a significant global health challenge, with hundreds of thousands of deaths reported annually. In 2020, the World Health Organization estimated 241 million clinical cases, resulting in approximately 627,000 deaths, predominantly among African children. This disease exacerbates the cycle of poverty, significantly impacting already struggling economies, [2].

The lack of an effective malaria vaccine is attributed to the parasite's ability to frequently alter its surface proteins, complicating vaccine development. Currently, antimalarial medications are the primary means of treatment and prevention, [3].

Incorporating mathematical models to study malaria's progression is vital for approximating the blood-stage infection dynamics and the associated erythropoietic processes. Delay differential equations (DDEs) have emerged as powerful tools for modeling biological systems where delays are inherent. These delays could be due to the incubation period of the pathogen, the time taken for the immune response to activate, or the delayed effect of treatment. The stability of equilibrium points in such systems is crucial for understanding the long-term behavior of the disease and the effectiveness of treatment strategies.

A stability theorem addressing the equilibria of delay differential equations in critical scenarios is presented, along with a model for cell evolution in malaria treatment that focuses on the immune system's role in [4]. Moreover, a delay differential equation model for cell evolution in Chikungunya is introduced, emphasizing the significance of delays in the disease's dynamics in [5].

A broader range of models relevant to the biological and biomedical sciences can be explored in works such as [6], [7], [8], [9], [10], [11], [12], [13]. These sources provide valuable insights for understanding the formulation of delay differential equation models and conducting detailed stability analysis. By studying these references, one can gain a deeper comprehension of the mathematical frameworks and methods used to evaluate the stability of various biological systems.

Furthermore, recent advancements in fractional calculus have significantly enhanced our understanding of complex biological systems. Fractional differential equations, especially those involving fractional calculus and hybrid fractional models, offer a comprehensive framework for analyzing the stability and dynamics of malaria infection models. These equations have proven effective in capturing the complexities of biological processes, providing critical insights into stability and solution behaviors. Future research could explore fractional delay models to extend these findings, while theoretical analysis of solutions could follow approaches similar to those outlined in, [14], [15], [16], [17], [18], [19].

The mathematical model of malaria is essential as it captures both the blood stage of the infection and the process of erythropoiesis, which is crucial for addressing the anemia linked with the disease. Initially, we enhanced the basic DDE model by introducing an equation to represent EPO concentration and another to account for cell cycle loss. Our goal is to deepen our understanding of malaria infection dynamics during treatment by examining the stability of equilibrium points through delay differential equations. We apply a critical case theorem after translating the problem to a zero state. This methodology will help us in future to identify conditions under which treatment strategies can effectively manage the infection and offer insights into the long-term progression of malaria with ongoing treatment.

2 Model under Study

In this section, we adopt the notation $y_\tau = y(t-\tau)$ to represent delayed variables. We utilize delay-differential equations to model the within-host dynamics of malaria infection, focusing on the following components: uninfected red blood cells (y_1), erythropoietin concentration (y_2), loss during the cell cycle (y_3), infected red blood cells (y_4), extracellular malaria parasites (merozoites, y_5), and gametocytes (y_6).

The First Delay Differential Equation:

$$\dot{y}_1 = m\left(\frac{1-y_1}{k}\right) - \mu y_1 - \rho y_1 y_5 \tag{1}$$

This equation represents the temporal change in the density of uninfected red blood cells (RBCs). In this model, m denotes the maximum rate at which depleted RBCs are replenished, while k represents the homeostatic equilibrium density, calculated as $\frac{tR^*}{t-\mu R^*}$, where R^* is the equilibrium RBC density. The final term captures the mass action of the infection process, where ρ indicates the rate at which merozoites invade RBCs upon contact, [20].

The Second Delay Differential Equation:

$$\dot{y}_2 = -dy_2 + \frac{a}{1+y_1^r} \tag{2}$$

This equation represents the concentration of erythropoietin (EPO), where d is the disappearance rate of EPO.

The Third Delay Differential Equation:

$$\dot{y}_3 = y_3\left(\frac{-k}{1+y_2^\alpha} + \frac{k}{1+y_{2\tau_1}^\alpha}\right) \tag{3}$$

This equation models the loss during the cell cycle, where $y_3 = e^{-\int h(s)\,ds}$ with $h(t) = -\frac{k}{1+y_2^\alpha}$ representing the stem cell loss. The parameter τ_1 denotes the time required for short-term hematopoietic stem cells to complete a cycle of self-renewal, differentiation, or asymmetric division, [21, 22].

The Fourth Delay Differential Equation:

$$\dot{y}_4 = \rho y_1 y_5 - \mu y_4 - \rho y_{1\tau_2} y_{5\tau_2} S \tag{4}$$

This equation outlines the dynamics of infected red blood cells (RBCs). The parameter ρ signifies the rate at which merozoites invade RBCs, while μ represents the background rate at which infected RBCs die. The delay τ_2 reflects the time it takes for infected RBCs to burst and release merozoites (such as 1 day for the rodent malaria parasite). Furthermore, S represents the proportion of infected RBCs that survive their development, calculated as $e^{-\mu\alpha}$ when $t > \alpha$ and in the absence of drugs, [20].

The Fifth Delay Differential Equation:

$$\dot{y}_5 = (1-c)B\rho y_{1\tau_2} y_{5\tau_2} S - \rho y_1 y_5 - M y_5 \tag{5}$$

This equation represents the dynamics of merozoites. In this model, c denotes the fraction of parasites that mature into gametocytes, while B represents the burst size of merozoites released from each infected RBC, defined as $B = B_a - B_t$ where B_a is the burst size without treatment and B_t represents the reduction in burst size due to treatment with Artemisinin.

The term $\rho y_1 y_5$ describes the infection process, and M indicates the death rate of merozoites, [20].

The Sixth Delay Differential Equation:

$$\dot{y}_6 = c\rho y_{1\tau_2} y_{5\tau_2} S - G y_6 \tag{6}$$

This equation represents the dynamics of gametocytes, where G is the rate at which gametocytes die, [20].

The model that incorporates the treatment response is given by:

$$\dot{y} = f_i(y; y_j); \quad (i = \overline{1;6}; j = 1;2), \tag{7}$$

$$\dot{y}_1 = m\left(\frac{1-y_1}{k}\right) - \mu y_1 - \rho y_1 y_5,$$

$$\dot{y}_2 = -d y_2 + \frac{a}{1+y_1^r},$$

$$\dot{y}_3 = y_3\left(\frac{-k}{1+y_2^\alpha} + \frac{k}{1+y_{2\tau_1}^\alpha}\right),$$

$$\dot{y}_4 = \rho y_1 y_5 - \mu y_4 - \rho y_{1\tau_2} y_{5\tau_2} S,$$

$$\dot{y}_5 = (1-c)B\rho y_{1\tau_2} y_{5\tau_2} S - \rho y_1 y_5 - M y_5,$$

$$\dot{y}_6 = c\rho y_{1\tau_2} y_{5\tau_2} S - G y_6,$$

Positivity of Solutions: The state variables y represent cell populations, and negative cell densities are biologically meaningless. Therefore, maintaining positivity in the solutions of the system is essential for preserving the integrity of the model described by equation (7).

Proposition 2.1. *Let $\tau = \{\max\ \tau_j\}$ for $j = 1, 2$ and Γ denote the initial conditions defined on the closed interval $-\tau$ and 0. If the initial conditions of the system (7) are positive, then the solutions y of the system (7) remain positive for all $\tau > 0$.*

2.1 Equilibrium Points

To determine the equilibrium points of the system, we solve the equations where the derivatives $\dot{y}$ are set to zero, that is, $f_i(y; y_j) = 0$. This yields the following conditions:

$$y_5\left[(1-c)B\rho y_1 S - \rho y_1 - M\right] = 0, \tag{8}$$

where, if $\hat{y}_5 = 0$, it follows that $\hat{y}_4 = \hat{y}_6 = 0$. Next, we have:

$$\hat{y}_3 = e^{-\left(\frac{k}{1+\hat{y}_2^\alpha}\right)\tau_1} < 1, \tag{9}$$

$$\hat{y}_2 = \frac{a}{d(1+\hat{y}_1^r)}, \tag{10}$$

$$\hat{y}_1 = \frac{t}{t+\mu k}, \tag{11}$$

When $\hat{y}_5 = 0$, the equilibrium point $E_1 = (\hat{y}_1, \hat{y}_2, \hat{y}_3, 0, 0, 0)$ represents a healthy state equilibrium. For $\hat{y}_5 \neq 0$, the equilibrium point $E_2 = (\hat{y}_1, \hat{y}_2, \hat{y}_3, \hat{y}_4, \hat{y}_5, \hat{y}_6)$ denotes the disease-free equilibrium.

2.2 Stability Analysis of E_1

Let $A = (a_{i;j})$ denote the matrix representing the linear approximation around E_1 for undelayed terms, $B = (b_{i;j})$ for terms with delay τ_1, and $C = (c_{i;j})$ for terms with delay τ_2. These matrices are defined as follows:

$$A = (a_{ij})_{6\times 6}\,, \tag{12}$$

such that $a_{ij} = \frac{\partial f}{\partial y_1}$.The elements of matrix A are:

$$a_{11} = -\frac{m}{k} - \mu - \rho\hat{y}_5,$$

$$a_{12} = a_{13} = a_{14} = 0,$$

$$a_{15} = -\rho\hat{y}_1,$$

$$a_{16} = 0,$$

$$a_{21} = -\frac{r\hat{y}_1^{r-1}a}{(1+y_1^r)^2},$$

$$a_{22} = -e_1,$$

$$a_{23} = a_{24} = a_{25} = a_{26} = 0,$$

$$a_{31} = 0,$$

$$a_{32} = \frac{k\alpha\hat{y}_3\hat{y}_2^{\alpha-1}}{(1+y_2^\alpha)^2},$$

$$a_{33} = a_{34} = a_{35} = a_{36} = 0,$$

$$a_{41} = \rho\hat{y}_5,$$

$$a_{42} = a_{43} = 0,$$

$$a_{44} = -\mu,$$

$$a_{45} = \rho\hat{y}_1,$$

$$a_{46} = 0,$$

$$a_{51} = -\rho\hat{y}_5,$$

$$a_{52} = a_{53} = a_{54} = 0,$$

$$a_{55} = -\rho\hat{y}_1 - M,$$

$$a_{56} = 0,$$

$$a_{61} = a_{62} = a_{63} = a_{64} = a_{65} = 0,$$

$$a_{66} = -G.$$

Similarly, the matrix B is given by:

$$B = \frac{\partial f}{\partial y_{\tau_1}} \tag{13}$$

The non-zero elements of matrix B are:

$$b_{32} = -\frac{k\alpha \hat{y}_3 \hat{y}_2^{\alpha-1}}{(1+y_2^{\alpha})^2},$$

with all other elements being zero.

The matrix C is defined as:

$$C = \frac{\partial f}{\partial y_{\tau_2}} \tag{14}$$

The non-zero elements of matrix C are:

$$\begin{aligned} c_{41} &= -\rho S \hat{y}_5, \\ c_{51} &= (1-c) B \rho S \hat{y}_5, \\ c_{61} &= c \rho S \hat{y}_5, \\ c_{45} &= -\rho S \hat{y}_1, \\ c_{55} &= (1-c) B \rho S \hat{y}_1, \\ c_{65} &= c \rho S \hat{y}_1. \end{aligned}$$

with all other elements being zero. Thus, the general characteristic equation is:

$$\det(\lambda I_n - A - Be^{-\lambda\tau_1} - Ce^{-\lambda\tau_2}) = 0 \tag{15}$$

For the equilibrium point E_1, substituting $\hat{y}_4 = \hat{y}_5 = \hat{y}_6 = 0$ yields the characteristic equation:

$$\begin{aligned} &(\lambda - a_{11})(\lambda - a_{22})(\lambda - a_{44})(\lambda - a_{66})(\lambda) \\ &\times(\lambda - a_{55} - e^{-\lambda\tau_2} c_{55}) = 0 \end{aligned} \tag{16}$$

The real roots of the characteristic equation (16) are:

$$\begin{aligned} \lambda_1 &= a_{11} = -\frac{m}{k} - \mu < 0, \\ \lambda_2 &= a_{22} = -e_1 < 0, \\ \lambda_3 &= a_{44} = -\mu < 0, \\ \lambda_4 &= a_{66} = -G < 0, \\ \lambda_5 &= 0. \end{aligned}$$

The zero eigenvalue ($\lambda = 0$) indicates a critical case for the stability of the nonlinear system. This scenario is further examined in, [4].

We perform a translation to zero by defining $z_i = y_i - \hat{y}_i$ for $i = 1, 2, 3$. The new system can be expressed as:

$$\dot{z} = \tilde{f}_i(z, z_{\tau_j}), \quad i = \overline{1,6},\ j = \overline{1,2} \tag{17}$$

where

$$\begin{aligned} \dot{z}_3 &= \tilde{f}_3(z_2, z_3, z_{2\tau_1}) \\ &= (z_3 + \hat{y}_3)\left(-\frac{k}{1+(z_2+\hat{y}_2)^{\alpha}} + \frac{k}{1+(z_{2\tau_1}+\hat{y}_2)^{\alpha}}\right) \end{aligned} \tag{18}$$

The matrices of partial derivatives for the new system are:

$$A = \frac{\partial \tilde{f}}{\partial z} = (a_{ij}), \tag{19}$$

$$B = \frac{\partial \tilde{f}}{\partial z_{\tau_1}} = (b_{ij}), \tag{20}$$

$$C = \frac{\partial \tilde{f}}{\partial z_{\tau_2}} = (c_{ij}). \tag{21}$$

The characteristic equation for the zero solution of the modified system corresponds to that of E_1. Since the linear component is not zero, we cannot directly apply the critical case theorem, [4]. Consequently, we transform the system into a canonical form suitable for applying the theorem.

Let $\xi = \alpha_1 z_1 + \alpha_2 z_2 + \cdots + \alpha_6 z_6$ where $\dot{z} = Az$. We have:

$$\dot{\xi} = \alpha_1 \dot{z}_1 + \alpha_2 \dot{z}_2 + \cdots + \alpha_6 \dot{z}_6 \tag{22}$$

This simplifies to:

$$\begin{aligned} \dot{\xi} &= \alpha_1 a_{11} z_1 + (\alpha_2 a_{22} + \alpha_3 a_{32}) z_2 && (23) \\ &+ \alpha_4 a_{44} z_4 + \alpha_5 a_{55} z_5 + \alpha_6 a_{66} z_6 && (24) \end{aligned}$$

Setting $\dot{\xi} = 0$ yields:

$$\alpha_2 a_{22} + \alpha_3 a_{32} = 0 \tag{25}$$

Assuming $\alpha_3 = 1$, we find $\alpha_2 = -\frac{a_{32}}{a_{22}}$.

Noting that:

$$\dot{z}_{2\tau_1} = a_{22} z_{2\tau_1} + R_{2\tau_1}, \tag{26}$$

where $R_{2\tau_1}$ contains terms of order two or higher, we define:

$$\xi_1 = \alpha_3 z_2 + z_3 - \frac{b_{32}}{a_{22}} z_{2\tau_1} \tag{27}$$

Then:

$$\dot{\xi}_1 = b_{32} z_{2\tau_1} - \frac{b_{32}}{a_{22}} \dot{z}_{2\tau_1} + R_3^{(1)} \tag{28}$$

$$= b_{32} z_{2\tau_1} - \frac{b_{32}}{a_{22}} \left(a_{22} z_{2\tau_1} + R_{2\tau_1} \right) + R_3^{(1)} \tag{29}$$

$$= R_3^{(2)}(y, y_{\tau_1}), \tag{30}$$

where $R_3^{(1)}$ and $R_3^{(2)}$ contain terms of order two or higher. Taking:

$$z_3 = \xi_1 - \alpha_2 z_2 + \frac{b_{32}}{a_{22}} z_{2\tau_1}, \tag{31}$$

by replacing the third equation with $\dot{\xi}_1$, we achieve a zero linear part. Substituting y_3 into the equations of the new system enables us to apply the critical case theorem from, [4], to analyze the stability of the zero solution in the transformed system. Given that $a_{11} < 0$, $a_{22} < 0$, $a_{44} < 0$, and $a_{66} < 0$, the stability analysis focuses on the transcendental term in the characteristic equation. Consider the equation:

$$\lambda - a_{55} - e^{-\lambda \tau_2} c_{55} = 0. \tag{32}$$

The stability of this equation is analyzed following the approach described in, [21].

- $a = -\rho \hat{y}_1 - M < 0$, it implies $a\tau < 1$.
- $b = c_{55} = (1-c) B \rho S \hat{y}_1 > 0$.
- Under the condition:

$$-\rho \hat{y}_1 - M < (c-1) B \rho S \hat{y}_1$$

then $a + b < 0$, indicating stability for $\tau_2 = 0$ and continued stability for $\tau_2 > 0$.

2.3 Stability Analysis of E_2

To analyze the stability of the equilibrium point E_2, we start by deriving the characteristic equation. This equation is given by:

$$(\lambda - a_{66})(\lambda - a_{44}) \left(\lambda e^{-\lambda \tau_2} \right) \times \left[\begin{array}{c} -a_{15}a_{51} + a_{11}c_{55} - c_{55}\lambda \\ + \left(\begin{array}{c} \lambda^2 - (a_{11} + a_{55})\lambda \\ + a_{11}a_{55} - a_{15}a_{51} \end{array} \right) \end{array} \right] = 0 \tag{33}$$

The real roots of this characteristic equation are:

$$\lambda_1 = a_{44} = -M < 0 \tag{34}$$

$$\lambda_2 = a_{66} = -G < 0 \tag{35}$$

$$\lambda_3 = 0 \tag{36}$$

The presence of a root at $\lambda = 0$ suggests that the system is in a critical stability case. Consequently, we must simplify the analysis by reducing the system to zero, similar to the approach used for the first equilibrium point. The assessment of stability will then depend on evaluating the transcendental term in the characteristic equation. Let $d(\lambda)$ be defined as:

$$\begin{aligned} d(\lambda) &= e^{-\lambda \tau_2} \left(-a_{15}a_{51} + a_{11}c_{55} - c_{55}\lambda \right) \\ &\quad + \left(\lambda^2 - (a_{11} + a_{55})\lambda + a_{11}a_{55} - a_{15}a_{51} \right), \end{aligned} \tag{37}$$

where $Q(\lambda)$ and $P(\lambda)$ are defined as:

$$Q(\lambda) = -a_{15}a_{51} + a_{11}c_{55} - c_{55}\lambda, \tag{38}$$

$$P(\lambda) = \lambda^2 - (a_{11} + a_{55})\lambda + a_{11}a_{55} - a_{15}a_{51}. \tag{39}$$

Thus, $d(\lambda)$ can be expressed as:

$$d(\lambda) = P(\lambda) + Q(\lambda) e^{-\lambda \tau_2} = 0. \tag{40}$$

The stability of $d(\lambda)$ is analyzed following the approach outlined in, [21]. The procedure includes: $P(\lambda)$ and $Q(\lambda)$ do not share any common imaginary parts. For imaginary arguments:

$$\begin{aligned} Q(iy) &= -a_{15}a_{51} + a_{11}c_{55} - c_{55} iy, \\ P(iy) &= y^2 - (a_{11} + a_{55}) iy + a_{11}a_{55} - a_{15}a_{51}, \\ Q(-iy) &= -a_{15}a_{51} + a_{11}c_{55} + c_{55} iy, \\ P(-iy) &= y^2 + (a_{11} + a_{55}) iy + a_{11}a_{55} - a_{15}a_{51}. \end{aligned}$$

Hence, $Q(iy) = \overline{Q(-iy)}$ and $P(iy) = \overline{P(-iy)}$.

If $\tau_2 = 0$, the characteristic equation simplifies to:

$$\lambda^2 - (a_{11} + a_{55} + c_{55})\lambda + a_{11}a_{55} - 2a_{15}a_{51} + a_{11}c_{55} \tag{41}$$

This results in a quadratic characteristic equation with at most two roots, implying finiteness. The function $F(y)$ is defined as:

$$F(y) \equiv |P(iy)|^2 - |Q(iy)|^2 = 0. \tag{42}$$

Simplifying, we get:

$$P_R^2(y) + P_I^2(y) = Q_R^2(y) + Q_I^2(y). \tag{43}$$

Let $P(\lambda) = \lambda^2 - u_1\lambda + v_1$ and $Q(\lambda) = u_2\lambda + v_2$, where:

$$u_1 = a_{11} + a_{55}, \tag{44}$$

$$u_2 = -c_{55}, \tag{45}$$

$$v_1 = a_{11}a_{55} - a_{15}a_{51}, \tag{46}$$

$$v_2 = -a_{15}a_{51} + a_{11}c_{55}. \tag{47}$$

Substituting these values into (43), we obtain:

$$y^4 + y^2(u_1^2 - 2v_1 - v_2^2) + v_1^2 - u_2^2 = 0. \quad (48)$$

By setting $\alpha = y^2$, the equation becomes:

$$\alpha^2 + \alpha(u_1^2 - 2v_1 - v_2^2) + v_1^2 - u_2^2 = 0. \quad (49)$$

For the equation (43) to have at least one positive simple root $y > 0$, the following conditions must be satisfied:

$$(u_1^2 - 2v_1 - v_2^2)^2 - 4(v_1^2 - u_2^2) > 0, \quad (50)$$

$$u_1^2 - 2v_1 - v_2^2 < 0. \quad (51)$$

Hence, the characteristic equation of E_2 is stable at $\tau_2 = 0$ and remains stable for all $\tau_2 \geq 0$ if at least one of the conditions (50) or (51) is not met.

3 Conclusion

In this study, we have conducted a comprehensive analysis of a delay differential equation (DDE) model to investigate the stability of malaria infection dynamics under the influence of treatment. Our research highlights the importance of accounting for delays in treatment and their impact on the stability and long-term behavior of the disease.

The main contributions of this paper include:

1. **Model Extensions:** We expanded the basic DDE model by adding an equation to represent the concentration of EPO and another equation to account for the loss occurring during the cell cycle. This extension enhances the model's applicability to real-world situations and offers a deeper understanding of how timing and intensity of treatment affect malaria dynamics.

2. **Stability Analysis:** We have established conditions for the stability of equilibrium points in our new delay differential equation (DDE) model using a critical case theorem. These conditions are crucial for understanding the effects of various treatment strategies on the disease's progression and serve as a basis for developing effective control measures.

Our findings suggest that incorporating delays into the model significantly influences the stability of malaria dynamics. Effective treatment strategies must account for these delays to optimize control measures and reduce the incidence of malaria.

Future research should focus on:

1. **Empirical Validation:** Conducting field studies to validate the model's predictions and adjust parameters based on real-world data is essential for ensuring the model's accuracy and relevance.

2. **Further Extensions:** Exploring additional factors such as population mobility, environmental changes, and varying levels of treatment adherence will further refine the model and improve its applicability to diverse epidemiological contexts.

3. **Comparison with Other Models:** Comparing our DDE model with other mathematical models will provide insights into its performance and accuracy, highlighting strengths and areas for improvement.

4. **Fractional Delay Models:** Future work should investigate the incorporation of fractional delay models to capture more complex dynamics of malaria infection. Fractional differential equations could offer additional insights into stability and behavior, providing a more comprehensive understanding of disease dynamics.

In conclusion, this study offers a robust framework for analyzing the impact of treatment delays on malaria dynamics. By enhancing our understanding of these delays, we can improve the design and implementation of more effective malaria control strategies. Future research incorporating fractional delay models and theoretical solution analysis could further advance our knowledge and optimize disease management approaches.

Authors' contributions:
The authors took full responsibility for every aspect of the study, from the conception and design to data collection, analysis, and writing. Their contributions to this article were equal.

Declaration of Generative AI and AI-assisted Technologies in the Writing Process:
During the preparation of this work, the author(s) used ChatGPT in order to assist with paraphrasing and improving the writing process. After using this tool, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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