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Research article

Global dynamics of SARS-CoV-2/malaria model with antibody immune response

A. D. Al Agha[1,*] **and A. M. Elaiw**[2,3]

[1] Department of Mathematical Science, College of Engineering, University of Business and Technology, Jeddah 21361, Saudi Arabia

[2] Department of Mathematics, Faculty of Science, King Abdulaziz University, P.O. Box 80203, Jeddah 21589, Saudi Arabia

[3] Department of Mathematics, Faculty of Science, Al-Azhar University, Assiut Branch, Assiut, Egypt

* **Correspondence:** Email: a.alagha@ubt.edu.sa.

Abstract: Coronavirus disease 2019 (COVID-19) is a new viral disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Malaria is a parasitic disease caused by Plasmodium parasites. In this paper, we explore a within-host model of SARS-CoV-2/malaria coinfection. This model consists of seven ordinary differential equations that study the interactions between uninfected red blood cells, infected red blood cells, free merozoites, uninfected epithelial cells, infected epithelial cells, free SARS-CoV-2 particles, and antibodies. We show that the model has bounded and non-negative solutions. We compute all steady state points and derive their existence conditions. We use appropriate Lyapunov functions to confirm the global stability of all steady states. We enhance the reliability of the theoretical results by performing numerical simulations. The steady states reflect the monoinfection and coinfection with malaria and SARS-CoV-2. The shared immune response reduces the concentrations of malaria merozoites and SARS-CoV-2 particles in coinfected patients. This response reduces the severity of SARS-CoV-2 infection in this group of patients.

Keywords: COVID-19; SARS-CoV-2; Malaria; immune response; global stability

1. Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory disease that emerged in China in late 2019. It is attributed to a virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It continues to spread and causes new cases and deaths daily around the world. According to the update published on 5 April 2022 by the World Health Organization (WHO) [1], over 489 million confirmed

cases and over 6 million deaths have been reported. The highest numbers of new deaths were registered in the United States of America, the Russian Federation, the Republic of Korea, Germany, and Brazil [1]. The coinfection of SARS-CoV-2 with other diseases represents an extra challenge to health care systems. One of the concerns is coinfection with malaria and COVID-19. In fact, many SARS-CoV-2/malaria coinfections have been reported in malaria-endemic countries [2]. This condition has increased the need to understand the dynamics of coinfection between malaria and SARS-CoV-2.

SARS-CoV-2 is a single-stranded positive-sense RNA virus [3]. It is a part of the family Coronaviridae [3]. It enters the host cell through the angiotensin-converting enzyme 2 (ACE2) receptor [4,5]. ACE2 is expressed in the heart, gastrointestinal tract, kidney, blood vessels and other organs [6]. However, it is expressed at high levels in the alveolar epithelial cells of the lungs [6]. The transmission of SARS-CoV-2 occurs through respiratory droplets that carry viral particles or by human-to-human contact [7]. Ten COVID-19 vaccines have been approved for use by the WHO, including Novavax, Serum Institute of India (Novavax formulation), Moderna, Pfizer/BioNTech, Janssen (Johnson & Johnson), Oxford/AstraZeneca, Serum Institute of India (Oxford/AstraZeneca formulation), Bharat Biotech, Sinopharm, and Sinovac [8]. The progress of mRNA-based vaccines is elaborately discussed in a previous study [9]. On October 22, 2020, the U.S. Food and Drug Administration (FDA) approved the antiviral drug Veklury (remdesivir) for the treatment of patients with COVID-19 requiring hospitalization [10]. It is used to treat adults and pediatric patients aged 12 years and older (with weight$\geq$ 40 kg) [10].

Malaria is a parasitic disease caused by Plasmodium parasites [7, 11]. Plasmodium falciparum is the deadliest parasite causing malaria. The other parasites causing malaria are P. vivax, P. ovale, P. malariae and P. knowlesi. In 2020, approximately 241 million confirmed cases of malaria and 627000 deaths were reported worldwide [12]. The African Region had 95% malaria cases and 96% malaria-related deaths [12]. Malaria is transmitted through the bites of infected Anopheles mosquitoes [11]. Malaria infection in humans consists of two stages: the liver stage and the blood stage [11]. Most of the clinical symptoms occur in the blood stage. During the blood stage, the parasites in the form of merozoites infect red blood cells and replicate within them [11]. After cells rupture, 8-32 daughter merozoites are released to infect healthy red blood cells [11]. Preventive chemotherapies are used to treat malaria infection and its consequences [12]. The WHO also recommended the use of RTS and the S/AS01 malaria vaccine for children living in regions with medium to high P. falciparum malaria transmission [12]. In this paper, we concentrate on malaria infection in the blood stage.

SARS-CoV-2 and malaria infections share many symptoms, such as fever, fatigue, difficulty breathing, headache, and myalgia [13–15]. This similarly may lead to problems in the clinical diagnosis of these diseases or ignoring the possibility of coinfection [6, 7]. SARS-CoV-2 and malaria also share a close incubation period of 7-14 days for Plasmodium falciparum malaria and 2-17 days for SARS-CoV-2, which increases the chance of coinfection [7, 16]. Indeed, SARS-CoV-2/malaria coinfection has been recorded in many countries [16–18]. Some studies mentioned that coinfection potentially increases the severity of COVID-19 [2, 16, 19]. However, a large number of studies have stated that neutralizing antibodies directed against Plasmodium falciparum are effective against SARS-CoV-2 particles, reducing the severity of SARS-CoV-2 infection in coinfected patients [6, 20–22]. Therefore, an understanding of the dynamics of coinfection is crucial to develop functional treatments that minimize the risk of death.

Mathematical models have been considered a robust tool to support biological and medical studies

of most epidemics. Malaria models have been widely developed and investigated (see, for example, [23–28]). Similarly, SARS-CoV-2 models have been developed in many studies (see, for example, [29–39]). Nevertheless, between-host models have attracted more attention than within-host models that study infection within a human body [40]. To the best of our knowledge, a SARS-CoV-2/malaria coinfection model has not yet been developed. In this paper, we develop a within-host model of SARS-CoV-2/malaria coinfection. This model inspects the interactions between seven components: healthy red blood cells, infected red blood cells, free merozoites, healthy epithelial cells, infected epithelial cells, free SARS-CoV-2 particles, and antibodies. Using the developed model, we (i) confirm the biological acceptance of solutions by proving the boundedness and nonnegativity, (ii) compute all steady-state points with the corresponding conditions of their existence, (iii) prove the global stability of all steady-state points, and (iv) validate the theoretical results by performing numerical simulations.

The article is arranged as described below. **Section 2** provides a description of the developed model. **Section 3** proves that all solutions are bounded and nonnegative. Moreover, it computes all steady state points. **Section 4** uses Lyapunov functions to prove the global stability of these solutions. **Section 5** presents some numerical simulations. Finally, **Section 6** discusses the results with some future directions.

2. SARS-CoV-2/malaria model with an antibody immune response

This section provides a description of the model under consideration. The model consists of seven ordinary differential equations and takes the form

$$\begin{cases} \dfrac{dX(t)}{dt} = \sigma_1 - \beta_m X(t)M(t) - d_1 X(t), \\ \dfrac{dI(t)}{dt} = \beta_m X(t)M(t) - d_2 I(t), \\ \dfrac{dM(t)}{dt} = \eta d_2 I(t) - q_1 M(t)Z(t) - d_3 M(t), \\ \dfrac{dY(t)}{dt} = \sigma_2 - \beta_v Y(t)V(t) - d_4 Y(t), \\ \dfrac{dN(t)}{dt} = \beta_v Y(t)V(t) - d_5 N(t), \\ \dfrac{dV(t)}{dt} = eN(t) - q_2 V(t)Z(t) - d_6 V(t), \\ \dfrac{dZ(t)}{dt} = p_1 M(t)Z(t) + p_2 V(t)Z(t) - d_7 Z(t), \end{cases} \tag{2.1}$$

where $X(t)$, $I(t)$, $M(t)$, $Y(t)$, $N(t)$, $V(t)$, and $Z(t)$ denote the concentrations of uninfected red blood cells, infected red blood cells, free merozoites, uninfected epithelial cells, infected epithelial cells, free SARS-CoV-2 particles, and antibodies, respectively. Uninfected red blood cells are recruited at a constant rate σ_1. They are infected by free merozoites at rate $\beta_m XM$ and die at rate $d_1 X$. Infected red blood cells burst to produce η merozoites per infected cell and die at rate $d_2 I$. Free merozoites are eliminated by antibodies at rate $q_1 MZ$ and die at rate $d_3 M$. Healthy epithelial cells are generated at a constant rate σ_2, infected by SARS-CoV-2 at rate $\beta_v YV$ and die at rate $d_4 Y$. Infected epithelial cells produce SARS-CoV-2 particles at rate eN and die at rate $d_5 N$. SARS-CoV-2 particles are eliminated

by antibodies at rate q_2VZ and die at rate d_6V. B cells are stimulated to produce antibodies to clear malaria merozoites and SARS-CoV-2 particles at rates p_1MZ and p_2VZ, respectively. Antibodies die at a natural rate of d_7Z. The meanings of the different parameters are summarized in Table 2.

3. Basic properties

This section verifies the basic properties of the model (2.1), including the existence, nonnegativity and boundedness. Additionally, it lists all possible steady state points of the model with the corresponding existence conditions.

Theorem 1. *Assume that* $\phi_i > 0$ *for* $i = 1, 2, 3, 4, 5$. *Define the compact set* $\Phi = \Big\{(X, I, M, Y, N, V, Z) \in \mathbb{R}^7_+ : 0 \le X(t), I(t) \le \phi_1, 0 \le Y(t), N(t) \le \phi_2, 0 \le M(t) \le \phi_3, 0 \le V(t) \le \phi_4, 0 \le Z(t) \le \phi_5\Big\}$. *Then,* Φ *is a positively invariant set for system* (2.1).

Proof. For system (2.1), we obtain

$$\begin{aligned}
&\frac{dX}{dt}|_{X=0} = \sigma_1 > 0,\\
&\frac{dI}{dt}|_{I=0} = \beta_m XM \ge 0 \quad \forall\, X, M \ge 0,\\
&\frac{dM}{dt}|_{M=0} = \eta d_2 I \ge 0 \quad \forall\, I \ge 0,\\
&\frac{dY}{dt}|_{Y=0} = \sigma_2 > 0,\\
&\frac{dN}{dt}|_{N=0} = \beta_v YV \ge 0 \quad \forall\, Y, V \ge 0,\\
&\frac{dV}{dt}|_{V=0} = eN \ge 0 \quad \forall\, N \ge 0,\\
&\frac{dZ}{dt}|_{Z=0} = 0.
\end{aligned}$$

This equation ensures that $(X(t), I(t), M(t), Y(t), N(t), V(t), Z(t)) \in \mathbb{R}^7_+$ for all $t \ge 0$ when the initial conditions $(X(0), I(0), M(0), Y(0), N(0), V(0), Z(0)) \in \mathbb{R}^7_+$.

We define the following equation to prove the boundedness of solutions:

$$\Omega_1(t) = X(t) + I(t).$$

By taking the derivative with respect to t, we obtain the following formula:

$$\begin{aligned}
\frac{d\Omega_1(t)}{dt} =& \sigma_1 - d_1X(t) - d_2I(t)\\
\le& \sigma_1 - \gamma_1 [X(t) + I(t)]\\
=& \sigma_1 - \gamma_1\Omega_1(t),
\end{aligned}$$

where $\gamma_1 = \min\{d_1, d_2\}$. Hence, we obtain

$$0 \le \Omega_1(t) \le \phi_1 \quad \text{if} \quad \Omega_1(0) \le \phi_1, \text{ for } t \ge 0,$$

where $\phi_1 = \dfrac{\sigma_1}{\gamma_1}$. Thus, $X(t) \leq \phi_1$ and $I(t) \leq \phi_1$. We define the following equation to prove the boundedness of $Y(t)$ and $N(t)$:

$$\Omega_2(t) = Y(t) + N(t).$$

Then, we obtain

$$\begin{aligned}\frac{d\Omega_2(t)}{dt} =& \sigma_2 - d_4 Y(t) - d_5 N(t)\\ \leq& \sigma_2 - \gamma_2 \left[Y(t) + N(t)\right]\\ =& \sigma_2 - \gamma_2 \Omega_2(t),\end{aligned}$$

where $\gamma_2 = \min\{d_4, d_5\}$. Therefore, the formula becomes

$$0 \leq \Omega_2(t) \leq \phi_2 \quad \text{if} \quad \Omega_2(0) \leq \phi_2, \text{ for } t \geq 0,$$

where $\phi_2 = \dfrac{\sigma_2}{\gamma_2}$. This equation implies that $Y(t) \leq \phi_2$ and $N(t) \leq \phi_2$. Finally, we define the following equation to prove the boundedness of $M(t)$, $V(t)$, and $Z(t)$:

$$\Omega_3(t) = M(t) + \frac{q_1 p_2}{p_1 q_2} V(t) + \frac{q_1}{p_1} Z(t).$$

Then, we obtain

$$\begin{aligned}\frac{d\Omega_3(t)}{dt} =& \eta d_2 I(t) + \frac{e q_1 p_2}{p_1 q_2} N(t) - d_3 M(t) - \frac{q_1 p_2 d_6}{p_1 q_2} V(t) - \frac{q_1 d_7}{p_1} Z(t)\\ \leq& \eta d_2 \phi_1 + \frac{e q_1 p_2}{p_1 q_2} \phi_2 - \gamma_3 \left[M(t) + \frac{q_1 p_2}{p_1 q_2} V(t) + \frac{q_1}{p_1} Z(t)\right]\\ =& \eta d_2 \phi_1 + \frac{e q_1 p_2}{p_1 q_2} \phi_2 - \gamma_3 \Omega_3(t),\end{aligned}$$

where $\gamma_3 = \min\{d_3, d_6, d_7\}$. Therefore, we have

$$0 \leq \Omega_3(t) \leq \frac{\eta d_2 \phi_1}{\gamma_3} + \frac{e q_1 p_2 \phi_2}{p_1 q_2 \gamma_3} \quad \text{if} \quad \Omega_3(0) \leq \frac{\eta d_2 \phi_1}{\gamma_3} + \frac{e q_1 p_2 \phi_2}{p_1 q_2 \gamma_3}, \text{ for } t \geq 0.$$

Thus, $M(t) \leq \phi_3$, $V(t) \leq \phi_4$, and $Z(t) \leq \phi_5$, where $\phi_3 = \dfrac{\eta d_2 \phi_1}{\gamma_3} + \dfrac{e q_1 p_2 \phi_2}{p_1 q_2 \gamma_3}$, $\phi_4 = \dfrac{\eta p_1 q_2 d_2 \phi_1}{q_1 p_2 \gamma_3} + \dfrac{e \phi_2}{\gamma_3}$, and $\phi_5 = \dfrac{\eta p_1 d_2 \phi_1}{q_1 \gamma_3} + \dfrac{e p_2 \phi_2}{q_2 \gamma_3}$.

From the equations listed above, the set Φ is positively invariant. □

Theorem 2. *The conditions $\mathcal{R}_{0m} > 0$, $\mathcal{R}_{1m} > 0$, $\mathcal{R}_p > 0$ $\mathcal{R}_{0v} > 0$, and $\mathcal{R}_{1v} > 0$ exist such that the model* (2.1) *has seven steady states when the following conditions are met:*

(1) The uninfected steady state E_0 always exists;

(2) The SARS-CoV-2-free steady state without an immune response E_1 exists if $\mathcal{R}_{0m} > 1$;

(3) The SARS-CoV-2-free steady state E_2 exists if $\mathcal{R}_{1m} > 1$;

(4) The malaria-free steady state without an immune response E_3 exists if $\mathcal{R}_{0v} > 1$;

(5) *The malaria-free steady state* E_4 *exists if* $\mathcal{R}_{1v} > 1$*;*

(6) *The SARS-CoV-2/malaria coinfection immune-free steady state* E_5 *exists if* $\mathcal{R}_{0m} > 1$ *and* $\mathcal{R}_{0v} > 1$*; and*

(7) *The SARS-CoV-2/malaria coinfection steady state* E_6 *exists if* $\mathcal{R}_p > 1 + \frac{\eta\beta_m\sigma_1 p_1 q_2}{q_1 d_6(p_1 d_1 + \beta_m d_7)}$, $\mathcal{R}_{0m} + \frac{q_1 d_6}{q_2 d_3} > 1 + \frac{e\beta_v q_1 \sigma_2 p_2}{q_2 d_3 d_5(p_2 d_4 + \beta_v d_7)}$, *and* $\mathcal{R}_{0m} + \frac{e\beta_m\sigma_2 p_2}{p_1 d_1 d_5 d_6} > 1 + \frac{\beta_m(p_2 d_4 + \beta_v d_7)}{\beta_v p_1 d_1}$.

Proof. The steady states of system (2.1) satisfy the following algebraic system:

$$\begin{cases} 0 = \sigma_1 - \beta_m XM - d_1 X, \\ 0 = \beta_m XM - d_2 I, \\ 0 = \eta d_2 I - q_1 MZ - d_3 M, \\ 0 = \sigma_2 - \beta_v YV - d_4 Y, \\ 0 = \beta_v YV - d_5 N, \\ 0 = eN - q_2 VZ - d_6 V, \\ 0 = p_1 MZ + p_2 VZ - d_7 Z. \end{cases} \tag{3.1}$$

By solving (3.1), we obtain the following steady states:

(1) The uninfected steady state $E_0 = (X_0, 0, 0, Y_0, 0, 0, 0)$, where

$$X_0 = \frac{\sigma_1}{d_1} > 0, \quad Y_0 = \frac{\sigma_2}{d_4} > 0.$$

Therefore, E_0 always exists.

(2) The SARS-CoV-2-free steady state without an immune response is designated $E_1 = (X_1, I_1, M_1, Y_1, 0, 0, 0)$, where

$$X_1 = \frac{d_3}{\eta\beta_m}, \quad I_1 = \frac{d_1 d_3}{\eta\beta_m d_2}(\mathcal{R}_{0m} - 1), \quad M_1 = \frac{d_1}{\beta_m}(\mathcal{R}_{0m} - 1), \quad Y_1 = \frac{\sigma_2}{d_4},$$

where $\mathcal{R}_{0m} = \frac{\eta\beta_m\sigma_1}{d_1 d_3}$. Notably, X_1 and Y_1 are positive, while I_1 and M_1 are positive for $\mathcal{R}_{0m} > 1$. Thus, E_1 exists when $\mathcal{R}_{0m} > 1$. The threshold parameter $\mathcal{R}_{0m}$ marks the initiation of malaria infection in the body.

(3) The SARS-CoV-2-free steady state with an immune response $E_2 = (X_2, I_2, M_2, Y_2, 0, 0, Z_2)$. The components are defined as follows:

$$X_2 = \frac{\sigma_1 p_1}{p_1 d_1 + \beta_m d_7}, \quad I_2 = \frac{\beta_m\sigma_1 d_7}{d_2(p_1 d_1 + \beta_m d_7)}, \quad M_2 = \frac{d_7}{p_1}, \quad Y_2 = \frac{\sigma_2}{d_4}, \quad Z_2 = \frac{d_3}{q_1}(\mathcal{R}_{1m} - 1),$$

where $\mathcal{R}_{1m} = \frac{\eta\beta_m\sigma_1 p_1}{d_3(p_1 d_1 + \beta_m d_7)}$. We note that X_2, I_2, M_2 and Y_2 are always positive, while $Z_2 > 0$ if $\mathcal{R}_{1m} > 1$. Hence, E_2 exists if $\mathcal{R}_{1m} > 1$. The threshold parameter $\mathcal{R}_{1m}$ determines the initiation of the antibody immune response against malaria merozoites.

(4) The malaria-free steady state without an immune response is defined as $E_3 = (X_3, 0, 0, Y_3, N_3, V_3, 0)$. The components are calculated using the following equation:

$$X_3 = \frac{\sigma_1}{d_1}, \quad Y_3 = \frac{d_5 d_6}{e\beta_v}, \quad N_3 = \frac{d_4 d_6}{e\beta_v}(\mathcal{R}_{0v} - 1), \quad V_3 = \frac{d_4}{\beta_v}(\mathcal{R}_{0v} - 1),$$

where $\mathcal{R}_{0v} = \dfrac{e\beta_v\sigma_2}{d_4 d_5 d_6}$. Clearly, X_3 and Y_3 are always positive, while N_3 and V_3 are positive if $\mathcal{R}_{0v} > 1$. The threshold parameter $\mathcal{R}_{0v}$ marks the initiation of SARS-CoV-2 infection in the body.

(5) The malaria-free steady state is $E_4 = (X_4, 0, 0, Y_4, N_4, V_4, Z_4)$, where

$$X_4 = \frac{\sigma_1}{d_1}, \quad Y_4 = \frac{\sigma_2 p_2}{p_2 d_4 + \beta_v d_7}, \quad N_4 = \frac{\beta_v \sigma_2 d_7}{d_5(p_2 d_4 + \beta_v d_7)}, \quad V_4 = \frac{d_7}{p_2}, \quad Z_4 = \frac{d_6}{q_2}(\mathcal{R}_{1v} - 1),$$

where $\mathcal{R}_{1v} = \dfrac{e\beta_v\sigma_2 p_2}{d_5 d_6(p_2 d_4 + \beta_v d_7)}$. Notably, X_4, Y_4, N_4 and V_4 are always positive, while $Z_4 > 0$ if $\mathcal{R}_{1v} > 1$. Hence, E_4 exists if $\mathcal{R}_{1v} > 1$. The threshold parameter $\mathcal{R}_{1v}$ establishes an antibody-mediated immune response against SARS-CoV-2 particles.

(6) The SARS-CoV-2/malaria coinfection immune-free steady state is defined as $E_5 = (X_5, I_5, M_5, Y_5, N_5, V_5, 0)$, where

$$X_5 = \frac{d_3}{\eta\beta_m}, \quad I_5 = \frac{d_1 d_3}{\eta\beta_m d_2}(\mathcal{R}_{0m} - 1), \quad M_5 = \frac{d_1}{\beta_m}(\mathcal{R}_{0m} - 1),$$
$$Y_5 = \frac{d_5 d_6}{e\beta_v}, \quad N_5 = \frac{d_4 d_6}{e\beta_v}(\mathcal{R}_{0v} - 1), \quad V_5 = \frac{d_4}{\beta_v}(\mathcal{R}_{0v} - 1).$$

The components X_5 and Y_5 are always positive. I_5 and M_5 are positive if $\mathcal{R}_{0m} > 1$, while N_5 and V_5 are positive if $\mathcal{R}_{0v} > 1$. Hence, E_5 exists if $\mathcal{R}_{0m} > 1$ and $\mathcal{R}_{0v} > 1$. These two conditions are needed to establish a SARS-CoV-2/malaria coinfection.

(7) The SARS-CoV-2/malaria coinfection steady state is defined as $E_6 = (X_6, I_6, M_6, Y_6, N_6, V_6, Z_6)$, where

$$X_6 = \frac{\sigma_1 p_1}{p_1 d_1 + \beta_m(d_7 - p_2 V_6)}, \quad I_6 = \frac{\sigma_1\beta_m(d_7 - p_2 V_6)}{d_2\left[p_1 d_1 + \beta_m(d_7 - p_2 V_6)\right]}, \quad M_6 = \frac{d_7 - p_2 V_6}{p_1},$$
$$Y_6 = \frac{q_2 d_3 d_5(p_1 d_1 + \beta_m d_7)(\mathcal{R}_{1m} - 1) + \beta_m p_2 q_2 d_3 d_5 V_6 + d_5 q_1 d_6\left[p_1 d_1 + \beta_m(d_7 - p_2 V_6)\right]}{e q_1\beta_v\left[p_1 d_1 + \beta_m(d_7 - p_2 V_6)\right]},$$
$$N_6 = \frac{q_2 d_3(p_1 d_1 + \beta_m d_7)(\mathcal{R}_{1m} - 1) + \beta_m p_2 q_2 d_3 V_6 + q_1 d_6\left[p_1 d_1 + \beta_m(d_7 - p_2 V_6)\right]}{e q_1\left[p_1 d_1 + \beta_m(d_7 - p_2 V_6)\right]} V_6,$$
$$Z_6 = \frac{d_3(p_1 d_1 + \beta_m d_7)(\mathcal{R}_{1m} - 1) + \beta_m p_2 d_3 V_6}{q_1\left[p_1 d_1 + \beta_m(d_7 - p_2 V_6)\right]}.$$

By substituting Y_6 in the fourth equation of the model (2.1), we obtain

$$e\beta_v q_1\sigma_2\left[p_1 d_1 + \beta_m(d_7 - p_2 V_6)\right] - d_4 d_5\left[p_1 d_1 + \beta_m(d_7 - p_2 V_6)\right]\left[q_1 d_6 - q_2 d_3\right] - \eta\beta_m\sigma_1 p_1 q_2 d_4 d_5$$
$$- \beta_v d_5 V_6\left[p_1 d_1 + \beta_m(d_7 - p_2 V_6)\right](q_1 d_6 - q_2 d_3) - \eta\beta_m\beta_v\sigma_1 p_1 q_2 d_5 V_6 = 0.$$

Thus, V_6 satisfies the following equation:

$$\beta_m\beta_v p_2 d_5(q_1 d_6 - q_2 d_3){V_6}^2 + \Big(\beta_m q_1 p_2 d_4 d_5 d_6 + \beta_v p_1 d_1 q_2 d_3 d_5 + \beta_m\beta_v q_2 d_3 d_5 d_7 - e\beta_m\beta_v q_1\sigma_2 p_2$$
$$- \beta_m p_2 q_2 d_3 d_4 d_5 - \beta_v p_1 q_1 d_1 d_5 d_6 - \beta_m\beta_v q_1 d_5 d_6 d_7 - \eta\beta_m\beta_v\sigma_1 p_1 q_2 d_5\Big)V_6 + e\beta_v p_1 q_1 d_1\sigma_2$$
$$+ e\beta_m\beta_v q_1\sigma_2 d_7 + p_1 d_1 q_2 d_3 d_4 d_5 + \beta_m q_2 d_3 d_4 d_5 d_7 - p_1 d_1 q_1 d_4 d_5 d_6 - \beta_m q_1 d_4 d_5 d_6 d_7 - \eta\beta_m\sigma_1 p_1 q_2 d_4 d_5 = 0.$$

We define a function $H(V)$ as follows:

$$H(V) = aV^2 + bV + c,$$

where

$$\begin{aligned}
a =&\beta_m\beta_v p_2 d_5(q_1 d_6 - q_2 d_3),\\
b =&\beta_m q_1 p_2 d_4 d_5 d_6 + \beta_v p_1 d_1 q_2 d_3 d_5 + \beta_m\beta_v q_2 d_3 d_5 d_7 - e\beta_m\beta_v q_1\sigma_2 p_2 - \beta_m p_2 q_2 d_3 d_4 d_5\\
&- \beta_v p_1 q_1 d_1 d_5 d_6 - \beta_m\beta_v q_1 d_5 d_6 d_7 - \eta\beta_m\beta_v\sigma_1 p_1 q_2 d_5,\\
c =&e\beta_v p_1 q_1 d_1\sigma_2 + e\beta_m\beta_v q_1\sigma_2 d_7 + p_1 d_1 q_2 d_3 d_4 d_5 + \beta_m q_2 d_3 d_4 d_5 d_7 - p_1 d_1 q_1 d_4 d_5 d_6\\
&- \beta_m q_1 d_4 d_5 d_6 d_7 - \eta\beta_m\sigma_1 p_1 q_2 d_4 d_5.
\end{aligned}$$

By evaluating the value of $H(V)$ at $V = 0$, we obtain

$$\begin{aligned}
H(0) =&e\beta_v q_1\sigma_2(p_1 d_1 + \beta_m d_7) + q_2 d_3 d_4 d_5(p_1 d_1 + \beta_m d_7) - q_1 d_4 d_5 d_6(p_1 d_1 + \beta_m d_7) - \eta\beta_m\sigma_1 p_1 q_2 d_4 d_5\\
=&q_1 d_4 d_5 d_6(p_1 d_1 + \beta_m d_7)\Big[\frac{e\beta_v q_1\sigma_2 + q_2 d_3 d_4 d_5}{q_1 d_4 d_5 d_6} - 1 - \frac{\eta\beta_m\sigma_1 p_1 q_2}{q_1 d_6(p_1 d_1 + \beta_m d_7)}\Big]\\
=&q_1 d_4 d_5 d_6(p_1 d_1 + \beta_m d_7)\Big[\mathcal{R}_p - 1 - \frac{\eta\beta_m\sigma_1 p_1 q_2}{q_1 d_6(p_1 d_1 + \beta_m d_7)}\Big],
\end{aligned}$$

where $\mathcal{R}_p = \dfrac{e\beta_v q_1\sigma_2 + q_2 d_3 d_4 d_5}{q_1 d_4 d_5 d_6}$. Notably, $H(0) > 0$ if

$$\mathcal{R}_p > 1 + \frac{\eta\beta_m\sigma_1 p_1 q_2}{q_1 d_6(p_1 d_1 + \beta_m d_7)}. \tag{3.2}$$

In addition, we find

$$\begin{aligned}
H\left(\frac{d_7}{p_2}\right) =&\frac{-1}{p_2}\Big[\eta\beta_m\sigma_1 p_1 q_2 d_5(p_2 d_4 + \beta_v d_7) + p_1 q_1 d_1 d_5 d_6(p_2 d_4 + \beta_v d_7) - p_1 d_1 q_2 d_3 d_5(p_2 d_4 + \beta_v d_7)\\
&- e\beta_v p_1 q_1 d_1\sigma_2 p_2\Big]\\
=&-\frac{p_1 d_1 q_2 d_3 d_5(p_2 d_4 + \beta_v d_7)}{p_2}\Big[\mathcal{R}_{0m} + \frac{q_1 d_6}{q_2 d_3} - 1 - \frac{e\beta_v q_1\sigma_2 p_2}{q_2 d_3 d_5(p_2 d_4 + \beta_v d_7)}\Big]
\end{aligned}$$

Thus, $H\left(\dfrac{d_7}{p_2}\right) < 0$ if

$$\mathcal{R}_{0m} + \frac{q_1 d_6}{q_2 d_3} > 1 + \frac{q_1 d_6}{q_2 d_3}\mathcal{R}_{1v}. \tag{3.3}$$

This result implies that a root $0 < V^* < \frac{d_7}{p_2}$ exists such that $H(V^*) = 0$. Let $V_6 = V^*$ and note that for $0 < V_6 < \frac{d_7}{p_2}$ and $\mathcal{R}_{1m} > 1$ ($\mathcal{R}_{1m} > 1$ is naturally satisfied at E_6 because E_2 coexists with E_6 when $\mathcal{R}_{1m} > 1$. However, it will not be stable as concluded from Theorem 5, where $X_6 > 0$, $I_6 > 0$, $M_6 > 0$, $Y_6 > 0$, $N_6 > 0$ and $Z_6 > 0$. Similarly, we determine the third existence condition of E_6 by formulating a function of Z and extracting the conditions under which a positive root is obtained as follows:

$$\mathcal{R}_{0m} + \frac{e\beta_m\sigma_2 p_2}{p_1 d_1 d_5 d_6} > 1 + \frac{\beta_m(p_2 d_4 + \beta_v d_7)}{\beta_v p_1 d_1}. \tag{3.4}$$

Therefore, E_6 exists if conditions (3.2), (3.3), and (3.4) are satisfied.

□

4. Global properties

This section proves the global stability of all steady states of model (2.1) by selecting proper Lyapunov functions.

We define a function $\Pi_i(X, I, M, Y, N, V, Z)$ and let $S_i^{'}$ be the largest invariant subset of $S = \left\{(X, I, M, Y, N, V, Z) \mid \frac{d\Pi_i}{dt} = 0\right\}$.

Theorem 3. *The steady state E_0 is globally asymptotically stable (GAS) if $\mathcal{R}_{0m} \leq 1$ and $\mathcal{R}_{0v} \leq 1$.*

Proof. We define a Lyapunov function as follows:

$$\Pi_0(t) = X_0\left(\frac{X}{X_0} - 1 - \ln\frac{X}{X_0}\right) + I + \frac{1}{\eta}M + \frac{eq_1p_2}{\eta p_1 q_2 d_5}Y_0\left(\frac{Y}{Y_0} - 1 - \ln\frac{Y}{Y_0}\right) + \frac{eq_1p_2}{\eta p_1 q_2 d_5}N + \frac{q_1p_2}{\eta p_1 q_2}V + \frac{q_1}{\eta p_1}Z.$$

By taking the time derivative of $\Pi_0(t)$, we obtain

$$\begin{aligned}
\frac{d\Pi_0}{dt} =& \left(1 - \frac{X_0}{X}\right)\left(\sigma_1 - \beta_m XM - d_1X\right) + \beta_m XM - d_2I + \frac{1}{\eta}\left(\eta d_2 I - q_1 MZ - d_3 M\right) \\
&+ \frac{eq_1p_2}{\eta p_1 q_2 d_5}\left(1 - \frac{Y_0}{Y}\right)\left(\sigma_2 - \beta_v YV - d_4Y\right) + \frac{eq_1p_2}{\eta p_1 q_2 d_5}\left(\beta_v YV - d_5N\right) \\
&+ \frac{q_1p_2}{\eta p_1 q_2}\left(eN - q_2VZ - d_6V\right) + \frac{q_1}{\eta p_1}\left(p_1MZ + p_2VZ - d_7Z\right) \\
=& \left(1 - \frac{X_0}{X}\right)\left(\sigma_1 - d_1X\right) + \frac{eq_1p_2}{\eta p_1 q_2 d_5}\left(1 - \frac{Y_0}{Y}\right)\left(\sigma_2 - d_4Y\right) + \left(\beta_m X_0 - \frac{d_3}{\eta}\right)M \\
&+ \left(\frac{eq_1p_2\beta_v}{\eta p_1 q_2 d_5}Y_0 - \frac{q_1p_2d_6}{\eta p_1 q_2}\right)V - \frac{q_1d_7}{\eta p_1}Z \\
=& -\frac{d_1\,(X - X_0)^2}{X} - \frac{eq_1p_2d_4}{\eta p_1 q_2 d_5}\frac{(Y - Y_0)^2}{Y} + \frac{d_3}{\eta}(\mathcal{R}_{0m} - 1)M + \frac{q_1p_2d_6}{\eta p_1 q_2}(\mathcal{R}_{0v} - 1)V - \frac{q_1d_7}{\eta p_1}Z.
\end{aligned}$$

In this case, $\frac{d\Pi_0}{dt} \leq 0$ if $\mathcal{R}_{0m} \leq 1$ and $\mathcal{R}_{0v} \leq 1$. Additionally, $\frac{d\Pi_0}{dt} = 0$ when $X = X_0$, $Y = Y_0$, and $M = V = Z = 0$. The solutions tend to $S_0^{'}$ which contains elements with $M = V = 0$ and then $\frac{dM}{dt} = 0$

and $\frac{dV}{dt} = 0$. From the third and sixth equations of the model (2.1), we obtain $I = N = 0$. Therefore, $S_0^{'} = \{E_0\}$, which guarantees the global asymptotic stability of E_0 when $\mathcal{R}_{0m} \leq 1$ and $\mathcal{R}_{0v} \leq 1$ according to LaSalle's invariance principle [41]. □

Theorem 4. *Suppose that $\mathcal{R}_{0m} > 1$. Then, the steady state E_1 is GAS if $\mathcal{R}_{0v} \leq 1$ and $\mathcal{R}_{1m} \leq 1$.*

Proof. We establish the following Lyapunov function:

$$\begin{aligned}\Pi_1(t) =& X_1\left(\frac{X}{X_1} - 1 - \ln\frac{X}{X_1}\right) + I_1\left(\frac{I}{I_1} - 1 - \ln\frac{I}{I_1}\right) + \frac{1}{\eta}M_1\left(\frac{M}{M_1} - 1 - \ln\frac{M}{M_1}\right) + \frac{eq_1p_2}{\eta p_1q_2d_5}Y_1\left(\frac{Y}{Y_1} - 1 - \ln\frac{Y}{Y_1}\right)\\ &+ \frac{eq_1p_2}{\eta p_1q_2d_5}N + \frac{q_1p_2}{\eta p_1q_2}V + \frac{q_1}{\eta p_1}Z.\end{aligned}$$

Then, we obtain

$$\begin{aligned}\frac{d\Pi_1}{dt} =& \left(1 - \frac{X_1}{X}\right)\left(\sigma_1 - \beta_m XM - d_1X\right) + \left(1 - \frac{I_1}{I}\right)\left(\beta_m XM - d_2I\right)\\ &+ \frac{1}{\eta}\left(1 - \frac{M_1}{M}\right)\left(\eta d_2I - q_1MZ - d_3M\right) + \frac{eq_1p_2}{\eta p_1q_2d_5}\left(1 - \frac{Y_1}{Y}\right)\left(\sigma_2 - \beta_v YV - d_4Y\right)\\ &+ \frac{eq_1p_2}{\eta p_1q_2d_5}\left(\beta_v YV - d_5N\right) + \frac{q_1p_2}{\eta p_1q_2}\left(eN - q_2VZ - d_6V\right) + \frac{q_1}{\eta p_1}\left(p_1MZ + p_2VZ - d_7Z\right). \quad (4.1)\end{aligned}$$

By applying the steady state conditions at E_1

$$\begin{cases}\sigma_1 = \beta_m X_1M_1 + d_1X_1,\\ \beta_m X_1M_1 = d_2I_1,\\ d_2I_1 = \dfrac{d_3}{\eta}M_1,\\ \sigma_2 = d_4Y_1,\end{cases}$$

and collecting the terms of Eq. (4.1), we obtain

$$\begin{aligned}\frac{d\Pi_1}{dt} =& \left(1 - \frac{X_1}{X}\right)\left(d_1X_1 - d_1X\right) + 3\beta_m X_1M_1 - \beta_m X_1M_1\frac{X_1}{X} - \beta_m X_1M_1\frac{XI_1M}{X_1IM_1}\\ &+ \frac{eq_1p_2}{\eta p_1q_2d_5}\left(1 - \frac{Y_1}{Y}\right)\left(d_4Y_1 - d_4Y\right) - \beta_m X_1M_1\frac{IM_1}{I_1M} + \left(\frac{eq_1p_2\beta_v}{\eta p_1q_2d_5}Y_1 - \frac{q_1p_2d_6}{\eta p_1q_2}\right)V\\ &+ \left(\frac{q_1}{\eta}M_1 - \frac{q_1d_7}{\eta p_1}\right)Z\\ =& -\frac{d_1\left(X - X_1\right)^2}{X} - \frac{eq_1p_2d_4}{\eta p_1q_2d_5}\frac{\left(Y - Y_1\right)^2}{Y} + \beta_m X_1M_1\left(3 - \frac{X_1}{X} - \frac{IM_1}{I_1M} - \frac{XI_1M}{X_1IM_1}\right)\\ &+ \frac{q_1p_2d_6}{\eta p_1q_2}(\mathcal{R}_{0v} - 1)V + \frac{q_1(p_1d_1 + \beta_m d_7)}{\eta p_1\beta_m}(\mathcal{R}_{1m} - 1)Z.\end{aligned}$$

Thus, $\frac{d\Pi_1}{dt} \leq 0$ if $\mathcal{R}_{0v} \leq 1$ and $\mathcal{R}_{1m} \leq 1$. Furthermore, $\frac{d\Pi_1}{dt} = 0$ when $X = X_1$, $I = I_1$, $M = M_1$, $Y = Y_1$, and $V = Z = 0$. The solutions tend to $S_1^{'}$ which has $V = 0$ and then $\frac{dV}{dt} = 0$. From the sixth equation of (2.1), we obtain $N = 0$. Hence, $S_1^{'} = \{E_1\}$. Accordingly, LaSalle's invariance principle [41] ensures the global asymptotic stability of E_1 if $\mathcal{R}_{0m} > 1$, $\mathcal{R}_{0v} \leq 1$ and $\mathcal{R}_{1m} \leq 1$. □

Theorem 5. *Assume that $\mathcal{R}_{1m} > 1$. Then, the steady state E_2 is GAS if $\mathcal{R}_p \leq 1 + \dfrac{\eta\beta_m\sigma_1 p_1 q_2}{q_1 d_6(p_1 d_1 + \beta_m d_7)}$.*

Proof. We define a Lyapunov function

$$\begin{aligned}\Pi_2(t) =& X_2\left(\frac{X}{X_2} - 1 - \ln\frac{X}{X_2}\right) + I_2\left(\frac{I}{I_2} - 1 - \ln\frac{I}{I_2}\right) + \frac{1}{\eta}M_2\left(\frac{M}{M_2} - 1 - \ln\frac{M}{M_2}\right) + \frac{eq_1p_2}{\eta p_1 q_2 d_5}Y_2\left(\frac{Y}{Y_2} - 1 - \ln\frac{Y}{Y_2}\right)\\ &+ \frac{eq_1p_2}{\eta p_1 q_2 d_5}N + \frac{q_1p_2}{\eta p_1 q_2}V + \frac{q_1}{\eta p_1}Z_2\left(\frac{Z}{Z_2} - 1 - \ln\frac{Z}{Z_2}\right).\end{aligned}$$

Then, we obtain

$$\begin{aligned}\frac{d\Pi_2}{dt} =& \left(1 - \frac{X_2}{X}\right)\left(\sigma_1 - \beta_m XM - d_1X\right) + \left(1 - \frac{I_2}{I}\right)\left(\beta_m XM - d_2I\right)\\ &+ \frac{1}{\eta}\left(1 - \frac{M_2}{M}\right)\left(\eta d_2 I - q_1 MZ - d_3M\right) + \frac{eq_1p_2}{\eta p_1 q_2 d_5}\left(1 - \frac{Y_2}{Y}\right)\left(\sigma_2 - \beta_v YV - d_4Y\right)\\ &+ \frac{eq_1p_2}{\eta p_1 q_2 d_5}\left(\beta_v YV - d_5N\right) + \frac{q_1p_2}{\eta p_1 q_2}\left(eN - q_2VZ - d_6V\right)\\ &+ \frac{q_1}{\eta p_1}\left(1 - \frac{Z_2}{Z}\right)\left(p_1MZ + p_2VZ - d_7Z\right).\end{aligned} \tag{4.2}$$

After collecting the terms of Eq. (4.2) and using the following steady state conditions at E_2

$$\begin{cases}\sigma_1 = \beta_m X_2M_2 + d_1X_2,\\ \beta_m X_2M_2 = d_2I_2,\\ d_2I_2 = \dfrac{d_3}{\eta}M_2 + \dfrac{q_1}{\eta}M_2Z_2,\\ \sigma_2 = d_4Y_2,\\ \dfrac{q_1}{\eta}M_2Z_2 = \dfrac{q_1d_7}{\eta p_1}Z_2,\end{cases}$$

we obtain

$$\begin{aligned}\frac{d\Pi_2}{dt} =& \left(1 - \frac{X_2}{X}\right)\left(d_1X_2 - d_1X\right) + \frac{eq_1p_2}{\eta p_1 q_2 d_5}\left(1 - \frac{Y_2}{Y}\right)\left(d_4Y_2 - d_4Y\right) + 3\beta_m X_2M_2 - \beta_m X_2M_2\frac{X_2}{X}\\ &- \beta_m X_2M_2\frac{XI_2M}{X_2IM_2} - \beta_m X_2M_2\frac{IM_2}{I_2M} + \left(\frac{eq_1p_2\beta_v}{\eta p_1 q_2 d_5}Y_2 - \frac{q_1p_2d_6}{\eta p_1 q_2} - \frac{q_1p_2}{\eta p_1}Z_2\right)V.\end{aligned} \tag{4.3}$$

Now, we must calculate the last term of Eq. (4.3). From Theorem 2, we obtain

$$\begin{aligned}\frac{eq_1p_2\beta_v}{\eta p_1 q_2 d_5}Y_2 - \frac{q_1p_2d_6}{\eta p_1 q_2} - \frac{q_1p_2}{\eta p_1}Z_2 =& \frac{e\beta_v q_1\sigma_2 p_2}{\eta p_1 q_2 d_4 d_5} - \frac{q_1p_2d_6}{\eta p_1 q_2} - \frac{q_1p_2\left(\eta\beta_m\sigma_1p_1 - p_1d_1d_3 - \beta_m d_3d_7\right)}{\eta p_1 q_1(p_1d_1 + \beta_m d_7)}\\ =& \frac{q_1p_2d_6}{\eta p_1 q_2}\left[\frac{e\beta_v q_1\sigma_2 + q_2d_3d_4d_5}{q_1d_4d_5d_6} - 1 - \frac{\eta\beta_m\sigma_1p_1q_2}{q_1d_6(p_1d_1 + \beta_m d_7)}\right]\\ =& \frac{q_1p_2d_6}{\eta p_1 q_2}\left[\mathcal{R}_p - 1 - \frac{\eta\beta_m\sigma_1p_1q_2}{q_1d_6(p_1d_1 + \beta_m d_7)}\right].\end{aligned}$$

Thus, the derivative in (4.3) is rewritten as follows:

$$\frac{d\Pi_2}{dt} = -\frac{d_1 (X - X_2)^2}{X} - \frac{eq_1p_2d_4}{\eta p_1q_2d_5}\frac{(Y - Y_2)^2}{Y} + \beta_m X_2 M_2\Big(3 - \frac{X_2}{X} - \frac{IM_2}{I_2M} - \frac{XI_2M}{X_2IM_2}\Big) + \frac{q_1p_2d_6}{\eta p_1q_2}\Big(\mathcal{R}_p - 1 - \frac{\eta\beta_m\sigma_1p_1q_2}{q_1d_6(p_1d_1 + \beta_m d_7)}\Big)V.$$

Importantly, $\frac{d\Pi_2}{dt} \leq 0$ if $\mathcal{R}_p \leq 1 + \frac{\eta\beta_m\sigma_1p_1q_2}{q_1d_6(p_1d_1 + \beta_m d_7)}$. In addition, $\frac{d\Pi_2}{dt} = 0$ when $X = X_2$, $I = I_2$, $M = M_2$, $Y = Y_2$, and $V = 0$. We easily show that the elements of $S_2^{'}$ satisfy $N = 0$ and $Z = Z_2$. This result implies that $S_2^{'} = \{E_2\}$. Therefore, the global asymptotic stability of E_2 follows LaSalle's invariance principle [41] when $\mathcal{R}_{1m} > 1$ and $\mathcal{R}_p \leq 1 + \frac{\eta\beta_m\sigma_1p_1q_2}{q_1d_6(p_1d_1 + \beta_m d_7)}$. □

Theorem 6. *Suppose that $\mathcal{R}_{0v} > 1$. Then, the steady state E_3 is GAS if $\mathcal{R}_{0m} \leq 1$ and $\mathcal{R}_{1v} \leq 1$.*

Proof. We establish a Lyapunov function as follows:

$$\Pi_3(t) = X_3\left(\frac{X}{X_3} - 1 - \ln\frac{X}{X_3}\right) + I + \frac{1}{\eta}M + \frac{eq_1p_2}{\eta p_1q_2d_5}Y_3\left(\frac{Y}{Y_3} - 1 - \ln\frac{Y}{Y_3}\right) + \frac{eq_1p_2}{\eta p_1q_2d_5}N_3\left(\frac{N}{N_3} - 1 - \ln\frac{N}{N_3}\right) + \frac{q_1p_2}{\eta p_1q_2}V_3\left(\frac{V}{V_3} - 1 - \ln\frac{V}{V_3}\right) + \frac{q_1}{\eta p_1}Z.$$

Then, we obtain

$$\begin{aligned}\frac{d\Pi_3}{dt} =& \Big(1 - \frac{X_3}{X}\Big)\Big(\sigma_1 - \beta_m XM - d_1X\Big) + \beta_m XM - d_2I \\ &+ \frac{1}{\eta}\Big(\eta d_2I - q_1MZ - d_3M\Big) + \frac{eq_1p_2}{\eta p_1q_2d_5}\Big(1 - \frac{Y_3}{Y}\Big)\Big(\sigma_2 - \beta_v YV - d_4Y\Big) \\ &+ \frac{eq_1p_2}{\eta p_1q_2d_5}\Big(1 - \frac{N_3}{N}\Big)\Big(\beta_v YV - d_5N\Big) + \frac{q_1p_2}{\eta p_1q_2}\Big(1 - \frac{V_3}{V}\Big)\Big(eN - q_2VZ - d_6V\Big) \\ &+ \frac{q_1}{\eta p_1}\Big(p_1MZ + p_2VZ - d_7Z\Big). \end{aligned} \tag{4.4}$$

Using the steady state conditions at E_3

$$\begin{cases}\sigma_1 = d_1X_3, \\ \sigma_2 = \beta_v Y_3V_3 + d_4Y_3, \\ \frac{eq_1p_2\beta_v}{\eta p_1q_2d_5}Y_3V_3 = \frac{eq_1p_2}{\eta p_1q_2}N_3, \\ \frac{eq_1p_2}{\eta p_1q_2}N_3 = \frac{q_1p_2d_6}{\eta p_1q_2}V_3,\end{cases}$$

the derivative in (4.4) is transformed to

$$\begin{aligned}\frac{d\Pi_3}{dt} =&\left(1-\frac{X_3}{X}\right)\left(d_1X_3-d_1X\right)+\frac{eq_1p_2}{\eta p_1q_2d_5}\left(1-\frac{Y_3}{Y}\right)\left(d_4Y_3-d_4Y\right)+3\frac{eq_1p_2\beta_v}{\eta p_1q_2d_5}\beta_vY_3V_3\\&-\frac{eq_1p_2}{\eta p_1q_2d_5}\beta_vY_3V_3\frac{Y_3}{Y}-\frac{eq_1p_2}{\eta p_1q_2d_5}\beta_vY_3V_3\frac{NV_3}{N_3V}-\frac{eq_1p_2}{\eta p_1q_2d_5}\beta_vY_3V_3\frac{YN_3V}{Y_3NV_3}+\left(\beta_mX_3-\frac{d_3}{\eta}\right)M\\&+\left(\frac{q_1p_2}{\eta p_1}-\frac{q_1d_7}{\eta p_1}\right)Z\\=&-\frac{d_1\left(X-X_3\right)^2}{X}-\frac{eq_1p_2d_4}{\eta p_1q_2d_5}\frac{\left(Y-Y_3\right)^2}{Y}+\frac{eq_1p_2}{\eta p_1q_2d_5}\beta_vY_3V_3\left(3-\frac{Y_3}{Y}-\frac{NV_3}{N_3V}-\frac{YN_3V}{Y_3NV_3}\right)\\&+\frac{d_3}{\eta}(\mathcal{R}_{0m}-1)M+\frac{q_1(p_2d_4+\beta_vd_7)}{\eta p_1\beta_v}(\mathcal{R}_{1v}-1)Z.\end{aligned}$$

This result implies that $\frac{d\Pi_3}{dt}\leq 0$ if $\mathcal{R}_{0m}\leq 1$ and $\mathcal{R}_{1v}\leq 1$. Additionally, $\frac{d\Pi_3}{dt}=0$ when $X=X_3$, $I=0$, $M=0$, $Y=Y_3$, $N=N_3$, $V=V_3$, and $Z=0$. Thus, $S_3^{'}=\{E_3\}$. Accordingly, LaSalle's invariance principle [41] ensures the global asymptotic stability of E_3 when $\mathcal{R}_{0v}>1$, $\mathcal{R}_{0m}\leq 1$ and $\mathcal{R}_{1v}\leq 1$. □

Theorem 7. *Assume that $\mathcal{R}_{1v}>1$. Then, the steady state E_4 is GAS if $\mathcal{R}_{0m}+\frac{q_1d_6}{q_2d_3}\leq 1+\frac{q_1d_6}{q_2d_3}\mathcal{R}_{1v}$.*

Proof. We consider the following Lyapunov function:

$$\begin{aligned}\Pi_4(t) =&X_4\left(\frac{X}{X_4}-1-\ln\frac{X}{X_4}\right)+I+\frac{1}{\eta}M+\frac{eq_1p_2}{\eta p_1q_2d_5}Y_4\left(\frac{Y}{Y_4}-1-\ln\frac{Y}{Y_4}\right)+\frac{eq_1p_2}{\eta p_1q_2d_5}N_4\left(\frac{N}{N_4}-1-\ln\frac{N}{N_4}\right)\\&+\frac{q_1p_2}{\eta p_1q_2}V_4\left(\frac{V}{V_4}-1-\ln\frac{V}{V_4}\right)+\frac{q_1}{\eta p_1}Z_4\left(\frac{Z}{Z_4}-1-\ln\frac{Z}{Z_4}\right).\end{aligned}$$

Then, we obtain

$$\begin{aligned}\frac{d\Pi_4}{dt} =&\left(1-\frac{X_4}{X}\right)\left(\sigma_1-\beta_mXM-d_1X\right)+\beta_mXM-d_2I\\&+\frac{1}{\eta}\left(\eta d_2I-q_1MZ-d_3M\right)+\frac{eq_1p_2}{\eta p_1q_2d_5}\left(1-\frac{Y_4}{Y}\right)\left(\sigma_2-\beta_vYV-d_4Y\right)\\&+\frac{eq_1p_2}{\eta p_1q_2d_5}\left(1-\frac{N_4}{N}\right)\left(\beta_vYV-d_5N\right)+\frac{q_1p_2}{\eta p_1q_2}\left(1-\frac{V_4}{V}\right)\left(eN-q_2VZ-d_6V\right)\\&+\frac{q_1}{\eta p_1}\left(1-\frac{Z_4}{Z}\right)\left(p_1MZ+p_2VZ-d_7Z\right).\end{aligned}\tag{4.5}$$

The steady state conditions at E_4 are written as follows:

$$\begin{cases}\sigma_1=d_1X_4,\\ \sigma_2=\beta_vY_4V_4+d_4Y_4,\\ \frac{eq_1p_2\beta_v}{\eta p_1q_2d_5}Y_4V_4=\frac{eq_1p_2}{\eta p_1q_2}N_4,\\ \frac{eq_1p_2}{\eta p_1q_2}N_4=\frac{q_1p_2d_6}{\eta p_1q_2}V_4+\frac{q_1p_2}{\eta p_1}V_4Z_4,\\ \frac{q_1p_2}{\eta p_1}V_4Z_4=\frac{q_1d_7}{\eta p_1}Z_4.\end{cases}\tag{4.6}$$

Using Eq. (4.6) to collect the terms of Eq. (4.5), we obtain

$$\begin{aligned}\frac{d\Pi_4}{dt} =& -\frac{d_1\,(X-X_4)^2}{X} - \frac{eq_1p_2d_4}{\eta p_1q_2d_5}\frac{(Y-Y_4)^2}{Y} + \frac{eq_1p_2}{\eta p_1q_2d_5}\beta_v Y_4V_4\Big(3-\frac{Y_4}{Y}-\frac{NV_4}{N_4V}-\frac{YN_4V}{Y_4NV_4}\Big)\\ &+(\beta_m X_4-\frac{d_3}{\eta}-\frac{q_1}{\eta}Z_4)M\\ =& -\frac{d_1\,(X-X_4)^2}{X} - \frac{eq_1p_2d_4}{\eta p_1q_2d_5}\frac{(Y-Y_4)^2}{Y} + \frac{eq_1p_2}{\eta p_1q_2d_5}\beta_v Y_4V_4\Big(3-\frac{Y_4}{Y}-\frac{NV_4}{N_4V}-\frac{YN_4V}{Y_4NV_4}\Big)\\ &+\frac{d_3}{\eta}\Big(\mathcal{R}_{0m}+\frac{q_1d_6}{q_2d_3}-1-\frac{q_1d_6}{q_2d_3}\mathcal{R}_{1v}\Big)M.\end{aligned}$$

Hence, $\frac{d\Pi_4}{dt} \le 0$ if $\mathcal{R}_{0m}+\frac{q_1d_6}{q_2d_3} \le 1+\frac{q_1d_6}{q_2d_3}\mathcal{R}_{1v}$. In addition, $\frac{d\Pi_4}{dt}=0$ when $X=X_4$, $M=0$, $Y=Y_4$, $N=N_4$, and $V=V_4$. In this case, $S_4^{'}=\{E_4\}$. According to LaSalle's invariance principle [41], the steady state E_4 is GAS if $\mathcal{R}_{1v}>1$ and $\mathcal{R}_{0m}+\frac{q_1d_6}{q_2d_3} \le 1+\frac{q_1d_6}{q_2d_3}\mathcal{R}_{1v}$. □

Theorem 8. *Suppose that $\mathcal{R}_{0m}>1$ and $\mathcal{R}_{0v}>1$. Then, the steady state E_5 is GAS if $\mathcal{R}_{0m}+\frac{e\beta_m\sigma_2p_2}{p_1d_1d_5d_6} \le 1+\frac{\beta_m(p_2d_4+\beta_vd_7)}{\beta_vp_1d_1}$.*

Proof. We consider the following Lyapunov function:

$$\begin{aligned}\Pi_5(t) =& X_5\left(\frac{X}{X_5}-1-\ln\frac{X}{X_5}\right)+I_5\left(\frac{I}{I_5}-1-\ln\frac{I}{I_5}\right)+\frac{1}{\eta}M_5\left(\frac{M}{M_5}-1-\ln\frac{M}{M_5}\right)+\frac{eq_1p_2}{\eta p_1q_2d_5}Y_5\left(\frac{Y}{Y_5}-1-\ln\frac{Y}{Y_5}\right)\\ &+\frac{eq_1p_2}{\eta p_1q_2d_5}N_5\left(\frac{N}{N_5}-1-\ln\frac{N}{N_5}\right)+\frac{q_1p_2}{\eta p_1q_2}V_5\left(\frac{V}{V_5}-1-\ln\frac{V}{V_5}\right)+\frac{q_1}{\eta p_1}Z.\end{aligned}$$

Then, we obtain

$$\begin{aligned}\frac{d\Pi_5}{dt} =& \Big(1-\frac{X_5}{X}\Big)\Big(\sigma_1-\beta_mXM-d_1X\Big)+\Big(1-\frac{I_5}{I}\Big)\Big(\beta_mXM-d_2I\Big)\\ &+\frac{1}{\eta}\Big(1-\frac{M_5}{M}\Big)\Big(\eta d_2I-q_1MZ-d_3M\Big)+\frac{eq_1p_2}{\eta p_1q_2d_5}\Big(1-\frac{Y_5}{Y}\Big)\Big(\sigma_2-\beta_vYV-d_4Y\Big)\\ &+\frac{eq_1p_2}{\eta p_1q_2d_5}\Big(1-\frac{N_5}{N}\Big)\Big(\beta_vYV-d_5N\Big)+\frac{q_1p_2}{\eta p_1q_2}\Big(1-\frac{V_5}{V}\Big)\Big(eN-q_2VZ-d_6V\Big)\\ &+\frac{q_1}{\eta p_1}\Big(p_1MZ+p_2VZ-d_7Z\Big).\end{aligned} \tag{4.7}$$

The steady state conditions for E_5 are written as follows:

$$\begin{cases} \sigma_1 = d_1 X_5 + \beta_m X_5 M_5, \\ \beta_m X_5 M_5 = d_2 I_5, \\ d_2 I_5 = \dfrac{d_3}{\eta} M_5, \\ \sigma_2 = \beta_v Y_5 V_5 + d_4 Y_5, \\ \dfrac{e q_1 p_2 \beta_v}{\eta p_1 q_2 d_5} Y_5 V_5 = \dfrac{e q_1 p_2}{\eta p_1 q_2} N_5, \\ \dfrac{e q_1 p_2}{\eta p_1 q_2} N_5 = \dfrac{q_1 p_2 d_6}{\eta p_1 q_2} V_5. \end{cases}$$

Using the aforementioned conditions, the derivative in (4.7) is transformed into

$$\begin{aligned} \frac{d\Pi_5}{dt} =& -\frac{d_1 (X - X_5)^2}{X} - \frac{e q_1 p_2 d_4}{\eta p_1 q_2 d_5} \frac{(Y - Y_5)^2}{Y} + \beta_m X_5 M_5 \Big(3 - \frac{X_5}{X} - \frac{I M_5}{I_5 M} - \frac{X I_5 M}{X_5 I M_5}\Big) \\ &+ \frac{e q_1 p_2}{\eta p_1 q_2 d_5} \beta_v Y_5 V_5 \Big(3 - \frac{Y_5}{Y} - \frac{N V_5}{N_5 V} - \frac{Y N_5 V}{Y_5 N V_5}\Big) + \Big(\frac{q_1}{\eta} M_5 + \frac{q_1 p_2}{\eta p_1} V_5 - \frac{q_1 d_7}{\eta p_1}\Big) Z. \end{aligned} \tag{4.8}$$

We evaluate the last term in (4.8) by computing

$$\begin{aligned} \frac{q_1}{\eta} M_5 + \frac{q_1 p_2}{\eta p_1} V_5 - \frac{q_1 d_7}{\eta p_1} =& \frac{q_1 \sigma_1}{d_3} + \frac{e q_1 \sigma_2 p_2}{\eta p_1 d_5 d_6} - \frac{q_1 d_1}{\eta \beta_m} - \frac{q_1 p_2 d_4}{\eta p_1 \beta_v} - \frac{q_1 d_7}{\eta p_1} \\ =& \frac{q_1 d_1}{\eta \beta_m} \Big[\frac{\eta \sigma_1 \beta_m}{d_1 d_3} + \frac{e \beta_m \sigma_2 p_2}{p_1 d_1 d_5 d_6} - 1 - \frac{\beta_m (p_2 d_4 + \beta_v d_7)}{\beta_v p_1 d_1} \Big] \\ =& \frac{q_1 d_1}{\eta \beta_m} \Big[\mathcal{R}_{0m} + \frac{e \beta_m \sigma_2 p_2}{p_1 d_1 d_5 d_6} - 1 - \frac{\beta_m (p_2 d_4 + \beta_v d_7)}{\beta_v p_1 d_1} \Big]. \end{aligned}$$

Thus, we obtain

$$\begin{aligned} \frac{d\Pi_5}{dt} =& -\frac{d_1 (X - X_5)^2}{X} - \frac{e q_1 p_2 d_4}{\eta p_1 q_2 d_5} \frac{(Y - Y_5)^2}{Y} + \beta_m X_5 M_5 \Big(3 - \frac{X_5}{X} - \frac{I M_5}{I_5 M} - \frac{X I_5 M}{X_5 I M_5}\Big) \\ &+ \frac{e q_1 p_2}{\eta p_1 q_2 d_5} \beta_v Y_5 V_5 \Big(3 - \frac{Y_5}{Y} - \frac{N V_5}{N_5 V} - \frac{Y N_5 V}{Y_5 N V_5}\Big) + \Big(\mathcal{R}_{0m} + \frac{e \beta_m \sigma_2 p_2}{p_1 d_1 d_5 d_6} - 1 - \frac{\beta_m (p_2 d_4 + \beta_v d_7)}{\beta_v p_1 d_1}\Big) Z. \end{aligned}$$

Hence, $\dfrac{d\Pi_5}{dt} \leq 0$ if $\mathcal{R}_{0m} + \dfrac{e \beta_m \sigma_2 p_2}{p_1 d_1 d_5 d_6} \leq 1 + \dfrac{\beta_m (p_2 d_4 + \beta_v d_7)}{\beta_v p_1 d_1}$. Additionally, $\dfrac{d\Pi_5}{dt} = 0$ when $X = X_5$, $I = I_5$, $M = M_5$, $Y = Y_5$, $N = N_5$, $V = V_5$, and $Z = 0$. Thus, $S_5^{'} = \{E_5\}$. According to LaSalle's invariance principle [41], E_5 is GAS if $\mathcal{R}_{0m} > 1$, $\mathcal{R}_{0v} > 1$, and $\mathcal{R}_{0m} + \dfrac{e \beta_m \sigma_2 p_2}{p_1 d_1 d_5 d_6} \leq 1 + \dfrac{\beta_m (p_2 d_4 + \beta_v d_7)}{\beta_v p_1 d_1}$. □

Theorem 9. *Suppose that* $\mathcal{R}_p > 1 + \dfrac{\eta \beta_m \sigma_1 p_1 q_2}{q_1 d_6 (p_1 d_1 + \beta_m d_7)}$, $\mathcal{R}_{0m} + \dfrac{q_1 d_6}{q_2 d_3} > 1 + \dfrac{q_1 d_6}{q_2 d_3} \mathcal{R}_{1v}$, *and* $\mathcal{R}_{0m} + \dfrac{e \beta_m \sigma_2 p_2}{p_1 d_1 d_5 d_6} > 1 + \dfrac{\beta_m (p_2 d_4 + \beta_v d_7)}{\beta_v p_1 d_1}$. *Then, the steady state* E_6 *is GAS.*

Proof. We consider the following Lyapunov function:

$$\Pi_6(t) = X_6\left(\frac{X}{X_6} - 1 - \ln\frac{X}{X_6}\right) + I_6\left(\frac{I}{I_6} - 1 - \ln\frac{I}{I_6}\right) + \frac{1}{\eta}M_6\left(\frac{M}{M_6} - 1 - \ln\frac{M}{M_6}\right) + \frac{eq_1p_2}{\eta p_1q_2d_5}Y_6\left(\frac{Y}{Y_6} - 1 - \ln\frac{Y}{Y_6}\right) + \frac{eq_1p_2}{\eta p_1q_2d_5}N_6\left(\frac{N}{N_6} - 1 - \ln\frac{N}{N_6}\right) + \frac{q_1p_2}{\eta p_1q_2}V_6\left(\frac{V}{V_6} - 1 - \ln\frac{V}{V_6}\right) + \frac{q_1}{\eta p_1}Z_6\left(\frac{Z}{Z_6} - 1 - \ln\frac{Z}{Z_6}\right).$$

By taking the time derivative, we obtain

$$\begin{aligned}\frac{d\Pi_6}{dt} =& \left(1 - \frac{X_6}{X}\right)\left(\sigma_1 - \beta_m XM - d_1X\right) + \left(1 - \frac{I_6}{I}\right)\left(\beta_m XM - d_2I\right)\\ &+ \frac{1}{\eta}\left(1 - \frac{M_6}{M}\right)\left(\eta d_2I - q_1MZ - d_3M\right) + \frac{eq_1p_2}{\eta p_1q_2d_5}\left(1 - \frac{Y_6}{Y}\right)\left(\sigma_2 - \beta_v YV - d_4Y\right)\\ &+ \frac{eq_1p_2}{\eta p_1q_2d_5}\left(1 - \frac{N_6}{N}\right)\left(\beta_v YV - d_5N\right) + \frac{q_1p_2}{\eta p_1q_2}\left(1 - \frac{V_6}{V}\right)\left(eN - q_2VZ - d_6V\right)\\ &+ \frac{q_1}{\eta p_1}\left(1 - \frac{Z_6}{Z}\right)\left(p_1MZ + p_2VZ - d_7Z\right). \end{aligned} \tag{4.9}$$

The equilibrium conditions at E_6 are written as follows:

$$\begin{cases}\sigma_1 = d_1X_6 + \beta_m X_6M_6,\\ \beta_m X_6M_6 = d_2I_6,\\ d_2I_6 = \dfrac{d_3}{\eta}M_6 + \dfrac{q_1}{\eta}M_6Z_6,\\ \sigma_2 = \beta_v Y_6V_6 + d_4Y_6,\\ \dfrac{eq_1p_2\beta_v}{\eta p_1q_2d_5}Y_6V_6 = \dfrac{eq_1p_2}{\eta p_1q_2}N_6,\\ \dfrac{eq_1p_2}{\eta p_1q_2}N_6 = \dfrac{q_1p_2d_6}{\eta p_1q_2}V_6 + \dfrac{q_1p_2}{\eta p_1}V_6Z_6,\\ \dfrac{q_1}{\eta}M_6Z_6 + \dfrac{q_1p_2}{\eta p_1}V_6Z_6 = \dfrac{q_1d_7}{\eta p_1}Z_6.\end{cases}$$

Utilizing the aforementioned conditions, Eq. (4.9) becomes

$$\begin{aligned}\frac{d\Pi_6}{dt} =& -\frac{d_1\left(X - X_6\right)^2}{X} - \frac{eq_1p_2d_4}{\eta p_1q_2d_5}\frac{\left(Y - Y_6\right)^2}{Y} + \beta_m X_6M_6\left(3 - \frac{X_6}{X} - \frac{IM_6}{I_6M} - \frac{XI_6M}{X_6IM_6}\right)\\ &+ \frac{eq_1p_2}{\eta p_1q_2d_5}\beta_v Y_6V_6\left(3 - \frac{Y_6}{Y} - \frac{NV_6}{N_6V} - \frac{YN_6V}{Y_6NV_6}\right).\end{aligned}$$

Hence, we have $\dfrac{d\Pi_6}{dt} \le 0$. Furthermore, $\dfrac{d\Pi_6}{dt} = 0$ when $X = X_6$, $I = I_6$, $M = M_6$, $Y = Y_6$, $N = N_6$, $V = V_6$, and $Z = Z_6$. Thus, $S_6^{'} = \{E_6\}$. Based on LaSalle's invariance principle [41], E_6 is GAS when $\mathcal{R}_p > 1 + \dfrac{\eta\beta_m\sigma_1p_1q_2}{q_1d_6(p_1d_1 + \beta_md_7)}$, $\mathcal{R}_{0m} + \dfrac{q_1d_6}{q_2d_3} > 1 + \dfrac{q_1d_6}{q_2d_3}\mathcal{R}_{1v}$, and $\mathcal{R}_{0m} + \dfrac{e\beta_m\sigma_2p_2}{p_1d_1d_5d_6} > 1 + \dfrac{\beta_m(p_2d_4 + \beta_vd_7)}{\beta_vp_1d_1}$. □

All steady states with their existence and stability conditions are summarized in Table 1.

5. Numerical simulations

In this section, we present some numerical simulations to verify the results of the previous sections. These numerical simulations are performed using MATLAB solver ode45 with the following sets of initial conditions:

(i) $X(0) = 5, I(0) = 0.0001, M(0) = 0.0002, Y(0) = 10, N(0) = 0.02, V(0) = 0.01, Z(0) = 0.1\times10^{10}$,

(ii) $X(0) = 10, I(0) = 0.0001, M(0) = 0.002, Y(0) = 5, N(0) = 0.03, V(0) = 0.001, Z(0) = 0.2\times10^{10}$,

(iii) $X(0) = 15, I(0) = 0.002, M(0) = 0.003, Y(0) = 1, N(0) = 0.04, V(0) = 0.002, Z(0) = 0.3\times10^{10}$.

The numerical simulations of model (2.1) are divided into seven cases according to the global stability of each of the steady states calculated in Theorem 2. In each case, the values of β_m, β_v, p_1, p_2, and d_7 vary, while the remaining parameters are predetermined as described in Table 2. The seven cases are as follows:

(1) We choose $\beta_m = 2\times10^{-10}$, $\beta_v = 0.1$, $p_1 = 3\times10^{-8}$, $p_2 = 0.96$, and $d_7 = 2\times10^{-1}$ to yield $\mathcal{R}_{0m} = 0.6667 < 1$ and $\mathcal{R}_{0v} = 0.9122 < 1$. This equation implies that the steady state $E_0 = (10\times10^9, 0, 0, 22.41, 0, 0, 0)$ is GAS (see Figure 1), which coincides with Theorem 3. This equation represents the case of a healthy individual who does not suffer from either malaria infection or SARS-CoV-2 infection.

(2) We select $\beta_m = 2\times10^{-9}$, $\beta_v = 0.1$, $p_1 = 2\times10^{-9}$, $p_2 = 0.96$, and $d_7 = 2\times10^{-1}$. Hence, we obtain $\mathcal{R}_{0m} = 6.6667 > 1$, $\mathcal{R}_{0v} = 0.9122 < 1$, and $\mathcal{R}_{1m} = 0.7407 < 1$. Consistent with Theorem 4, the steady state $E_1 = (1.5\times10^9, 4.25\times10^8, 7.08\times10^7, 22.41, 0, 0, 0)$ is GAS (see Figure 2) and represents the case of a patient who only has malaria in the absence of an antibody-mediated immune response.

(3) We take $\beta_m = 2\times10^{-9}$, $\beta_v = 0.1$, $p_1 = 3\times10^{-8}$, $p_2 = 0.96$, and $d_7 = 2\times10^{-1}$. The threshold parameters are obtained as $\mathcal{R}_{1m} = 4.3478 > 1$ and $\mathcal{R}_p = 44.6137 < 1 + \dfrac{\eta\beta_m\sigma_1 p_1 q_2}{q_1 d_6(p_1 d_1 + \beta_m d_7)} = 191.0065$. This calculation implies that the steady state $E_2 = (6.522\times10^9, 1.739\times10^8, 6.667\times10^6, 22.41, 0, 0, 1.607\times10^{10})$ is GAS (see Figure 3), which supports Theorem 5. At this point, the antibody-mediated immune response is activated to eliminate free merozoites from the blood of patients with malaria.

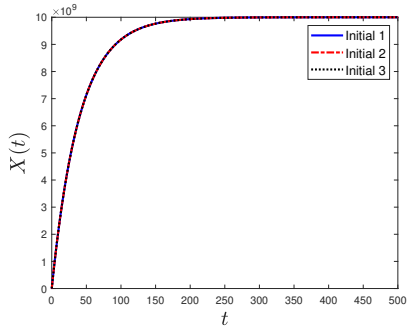
(4) We set $\beta_m = 2\times10^{-10}$, $\beta_v = 0.9$, $p_1 = 3\times10^{-8}$, $p_2 = 0.96$, and $d_7 = 2\times10^{-1}$. This gives $\mathcal{R}_{0v} = 8.2099 > 1$, $\mathcal{R}_{0m} = 0.6667 < 1$, and $\mathcal{R}_{1v} = 0.0436 < 1$. This calculation leads to the global asymptotic stability of the steady state $E_3 = (10\times10^9, 0, 0, 2.73, 0.1789, 0.008, 0)$ as approved by Theorem 6 (see Figure 4). The patient in this case suffered only from SARS-CoV-2 infection, while the antibody-mediated immune response had not yet been activated.

(5) We choose $\beta_m = 2\times10^{-10}$, $\beta_v = 0.9$, $p_1 = 3\times10^{-8}$, $p_2 = 3.9$, and $d_7 = 1\times10^{-2}$. These values produce $\mathcal{R}_{1v} = 2.4821 > 1$, $\mathcal{R}_{0m} + \dfrac{q_1 d_6}{q_2 d_3} = 0.6895 < 1 + \dfrac{e\beta_v q_1 \sigma_2 p_2}{q_2 d_3 d_5(p_2 d_4 + \beta_v d_7)} = 1.0568$.

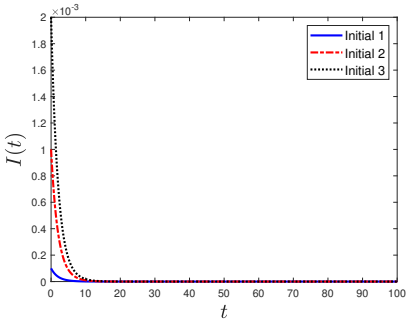
Accordingly, the steady state $E_4 = (10 \times 10^9, 0, 0, 6.775, 0.1421, 0.0026, 1.628 \times 10^8)$ is GAS (see Figure 5). This result is consistent with Theorem 7. At this point, the antibody-mediated immune response is activated to clear SARS-CoV-2 particles from the body of patients with COVID-19, reducing the concentration of SARS-CoV-2 particles.

(6) We consider $\beta_m = 4 \times 10^{-10}$, $\beta_v = 0.9$, $p_1 = 3 \times 10^{-8}$, $p_2 = 0.96$, and $d_7 = 0.8$. This gives $\mathcal{R}_{0m} = 1.3333 > 1$, $\mathcal{R}_{0v} = 8.2099 > 1$, and $\mathcal{R}_{0m} + \frac{e\beta_m\sigma_2 p_2}{p_1 d_1 d_5 d_6} = 1.338 < 1 + \frac{\beta_m(p_2 d_4 + \beta_v d_7)}{\beta_v p_1 d_1} = 1.4272$. Thus, the steady state $E_5 = (7.5 \times 10^9, 1.25 \times 10^8, 2.08 \times 10^7, 2.73, 0.1789, 0.008, 0)$ is GAS (see Figure 6), consistent with Theorem 8. In this situation, SARS-CoV-2/malaria coinfection occurs in the absence of an antibody-mediated immune response. Coinfection increases the concentrations of malaria merozoites and SARS-CoV-2 particles and worsens the medical condition of the patient.

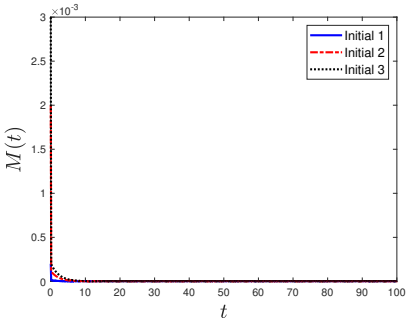
(7) We take $\beta_m = 4 \times 10^{-10}$, $\beta_v = 3.9$, $p_1 = 3 \times 10^{-8}$, $p_2 = 0.5$, and $d_7 = 0.3$. In this case, the threshold parameters are $\mathcal{R}_p = 79.2777 > 1 + \frac{\eta\beta_m\sigma_1 p_1 q_2}{q_1 d_6(p_1 d_1 + \beta_m d_7)} = 51.2316$, $\mathcal{R}_{0m} + \frac{q_1 d_6}{q_2 d_3} = 1.3562 > 1 + \frac{e\beta_v q_1 \sigma_2 p_2}{q_2 d_3 d_5 (p_2 d_4 + \beta_v d_7)} = 1.0003$, and $\mathcal{R}_{0m} + \frac{e\beta_m\sigma_2 p_2}{p_1 d_1 d_5 d_6} = 1.3358 > 1 + \frac{\beta_m(p_2 d_4 + \beta_v d_7)}{\beta_v p_1 d_1} = 1.1601$. Consistent with Theorem 9, the steady state $E_6 = (8.623 \times 10^9, 6.887 \times 10^7, 9.994 \times 10^6, 4.75, 0.1605, 0.0015, 7.185 \times 10^8)$ is GAS (see Figure 7). At this point, the antibody-mediated immune response is directed against both malaria and SARS-CoV-2 infections. This immune response works to reduce the concentrations of both malaria merozoites and viral particles.



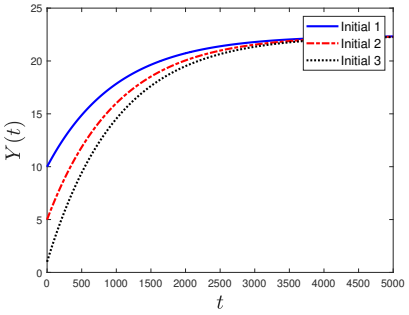
(a) Uninfected red blood cells



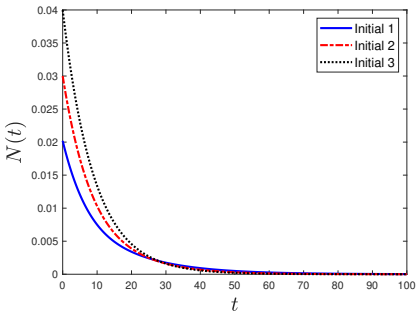
(b) Infected red blood cells



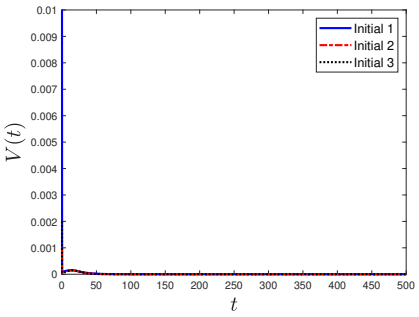
(c) Free merozoites



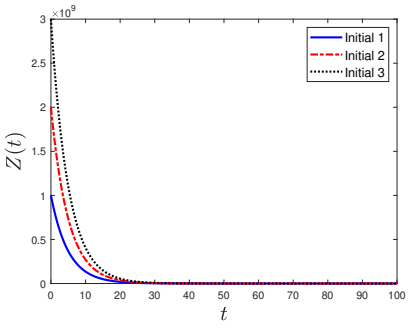
(d) Uninfected epithelial cells



(e) Infected epithelial cells

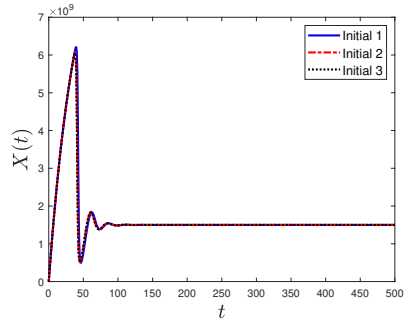


(f) Free SARS-CoV-2 particles

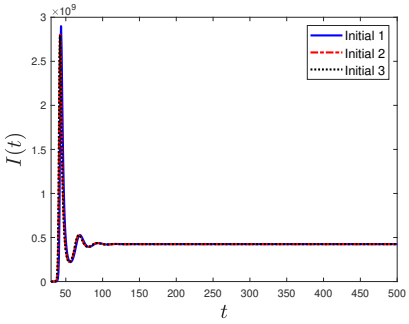


(g) Antibodies

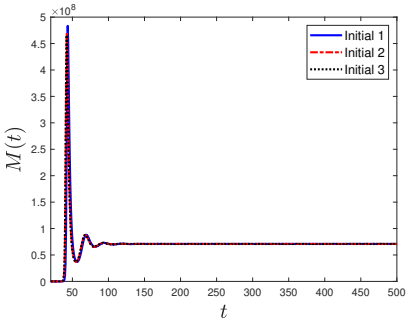
Figure 1. The numerical simulations of model (2.1) for $\beta_m = 2 \times 10^{-10}$, $\beta_v = 0.1$, $p_1 = 3 \times 10^{-8}$, $p_2 = 0.96$, and $d_7 = 2 \times 10^{-1}$ with three different sets of initial conditions. The uninfected steady state $E_0 = (10 \times 10^9, 0, 0, 22.41, 0, 0, 0)$ is GAS.



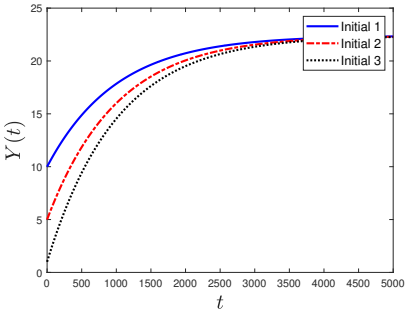
(a) Uninfected red blood cells



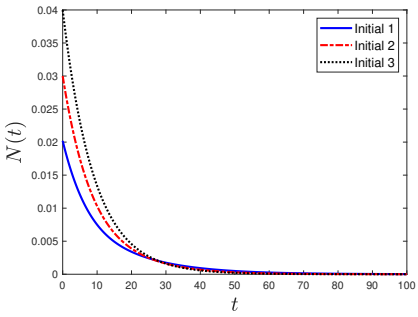
(b) Infected red blood cells



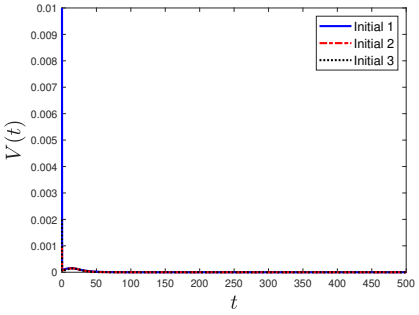
(c) Free merozoites



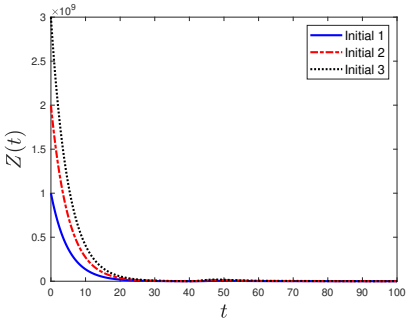
(d) Uninfected epithelial cells



(e) Infected epithelial cells

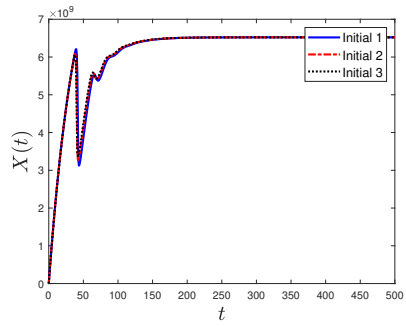


(f) Free SARS-CoV-2 particles

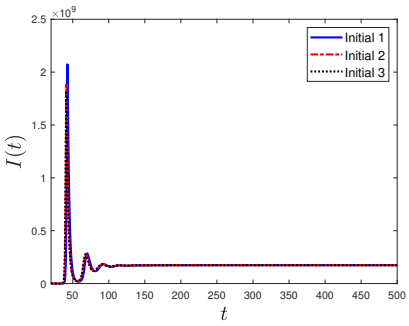


(g) Antibodies

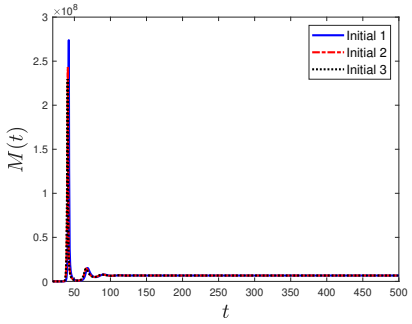
Figure 2. The numerical simulations of model (2.1) for $\beta_m = 2\times10^{-9}, \beta_v = 0.1$, $p_1 = 2\times10^{-9}$, $p_2 = 0.96$, and $d_7 = 2 \times 10^{-1}$ with three different sets of initial conditions. The steady state $E_1 = (1.5 \times 10^9, 4.25 \times 10^8, 7.08 \times 10^7, 22.41, 0, 0, 0)$ is GAS.



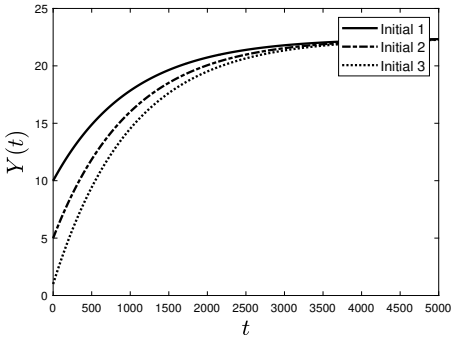
(a) Uninfected red blood cells



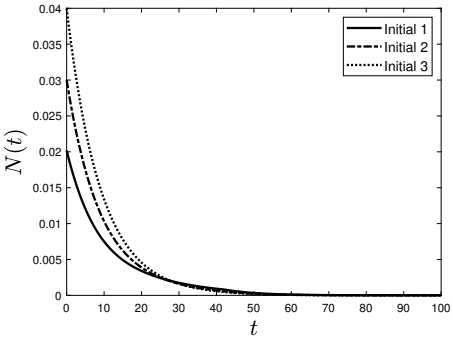
(b) Infected red blood cells



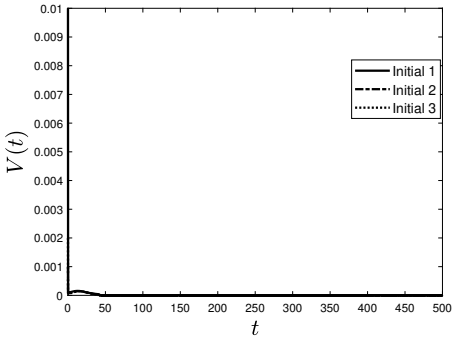
(c) Free merozoites



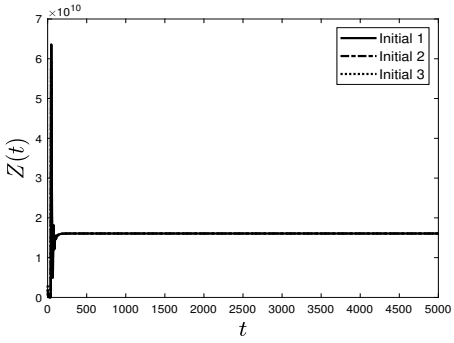
(d) Uninfected epithelial cells



(e) Infected epithelial cells

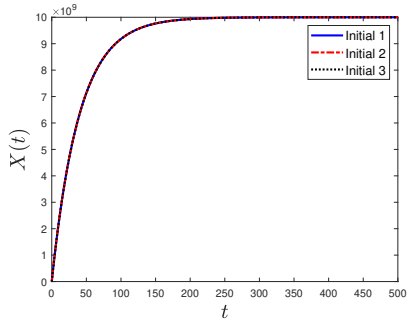


(f) Free SARS-CoV-2 particles

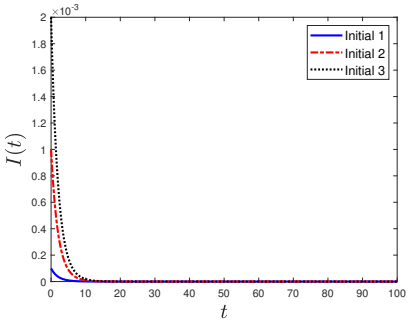


(g) Antibodies

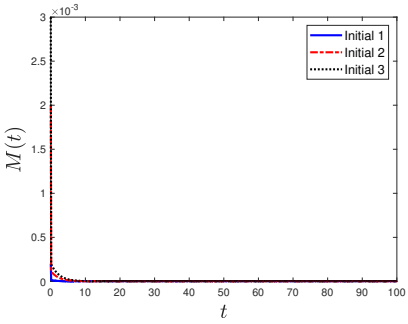
Figure 3. The numerical simulations of model (2.1) for $\beta_m = 2\times10^{-9}, \beta_v = 0.1$, $p_1 = 3\times10^{-8}$, $p_2 = 0.96$, and $d_7 = 2 \times 10^{-1}$ with three different sets of initial conditions. The steady state $E_2 = (6.522 \times 10^9, 1.739 \times 10^8, 6.667 \times 10^6, 22.41, 0, 0, 1.607 \times 10^{10})$ is GAS.



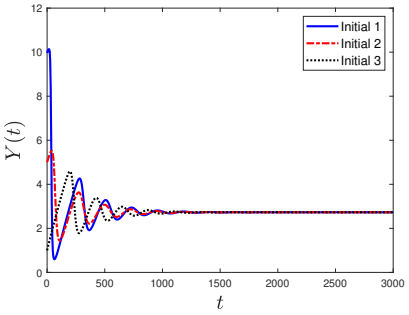
(a) Uninfected red blood cells



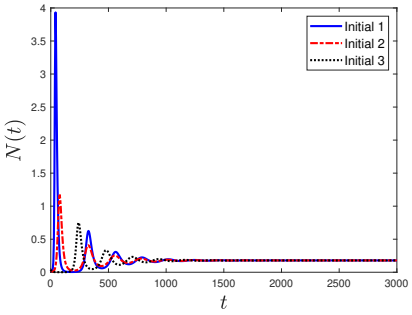
(b) Infected red blood cells



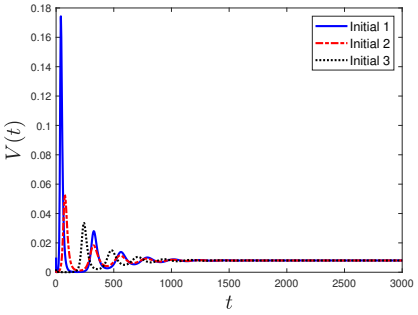
(c) Free merozoites



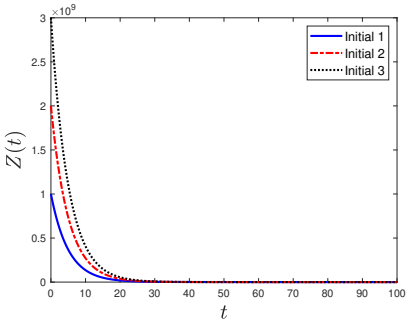
(d) Uninfected epithelial cells



(e) Infected epithelial cells

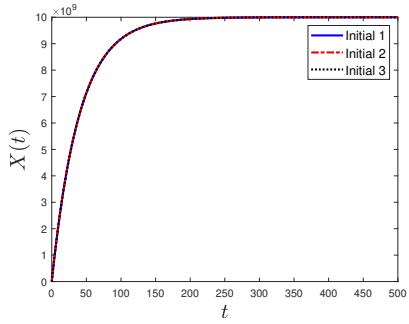


(f) Free SARS-CoV-2 particles

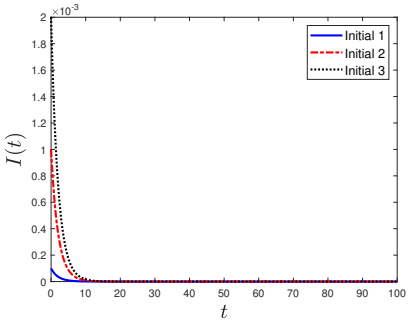


(g) Antibodies

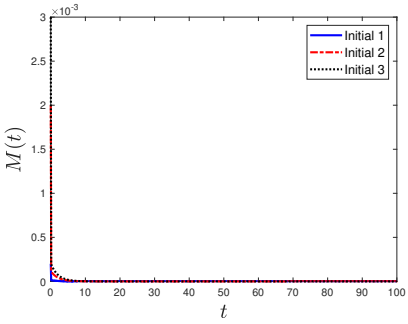
Figure 4. The numerical simulations of model (2.1) for $\beta_m = 2 \times 10^{-10}$, $\beta_v = 0.9$, $p_1 = 3 \times 10^{-8}$, $p_2 = 0.96$, and $d_7 = 2 \times 10^{-1}$ with three different sets of initial conditions. The steady state $E_3 = (10 \times 10^9, 0, 0, 2.73, 0.1789, 0.008, 0)$ is GAS.



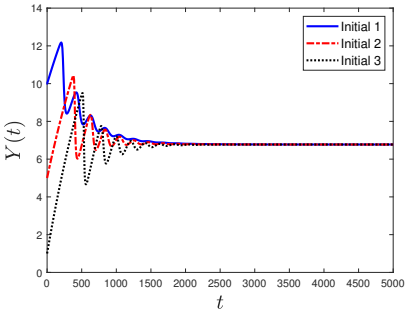
(a) Uninfected red blood cells



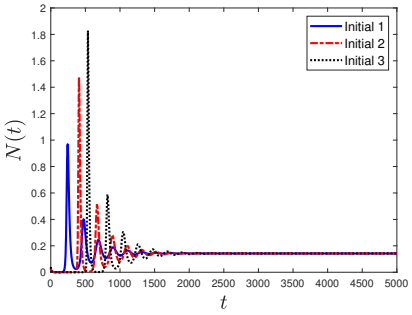
(b) Infected red blood cells



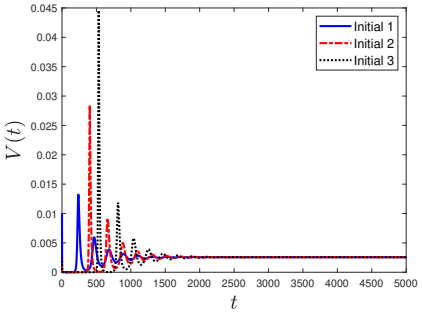
(c) Free merozoites



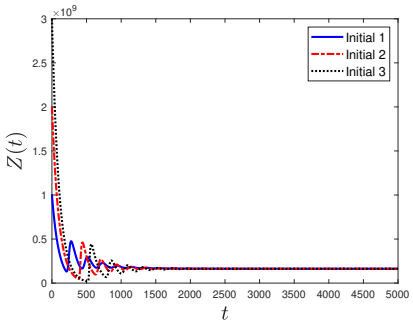
(d) Uninfected epithelial cells



(e) Infected epithelial cells

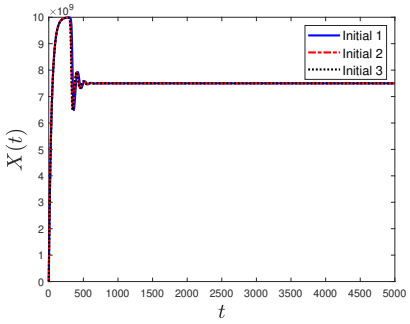


(f) Free SARS-CoV-2 particles

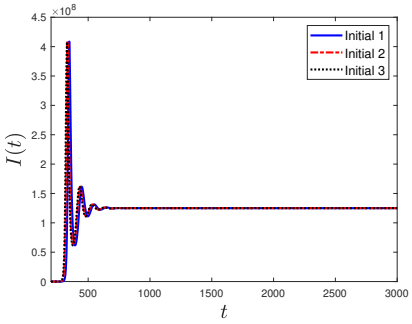


(g) Antibodies

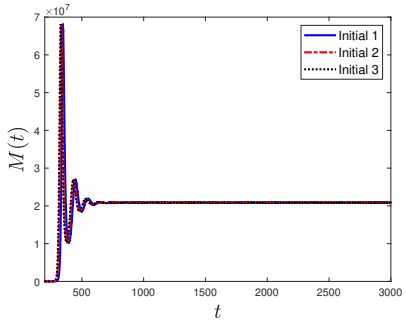
Figure 5. The numerical simulations of model (2.1) for $\beta_m = 2 \times 10^{-10}$, $\beta_v = 0.9$, $p_1 = 3 \times 10^{-8}$, $p_2 = 3.9$, and $d_7 = 1 \times 10^{-2}$ with three different sets of initial conditions. The steady state $E_4 = (10 \times 10^9, 0, 0, 6.775, 0.1421, 0.0026, 1.628 \times 10^8)$ is GAS.



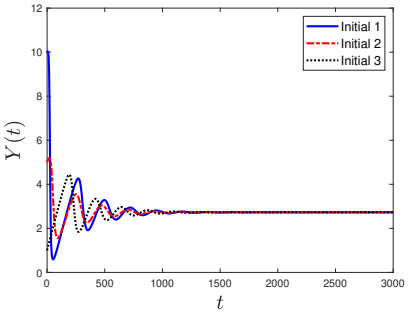
(a) Uninfected red blood cells



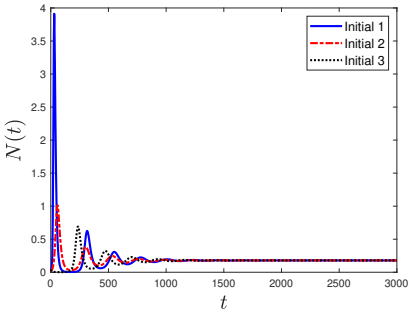
(b) Infected red blood cells



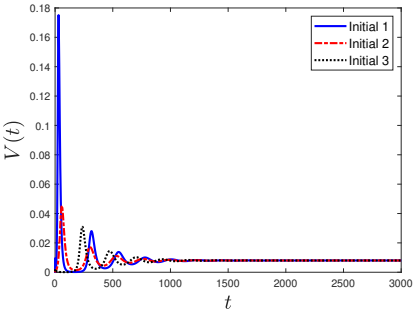
(c) Free merozoites



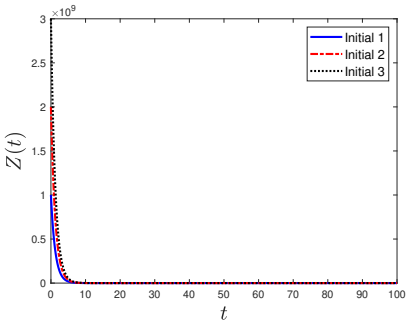
(d) Uninfected epithelial cells



(e) Infected epithelial cells

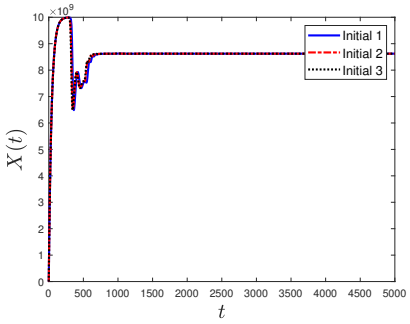


(f) Free SARS-CoV-2 particles

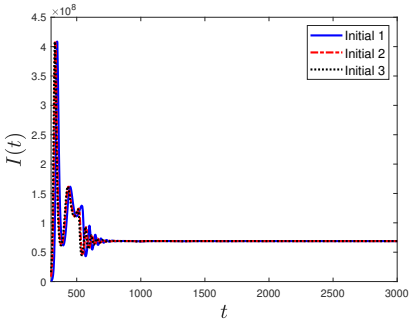


(g) Antibodies

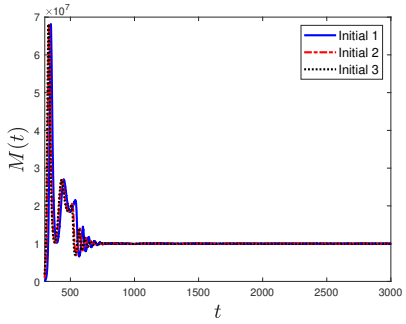
Figure 6. The numerical simulations of model (2.1) for $\beta_m = 4 \times 10^{-10}$, $\beta_v = 0.9$, $p_1 = 3 \times 10^{-8}$, $p_2 = 0.96$, and $d_7 = 0.8$ with three different sets of initial conditions. The steady state $E_5 = (7.5 \times 10^9, 1.25 \times 10^8, 2.08 \times 10^7, 2.73, 0.1789, 0.008, 0)$ is GAS.



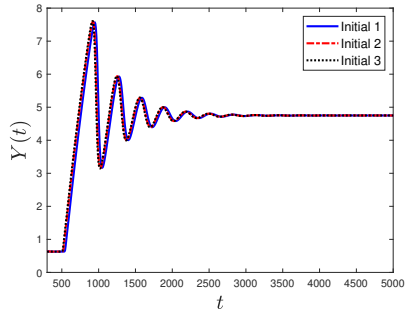
(a) Uninfected red blood cells



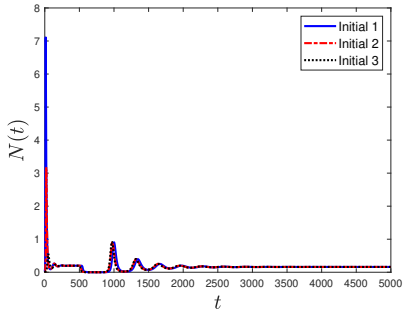
(b) Infected red blood cells



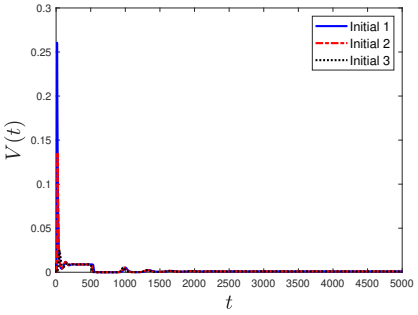
(c) Free merozoites



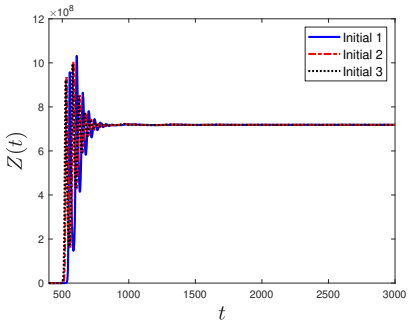
(d) Uninfected epithelial cells



(e) Infected epithelial cells



(f) Free SARS-CoV-2 particles



(g) Antibodies

Figure 7. The numerical simulations of model (2.1) for $\beta_m = 4 \times 10^{-10}$, $\beta_v = 3.9$, $p_1 = 3 \times 10^{-8}$, $p_2 = 0.5$, and $d_7 = 0.3$ with three different sets of initial conditions. The steady state $E_6 = (8.623\times10^9, 6.887\times10^7, 9.994\times10^6, 4.75, 0.1605, 0.000953, 7.185\times10^8)$ is GAS.

Table 1. Stability and conditions for the existence of steady states in model (2.1).

Steady state	Existence conditions	Stability conditions
E_0	-	$\mathcal{R}_{0m} \leq 1$ and $\mathcal{R}_{0v} \leq 1$
E_1	$\mathcal{R}_{0m} > 1$	$\mathcal{R}_{0v} \leq 1$ and $\mathcal{R}_{1m} \leq 1$
E_2	$\mathcal{R}_{1m} > 1$	$\mathcal{R}_p \leq 1 + \frac{\eta\beta_m\sigma_1 p_1 q_2}{q_1 d_6(p_1 d_1 + \beta_m d_7)}$
E_3	$\mathcal{R}_{0v} > 1$	$\mathcal{R}_{0m} \leq 1$ and $\mathcal{R}_{1v} \leq 1$
E_4	$\mathcal{R}_{1v} > 1$	$\mathcal{R}_{0m} + \frac{q_1 d_6}{q_2 d_3} \leq 1 + \frac{q_1 d_6}{q_2 d_3}\mathcal{R}_{1v}$
E_5	$\mathcal{R}_{0m} > 1$ and $\mathcal{R}_{0v} > 1$	$\mathcal{R}_{0m} + \frac{e\beta_m\sigma_2 p_2}{p_1 d_1 d_5 d_6} \leq 1 + \frac{\beta_m(p_2 d_4 + \beta_v d_7)}{\beta_v p_1 d_1}$
E_6	$\mathcal{R}_p > 1 + \frac{\eta\beta_m\sigma_1 p_1 q_2}{q_1 d_6(p_1 d_1 + \beta_m d_7)}$ $\mathcal{R}_{0m} + \frac{q_1 d_6}{q_2 d_3} > 1 + \frac{q_1 d_6}{q_2 d_3}\mathcal{R}_{1v}$ $\mathcal{R}_{0m} + \frac{e\beta_m\sigma_2 p_2}{p_1 d_1 d_5 d_6} > 1 + \frac{\beta_m(p_2 d_4 + \beta_v d_7)}{\beta_v p_1 d_1}$	$\mathcal{R}_p > 1 + \frac{\eta\beta_m\sigma_1 p_1 q_2}{q_1 d_6(p_1 d_1 + \beta_m d_7)}$ $\mathcal{R}_{0m} + \frac{q_1 d_6}{q_2 d_3} > 1 + \frac{q_1 d_6}{q_2 d_3}\mathcal{R}_{1v}$ $\mathcal{R}_{0m} + \frac{e\beta_m\sigma_2 p_2}{p_1 d_1 d_5 d_6} > 1 + \frac{\beta_m(p_2 d_4 + \beta_v d_7)}{\beta_v p_1 d_1}$

6. Discussion

SARS-CoV-2/malaria coinfection represents a real concern, especially in malaria-endemic areas. Thus, a crucial goal is to address the dynamics of this coinfection. Here, we develop a within-host SARS-CoV-2/malaria coinfection model. This model considers the interactions between uninfected red blood cells, infected red blood cells, free merozoites, uninfected epithelial cells, infected epithelial cells, free SARS-CoV-2 particles, and antibodies. The model has seven steady states as follows:

(1) The uninfected steady state E_0 always exists. It is GAS when $\mathcal{R}_{0m} \leq 1$ and $\mathcal{R}_{0v} \leq 1$. This point simulates the condition of a person without SARS-CoV-2 or malaria infections.

(2) The SARS-CoV-2-free steady state without an antibody-mediated immune response E_1 exists if $\mathcal{R}_{0m} > 1$. It is GAS when $\mathcal{R}_{0v} \leq 1$ and $\mathcal{R}_{1m} \leq 1$. This state represents the condition of a malaria monoinfected patient with an inactive immune response.

(3) The SARS-CoV-2-free steady state E_2 exists if $\mathcal{R}_{1m} > 1$. It is GAS when $\mathcal{R}_p \leq 1 + \frac{\eta\beta_m\sigma_1 p_1 q_2}{q_1 d_6(p_1 d_1 + \beta_m d_7)}$. Here, the antibody-mediated immune response is activated to eliminate malaria merozoites.

(4) The malaria-free steady state without an immune response E_3 exists if $\mathcal{R}_{0v} > 1$. It is GAS when $\mathcal{R}_{0m} \leq 1$ and $\mathcal{R}_{1v} \leq 1$. This point simulates the situation of a SARS-CoV-2 monoinfected patient with an inactive immune response.

(5) The malaria-free steady state E_4 exists if $\mathcal{R}_{1v} > 1$. It is GAS when $\mathcal{R}_{0m} + \frac{q_1 d_6}{q_2 d_3} \leq 1 + \frac{e\beta_v q_1 \sigma_2 p_2}{q_2 d_3 d_5(p_2 d_4 + \beta_v d_7)}$. The immune response is activated in SARS-CoV-2 monoinfected patients.

Table 2. Values for the parameters in model (2.1).

Parameter	Description	Value	Reference
σ_1	Recruitment rate of uninfected red blood cells	2.5×10^8	[42]
σ_2	Recruitment rate of uninfected epithelial cells	0.02241	[32]
β_m	Infection rate constant of red blood cells	Varied	–
β_v	Infection rate constant of epithelial cells	Varied	–
η	Number of merozoites released per infected cell	16	[43]
q_1	Removal rate constant of merozoites by antibodies	10^{-8}	[42]
q_2	Removal rate constant of SARS-CoV-2 particles by antibodies	4.88×10^{-8}	[31]
e	Production rate constant of SARS-CoV-2 by infected epithelial cells	0.24	[32]
p_1	Stimulation rate constant of antibodies by merozoites	Varied	–
p_2	Stimulation rate constant of antibodies induced by SARS-CoV-2	Varied	–
d_1	Death rate constant of uninfected red blood cells	0.025	[42]
d_2	Death rate constant of infected red blood cells	0.5	[44]
d_3	Death rate constant of merozoites	48	[42]
d_4	Death rate constant of uninfected epithelial cells	10^{-3}	[32]
d_5	Death rate constant of infected epithelial cells	0.11	[32]
d_6	Death rate constant of SARS-CoV-2 particles	5.36	[32]
d_7	Death rate constant of antibodies	Varied	–

(6) The SARS-CoV-2/malaria coinfection immune-free steady state E_5 exists if $\mathcal{R}_{0m} > 1$ and $\mathcal{R}_{0v} > 1$. It is GAS when $\mathcal{R}_{0m} + \frac{e\beta_m\sigma_2 p_2}{p_1 d_1 d_5 d_6} \leq 1 + \frac{\beta_m(p_2 d_4 + \beta_v d_7)}{\beta_v p_1 d_1}$. Here, coinfection occurs in the absence of an immune response.

(7) The SARS-CoV-2/malaria coinfection steady state E_6 exists, and it is GAS if $\mathcal{R}_p > 1 + \frac{\eta\beta_m\sigma_1 p_1 q_2}{q_1 d_6(p_1 d_1 + \beta_m d_7)}$, $\mathcal{R}_{0m} + \frac{q_1 d_6}{q_2 d_3} > 1 + \frac{q_1 d_6}{q_2 d_3}\mathcal{R}_{1v}$, and $\mathcal{R}_{0m} + \frac{e\beta_m\sigma_2 p_2}{p_1 d_1 d_5 d_6} > 1 + \frac{\beta_m(p_2 d_4 + \beta_v d_7)}{\beta_v p_1 d_1}$. This state represents the occurrence of SARS-CoV-2/malaria coinfection in the presence of an antibody-mediated immune response.

The numerical results are fully consistent with the theoretical results. We found that SARS-CoV-2/malaria coinfection may be protective, as the shared antibody-mediated immune response works by eliminating SARS-CoV-2 particles from the body. This immune response may cause less severe SARS-CoV-2 infection. This result is consistent with many studies that confirmed the positive effect of the

shared antibody immune response [6, 20–22]. However, other studies mentioned an increased risk of death in patients with malaria who are infected with SARS-CoV-2 [2, 16, 19] or that malaria infection does not elicit an antibody immune response against COVID-19 [45]. Therefore, further studies are needed to evaluate the effect of coinfection of malaria and SARS-CoV-2, to inspect the role of the immune system during coinfection and to develop better methods to treat coinfected patients. The model investigated in the present study can be developed (i) using real data to estimate the values for the parameters and examine the accuracy of the model by analyzing other Plasmodium parasites responsible for human infection, (ii) testing the effect of time delays that may occur during infection or the production of malaria merozoites and SARS-CoV-2 particles, (iii) expanding to a multiscale model to obtain a deeper understanding of coinfection dynamics [40,46,47], (iv) considering a coinfection model with more aggressive variants of SARS-CoV-2 (variants of concern), such as alpha, beta, gamma, delta, lambda, and omicron [9,46,47], and (v) incorporating the role of CTLs in killing infected cells.

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Conflict of interest

The authors declare there is no conflict of interest.

References

1. Coronavirus disease (COVID-19), weekly epidemiological update (5 April 2022), World Health Organization (WHO), 2022. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20220405_weekly_epi_update_86.pdf?sfvrsn=3f01a460_4&download=true
2. P. Wilairatana, F. Masangkay, K. Kotepui, G. Milanez, M. Kotepui, Prevalence and characteristics of malaria among COVID-19 individuals: A systematic review, meta-analysis, and analysis of case reports, *PLoS Negl. Trop. Dis.*, **15** (2021), 1–18. https://doi.org/10.1371/journal.pntd.0009766
3. S. M. Akula, S. L. Abrams, L. S. Steelman, S. Candido, M. Librabc, K. Lerpiriyapong, et al., Cancer therapy and treatments during COVID-19 era, *Adv. Biol. Regul.*, **77** (2020), 100739. https://doi.org/10.1016/j.jbior.2020.100739
4. N. Jyotsana, M. King, The impact of COVID-19 on cancer risk and treatment, *Cell. Mol. Bioeng.*, (2020). https://doi.org/10.1155/2016/5230219
5. Y. Cao, *The impact of the hypoxia-VEGF-vascular permeability on COVID-19-infected patients*, *Exploration*, **1** (2021), 1–5. https://doi.org/10.1002/EXP.20210051
6. M. Hussein, A. Albashir, O. Elawad, A. Homeida, Malaria and COVID-19: Unmasking their ties, *Malar. J.*, **19** (2020), 1–10. https://doi.org/10.1186/s12936-020-03541-w

7. F. Di Gennaro, C. Marotta, P. Locantore, D. Pizzol, G. Putoto, Malaria and COVID-19: Common and different findings, *Trop. Med. Infect. Dis.*, **5** (2020), 1–10. https://doi.org/10.3390/tropicalmed5030141
8. Coronavirus disease (COVID-19), Vaccine tracker, World Health Organization (WHO), 2021. Available from: https://covid19.trackvaccines.org/agency/who/
9. A. Hussain, H. Yang, M. Zhang, Q. Liu, G. Alotaibib, M. Irfan, et al., mRNA vaccines for COVID-19 and diverse diseases, *J. Control. Release*, **345** (2022), 314–333. https://doi.org/10.1016/j.jconrel.2022.03.032
10. The U.S. Food and Drug Administration, Know your treatment options for COVID-19, 2021. Available from: https://www.fda.gov/consumers/consumer-updates/know-your-treatment-options-covid-19
11. A. M. Elaiw, A. D. Al Agha, Global analysis of a reaction-diffusion within-host malaria infection model with adaptive immune response, *Mathematics*, **8** (2020), 1–32. https://doi.org/10.3390/math8040563
12. Malaria, Fact sheets, World Health Organization (WHO), 2021. Available from: https://www.who.int/news-room/fact-sheets/detail/malaria
13. C. Sebastiao, C. Gaston, J. Paixao, E. Sacomboio, Z. Neto, J. N. de Vasconcelos, et al., Coinfection between SARS-CoV-2 and vector-borne diseases in Luanda, Angola, *J. Med. Virol.*, **94** (2021), 366–371. https://doi.org/10.1002/jmv.27354
14. A. Pusparani, J. Henrina, A. Cahyadi, Co-infection of COVID-19 and recurrent malaria, *J. Infect. Dev. Ctries.*, **15** (2021), 625–629.https://doi.org/10.3855/jidc.13793
15. P. Chanda-Kapata, N. Kapata, A. Zumla, COVID-19 and malaria: A symptom screening challenge for malaria endemic countries, *Int. J. Infect. Dis.*, **94** (2020), 151–153.https://doi.org/10.1016/j.ijid.2020.04.007
16. O. Indari, B. Baral, K. Muduli, A. Mohanty, N. Swaind, N. K. Mohakud, et al., Insights into Plasmodium and SARS-CoV-2 co-infection driven neurological manifestations, *Biosafety Health*, **3** (2021), 230–234. https://doi.org/10.1016/j.bsheal.2021.04.001
17. N. Mahajan, S. Kesarwani, S. Shinde, A. Nayak, D. N. Modi, S. D. Mahale, et al., Co-infection of malaria and dengue in pregnant women with SARS-CoV-2, *Int. J. Gynaecol. Obstet.*, **151** (2020), 459–462. https://doi.org/10.1002/ijgo.13415
18. N. Mahajan, R. Gajbhiye, S. Bahirat, P. Lokhande, A. Mathe, S. Rathi, et al., Co-infection of malaria and early clearance of SARS-CoV-2 in healthcare workers, *J. Med. Virol.*, **93** (2021), 2431–2438. https://doi.org/10.1002/jmv.26760
19. R. Hussein, M. H. Guedes, N. Ibraheim, M. M. Ali,A. El-Tahir, N. Allam, et al., Impact of COVID-19 and malaria coinfection on clinical outcomes: A retrospective cohort study, *Clin. Microbiol. Infect.*, (2022), S1198-743X(22)00167-7. https://doi.org/10.1016/j.cmi.2022.03.028
20. A. Kalungi, E. Kinyanda, D. Akena, P. Kaleebu, I. Bisangwa, Less severe cases of COVID-19 in Sub-Saharan Africa: Could co-infection or a recent history of Plasmodium falciparum infection be protective?, *Front. Immunol.*, **12** (2021), 1–5. https://doi.org/10.3389/fimmu.2021.565625

21. A. Parodi, E. Cozzani, Coronavirus disease 2019 (COVID 19) and malaria, *Med. Hypoth.*, **143** (2020), 110036. https://doi.org/10.1016/j.mehy.2020.110036
22. M. Iesa, M. Osman, M. Hassan, A. Dirar, N. Abuzeid, J. J.Mancuso, et al., SARS-CoV-2 and Plasmodium falciparum common immunodominant regions may explain low COVID-19 incidence in the malaria-endemic belt, *New Microbes New Infect.*, **38** (2020), 100817. https://doi.org/10.1016/j.nmni.2020.100817
23. A. M. Elaiw, A. D. Al Agha, Global analysis of a reaction-diffusion within-host malaria infection model with adaptive immune response, *Mathematics*, **8** (2020), 1–32. https://doi.org/10.3390/math8040563
24. H. Chen, W. Wang, R. Fu, J. Luo, Global analysis of a mathematical model on malaria with competitive strains and immune responses, *Appl. Math. Comput.*, **259** (2015), 132–152. https://doi.org/10.1016/j.amc.2015.02.073
25. D. Khoury, R. Aogo, G. Randriafanomezantsoa-Radohery, J. McCaw et al., Within-host modeling of blood-stage malaria, *Immunol. Rev.*, **285** (2018), 168–193. https://doi.org/10.1111/imr.12697
26. F. Agusto, M. Leite, M. Orive, The transmission dynamics of a within-and between-hosts malaria model, *Ecol. Complex.*, **38** (2019), 31–55. https://doi.org/10.1016/j.ecocom.2019.02.002
27. T. Song, C. Wang, B. Tian, Mathematical models for within-host competition of malaria parasites, *Math. Biosci. Eng.*, **16** (2019), 6623–6653. https://doi.org/10.3934/mbe.2019330
28. E. Takoutsing, A. Temgoua, D. Yemele, S. Bowong, Dynamics of an intra-host model of malaria with periodic antimalarial treatment, *Int. J. Nonlinear Sci.*, **27** (2019), 148–164.https://doi.org/10.11948/20160266
29. A. M. Elaiw, A. D. Al Agha, Global dynamics of SARS-CoV-2/cancer model with immune responses, *Appl. Math. Comput.*, **408** (2021), 1–19. https://doi.org/10.1016/j.amc.2021.126364
30. C. Li, J. Xu, J. Liu, Y. Zhou, The within-host viral kinetics of SARS-CoV-2, *Math. Biosci. Eng.*, **17** (2020), 2853–2861. https://doi.org/10.3934/mbe.2020159
31. A. S. Almocera, G. Quiroz, E. A. Hernandez-Vargas, Stability analysis in COVID-19 within-host model with immune response, *Commun. Nonlinear Sci. Numer. Simul.*, (2020), 105584. https://doi.org/10.1016/j.cnsns.2020.105584
32. S. Q. Du, W. Yuan, Mathematical modeling of interaction between innate and adaptive immune responses in COVID-19 and implications for viral pathogenesis, *J. Med. Virol.*, **92** (2020), 1615–1628. https://doi.org/10.1002/jmv.25866
33. L. Pinky, H. M. Dobrovolny, SARS-CoV-2 coinfections: Could influenza and the common cold be beneficial?, *J. Med. Virol.*, (2020), 1–8. https://doi.org/10.1002/jmv.26098
34. C. Currie, J. Fowler, K. Kotiadis, T. Monks, How simulation modelling can help reduce the impact of COVID-19, *J. Simul.*, **14** (2020), 83–97. https://doi.org/10.1080/17477778.2020.1751570
35. M. V. Krishna, J. Prakash, Mathematical modelling on phase based transmissibility of Coronavirus, *Infect. Dis. Model.*, **5** (2020), 375–385.https://doi.org/10.1016/j.idm.2020.06.005
36. K. Rajagopal, N. Hasanzadeh, F. Parastesh, I. Hamarash, S. Jafari, I, Hussain, A fractional-order model for the novel coronavirus (COVID-19) outbreak, *Nonlinear Dyn.*, **101** (2020), 711–718. https://doi.org/10.1007/s11071-020-05757-6

37. T. Chen, J. Rui, Q. Wang, Z. Zhao, J. A. Cui, L. Yin, A mathematical model for simulating the phase-based transmissibility of a novel coronavirus, *Infect. Dis. Poverty.*, **9** (2020), 1–8. https://doi.org/10.1186/s40249-020-00640-3

38. C. Yang, J. Wang, A mathematical model for the novel coronavirus epidemic in Wuhan, China, *Math. Biosci. Eng.*, **17** (2020), 2708–2724. https://doi.org/10.3934/mbe.2020148

39. Z. Liu, P. Magal, O. Seydi, G. Webb, Understanding unreported cases in the 2019-nCoV epidemic outbreak in Wuhan, China, and the importance of major public health interventions, *SSRN Electron. J.*, (2020), 1–12. http://dx.doi.org/10.2139/ssrn.3530969

40. N. Bellomo, R. Bingham, M. A. J. Chaplain, G. Dosi, G. Forni, D. A. Knopoff, et al., A multiscale model of virus pandemic: heterogeneous interactive entities in a globally connected world, *Math. Models Methods Appl. Sci.*, **30** (2020), 1591–1651.https://doi.org/10.1142/S0218202520500323

41. H. K. Khalil, *Nonlinear Systems*, Prentice-Hall, New Jersey, (1996).

42. C. Hetzel, R. Anderson, The within-host cellular dynamics of bloodstage malaria: Theoretical and experimental studies, *Parasitology*, **113** (1996), 25–38. https://doi.org/10.1017/s0031182000066245

43. R. Anderson, R. May, S. Gupta, Non-linear phenomena in host-parasite interactions, *Parasitology*, **99** (1989), S59–S79. https://doi.org/10.1017/s0031182000083426

44. T. Orwa, R. Mbogo, L. Luboobi, Mathematical model for the in-host malaria dynamics subject to malaria vaccines, *Lett. Biomath.*, **5** (2018), 222–251. https://doi.org/10.1080/23737867.2018.1526132

45. G. T. Grassia, C. F. Markwalter, W. P. O'Meara, S. M. Taylor, A. A. Obala, SARS-CoV-2 cross-reactivity in prepandemic serum from rural malaria-infected persons, Cambodia, *Emerg. Infect. Dis.*, **28** (2022), 1080–1081. https://doi.org/10.3201/eid2802.211725

46. N. Bellomo, D. Burini, N. Outada, Multiscale models of Covid-19 with mutations and variants, *Netw. Heterog. Media.*, **17** (2022), 293–310. https://doi.org/10.3934/nhm.2022008

47. N. Bellomo, D. Burini, N. Outada, Pandemics of mutating virus and society: A multiscale active particles approach, *Philos. Trans. A. Math. Phys. Eng. Sci.*, **380** (2022), 1–14. https://doi.org/https://doi.org/10.1098/rsta.2021.0161

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