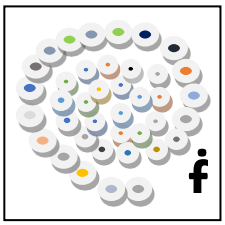

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Numerical simulation of the intracellular dynamics of HBV/Malaria co-infection with immune control and treatment

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Abstract

In this paper, we proposed an intracellular mathematical model to describe the dynamics of the co-infection of hepatitis B virus (HBV) and malaria co-infection by taking into account the immune response and treatment. We established the wellposedness of the model by proving the existence, positivity and boundedness of solution of the problem. The basic reproduction number of HBV only model in the hepatocyte and malaria only model, both in the hepatocyte and erythrocyte were obtained, and when combined gives the basic reproduction number of the co-infection model. The local stability of the disease free equilibrium is obtained using characteristic equation. We showed that the disease-free equilibrium with treatment effect exists and is asymptotically stable if $R_{0H\pi} < 1, R_{0MH\pi_1} < 1$ and $R_{0MR\pi_2} < 1$ and unstable if $R_{0H\pi} > 1, R_{0MH\pi_1} > 1$and $R_{0MR\pi_2} > 1$. Finally, we noticed from the numerical result that when the immune response is large, strong and faster and treatment is effective than the rate at which both infections replicate in the hepatocytes and erythrocytes, HBV only infected hepatocytes and malaria only infected hepatocytes and erythrocytes can be controlled with malaria resurfacing after some time as indicated by the oscillation in the malaria infected erythrocytes. There will be resistance in the co-infected hepatocytes and this may cause liver dysfunction.

Keywords: Hepatitis B virus; Malaria; hepatocytes; erythrocytes; intracellular transmission; stability; immune response; treatment

1 Introduction

Hepatits B virus (HBV) infection which has become a major global health problem is a noncytopathic, enveloped virus that causes acute and chronic hepatitis with hepatocellular carcinomas (HCC). HBV is transmitted only through direct contact with an infected persons body

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fluid, such as sexual contact, blood to blood transmission and vertical transmission (mother to child). HBV depends upon the host cell for their reproduction but must overcome certain cellular constraints. The objective of a viral particle is to move the genome from an infected cell to an uninfected cell in a replication competent form [47]. For successful elimination of HBV, antiviral cytokines such as type I interferon (INF-α and INF-β) [8] and natural killer cell are respectively released and activated against HBV. Also, $CD4^+$ and $CD8^+T$ cells responses play a central role in the elimination of HBV infection [21]. The T cell response during acute self-limited hepatitis B in people is characterized by a vigorous, polyclonal and multi-specific cytotonic and helper T cell response. Studies have shown that transferred virus specific cytotonic T cell can abolish HBV gene expression and replication in the liver without killing the hepatocytes [16]. Also, in acute HBV infection, a vigorous polyclonal cellular immune response of INF-γ is one of the most important mediator.

Malaria is a life threatening mosquito borne blood disease cause by a plasmodium parasite. The infection is initiated when sporozites are injected with the saliva of a feeding mosquito into the blood [19],[32], and then carried by the circulatory system to the liver which finally invades hepatocyte. The highly motile intracellular parasite in the hepatocyte [37],[43],[29] undergoes an asexual replication, called exocrytocythic schizogony which culminates in the production of merozoites that are released into the blood stream. Hypnozoites react several weeks to months or years after primary infection and are responsible for relapses [24]. Merozoites invades erythrocytes [24] and undergo a trophic period in which the parasite enlarge [38],[48]. The early trophozoite is often referred to as ring form because of its morphology. Trophozoite enlargement is accompanied by an active metabolism including the injection of host cytoplasm and proteolysis of hemoglobin into amino acids. The end of the trophic period is manifested by multiple rounds of nuclear divisions without cytokinesis resulting in a schizont[39]. Merozoites bud from the mature schizonts, also called a segmenter [44] and the merozoites are released following rapture of the infected erythrocyte [3]. The blood stage is responsible for the pathology associated with malaria.

There are several geographical areas mainly in Sub Sahara Africa, (SSA), where endemicity of HBV and Malaria overlap despite having different transmission route [5],[2],[7]. In tropical areas HBV is highly contagious from one infected individual to another and sometimes can present same route of transmission of plasmodium (By Blood-to-Blood Contact, sharing needles and blood transfusions). Therefore, it is not rare that and viral infections may be present in the same individual, influencing each other from a clinical perspective.

Co-infection is the process in which a host becomes infected with multiple pathogen species simultaneously [25] it is of vital health importance since there is an interaction and interface of the pathogen species within the host [1]. Both diseases have sessions of high activities in the heptocyte and their consequences on the erythrocyte (red blood cells) may result to a suppressed immunity in an individual, making them susceptible to the infections; this will also lead to increased mortality and morbidity [2].

Similarity between HBV and malaria biology is the participation of the liver and a key organ part of the immunopathogenesis in both infection [33],[13],[4],[46]. Notably, severe vivax malaria is

associated with remarkable hepatic involvement [13][4],[4],[30], whereas tissue damage is determinant for the presentation of cirrhosis and hepatocellular carcinoma in chronic HBV infections [49],[45],[28]. Counter intuitively, HBV infection has been to lead a distinct systemic inflammatory response in plasmodium infections, results in increasing odds for asymptomatic malaria [4].

Pasquetto et al in [14], described the immunological features of malaria and HBV co-infection where they describe that the hepatic stage infection seems to trigger an early T cell independent cytokine response along with a delayed cytokine response that was simultaneous with the infiltration of T cells. On the other hand, the T cell response appeared earlier in the blood stage than in the hepatic stage infection, possibly because parasitemia was detectable earlier in those individuals and a T cell independent phase was not seen, perhaps reflecting that it was induced primarily by infected hepatocytes. In both cases, however, the generated cytokine ripostes were accompanied with a decline in HBV RNA and DNA in the liver.

Malaria can normally be treated with antimalaria drugs. The type of treatment depends on which kind of malaria is diagnosed, where the patient was infected, the age f patient and how the patient was at the start of treatment [40]. Acute hepatitis B infection does not usually require treatment because about 95% of most adults clear the infection spontaneously [35],[26]. Early antiviral treatment may only be required in fewer than one percent of patients, whose infection are of great severity (fulminant hepatitis) or who are immunocompromised. In patients with fulminant infection, intravenous (IV) feeding may be needed, if the patient has persistent vomiting and can't take oral foods. Ninety percent of patients with acute HBV infection have a favorable course and recover completely [20]. On the other hand, treatment of chronic HBV infection may be necessary to reduce the risk of cirrhosis and liver cancer. Chronically infected individuals with persistently elevated serum alamine aminotranferase, a marker of liver damage and HBV DNA level are candidates for therapy [36]. Thirty to forty percent of patients with chronic hepatitis B respond to $IFN\alpha$ treatment. Immune defense is partially active in chronic hepatitis B patients, since the viral load and HBsAg level are lower [23].

Many epidemic models that study the dynamics of cell-to-cell transmission were developed [50],[18],[11]. In other studies, mathematical models, that describe the dynamics of hepatitis B virus infection with cell-to-cell transmission and immune control were proposed by [6],[9],[15]. Also, [10], included treatment and investigated the intracellular delay effect on the stability of the endemically infected steady state. Gurarie et al, [17] developed a new agent-based model that accounts for the essential in – host processes: parasite replication and its regulation by innate and adaptive immunity. Subsequently, [41] proposed within host mathematical model and considered the dynamics f P. falciparum malaria from the liver to the blood in human host and then to the mosquito. Orwa et al, [31] present a mathematical model of in – host P.falciparum malaria dynamics in the presence of vaccines. Chinebu et al, [12] designed simulation of an intracellular differential equation model of the dynamics of malaria with immune control and treatment which considered the parasite in the liver and blood. However, Scotto et al [34], performed a systemic search of the epidemiology of HBV/Malaria co-infection in particular, their overlapping clinical and histological features and their reciprocal conditioning.

2 Model of HBV and Malaria co-infection

2.1 Model formulation

The formulation of this intracellular co-infection mode, closely follows the epidemiological dynamics of the two diseases in the hepatocytes and erythrocytes i.e., Red Blood Cells (RBCs).

Table 1: Variables with their description

Varibles	***Description***
x	Susceptible hepatocytes
y_H	HBV only infected hypatocytes
z_H	CTL response to HBV
y_M	Malaria (sporozoite) only infected hepatocytes
z_M	CTL response to sporozoite infected hepatocytes
B	Uninfected susceptible erythrocytes (Red blood cells)
y_{HM}	Dually infected hepatocytes with HBV and Malaria (sporozoites)
C	Infected erythrocytes with merozoites
z_{MB}	CTL response to merozoite infected erythrocytes

Table 2: Parameters with their description

Parameters	***Description***
$\boldsymbol{\psi}$	Recruitment rate of susceptible hepatocytes
$\boldsymbol{a_1}$	Natural death rate of hepatocytes
$\frac{\beta a_3}{\mu}$	HBV infected rate of uninfected hepatocytes by free virus
σ	infection rate of uninfected hepatocytes by direct contact of both infected and uninfected hepatocytes
$\frac{\eta b_3}{\Lambda}$	Malaria parasite infection rate of uninfected hepatocytes with sporozoites
$\zeta_1 y_H, \zeta_2 y_M, \zeta_3 y_{HM}$	Proliferation rate of HBV only infected hepatocytes, malaria only infected hepatocytes and HBV-Malaria co-infected hepatoctes respectively
$a_2 y_H z_H$	Rate at which HBV infected hepatocytes are killed by CTL response
$b_1 y_H z_H$	Rate of curing HBV infected hepatocytes by CTL response
$a_5 y_H z_H$	Antigen dependent proliferation (secondary immune response to HBV infected hepatocytes)
$a_3 y_H$	Production rate of free HBV from infected hepatocytes
μv	The removal rate of free virus (natural death)
$\gamma_1, \gamma_2, \gamma_3$	Antigen independent proliferation (primary immune response)
τ	Probability of acquiring Malaria (sporozoites) by HBV infected hepatocytes

$a_6 y_M z_M$	Rate at which Sporozoites infected hepatocytes are killed by CTL response
$a_4 y_M z_M$	Secondary immune response to malaria (sporozoites) infected hepatocytes
φ	Recruitment rate of enrythrocytes (RBCs)
k_1	Natural death rate of enrythrocytes
$d_1 C z_{MB}$	Rate of curing merozoite infected enrythrocytes by CTL response
$b_2 y_M z_M$	Rate of curing sporozoites infected hepatocytesby CTL response
ρ	Probability of acquiring HBV by sporozoite infected hepatocytes
$d_2 C z_{MB}$	Killing rate of merozoite infected enrythrocytes by CTL response
d_3	Proliferation rate of infected erythrocytes
$d_4 C z_{MB}$	Secondary immune response to merozoites infected erythrocytes
k_2	Natural death rate of merozoites
k	Rate at which merozoitesare produced per bursting of infected hepatocytes
α	Rate at which uninfected erythrocytes are being infected by merozoites
π	Treatment rate of HBV infected hepatocytes
π_1	Treatment rate of malaria (sporozoite) infected hepatocytes
π_2	Treatment rate of malaria (merozoite) infected erythrocytes
$\omega y_{HM} z_H z_M$	Rate at which co-infected hepatocytes are killed by CTL response

2.2 The model

The variable and parameters that describe the intracellular co-infection dynamics of HBV and malaria are in Table 1 and 2 respectively and the transmission dynamics of the co-infection of HBV and malaria are summarized in the compartmental diagram in figure 1. From the description of the intracellular dynamics of the co-infection in figure 1, we deserve the following system of non linear ordinary differential equation:

$$\left.\begin{aligned}
\frac{dx}{dt} &= \psi + b_1 y_H z_H + b_2 y_m z_M - a_1 x - \frac{(1-\pi_1)\eta b_3 x y_M}{\Lambda} - (1-\pi)\left[\frac{\beta a_3}{\mu} + \sigma\right] x y_H \\
\frac{dy_H}{dt} &= \zeta_1 y_H + (1-\pi)\left[\frac{\beta a_3}{\mu} + \sigma\right] x y_H - a_1 y_H - (a_2 + b_1) y_H z_H - (1-\pi_1)\frac{\tau\eta b_3 y_M}{\Lambda} \\
\frac{dz_H}{dt} &= \gamma_1 + a_5 y_H z_H - b_4 z_H \\
\frac{dy_M}{dt} &= \zeta_2 y_M + (1-\pi_1)\left(\frac{\eta b_3 x y_M}{\Lambda}\right) - (b_2 + a_6) y_H z_M - a_1 y_M - k y_M - \rho(1-\pi)\left[\frac{\beta a_3}{\mu} + \sigma\right] y_H \\
\frac{dz_M}{dt} &= \gamma_2 + a_4 y_M z_M - b_4 z_M \\
\frac{dy_{HM}}{dt} &= \zeta_3 y_{HM} + \rho(1-\pi)\left[\frac{\beta a_3}{\mu} + \sigma\right] y_H + (1-\pi_1)\left(\frac{\zeta\eta b_3 y_M}{\Lambda}\right) - a_1 y_{HM} - \omega y_{HM} z_H z_M \\
\frac{dB}{dt} &= \varphi + d_1 C z_{MB} - (1-\pi_2)\alpha B M - k_1 B \\
\frac{dM}{dt} &= kC - k_2 M \\
\frac{dC}{dt} &= (1-\pi_2)\,\alpha B M + d_3 C - k_1 C - (d_1 + d_2) z_{MB} \\
\frac{dz_{MB}}{dt} &= \gamma_3 + d_4 C z_{MB} - b_4 z_{MB}
\end{aligned}\right\} \quad (2.1)$$

From system (2.1) we have that

$$kC - k_2 M = 0 \Longrightarrow M = \frac{kC}{k_2} \qquad (2.2)$$

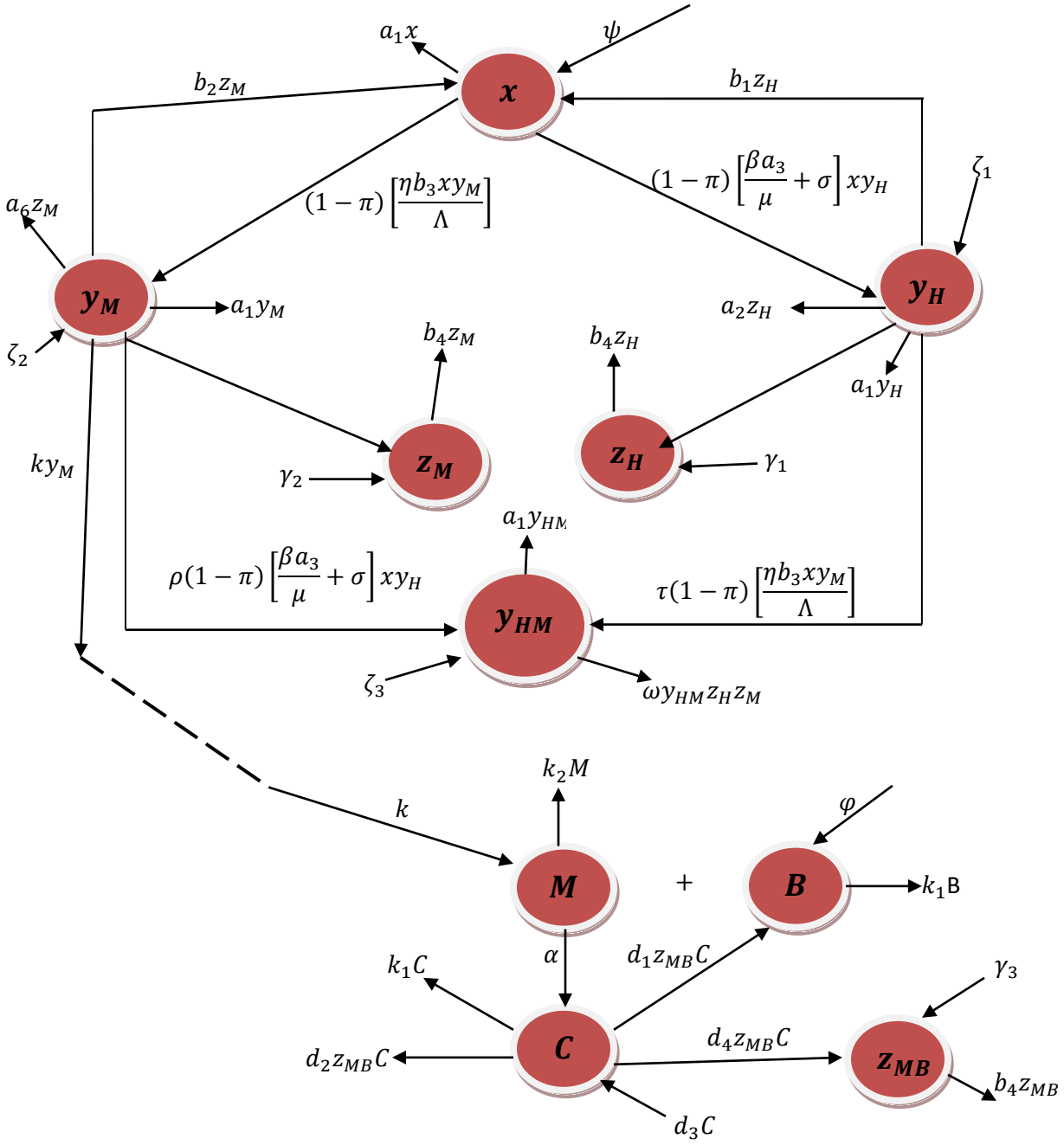

Figure 1: Schematic diagram of the Dynamics of HBV/Malaria Co-infection

Substituting (2.2) into (2.1) we obtain

$$\left.\begin{aligned}
\frac{dx}{dt} &= \psi + b_1 y_H z_H + b_2 y_M z_H - a_1 x - (1-\pi_1)\left(\frac{\tau\eta b_3 x y_M}{\Lambda}\right) - (1-\pi)\left[\frac{\beta a_3}{\mu} + \sigma\right] x y_H \\
\frac{dy_H}{dt} &= \zeta_1 y_H + (1-\pi)\left[\frac{\beta a_3}{\mu} + \sigma\right] x y_H - a_1 y_H - (b_1 + a_2) y_M z_H - (1-\pi_1)\left(\frac{\tau\eta b_3 x y_M}{\Lambda}\right) \\
\frac{dz_H}{dt} &= \gamma_1 + a_5 y_H z_H - b_4 z_H \\
\frac{dy_M}{dt} &= \zeta_2 y_M + (1-\pi_1)\left(\frac{\tau\eta b_3 x y_M}{\Lambda}\right) - (b_2 + a_6) y_M z_M - a_1 y_M - k_1 y_M - \rho(1-\pi)\left[\frac{\beta a_3}{\mu} + \sigma\right] y_H \\
\frac{dZ_M}{dt} &= \gamma_2 + a_4 y_M z_M - b_4 z_M \\
\frac{dy_{HM}}{dt} &= \zeta_3 y_{HM} + \rho(1-\pi)\left[\frac{\beta a_3}{\mu} + \sigma\right] y_H + (1-\pi_1)\left(\frac{\tau\eta b_3 Y_M}{\Lambda}\right) - a_1 y_{HM} - \omega y_{HM} z_H z_M \\
\frac{dB}{dt} &= \varphi - (1-\pi_2)\frac{\alpha k B C}{k_2} - k_1 B + d_1 C z_{MB} \\
\frac{dC}{dt} &= (1-\pi_2)\frac{\alpha k B C}{k_2} + d_3 C - k_1 C - (d_1 + d_2) C z_{MB} \\
\frac{dz_{MB}}{dt} &= \gamma_3 + d_4 C z_{MB} - b_4 z_{MB}
\end{aligned}\right\} \quad (2.3)$$

2.3 Basic frame work

The model sub divides the total population at time t denoted by $N(t)$, into various mutually exclusive compartments depending on their disease status: susceptible (uninfected) hepatocytes to both diseases $x(t)$HBV infected hepatocytes $y_H(t)$; CTL response to HBV infected hepatocytes; $z_H(t)$; Malaria (sporozoites) infected hepatocytes $z_M(t)$; Dually infected hepatocytes with HBV and Malaria (sporozoites) $y_{HM}(t)$; Susceptible (uninfected) erythrocytes with malaria (merozoites) $B(t)$, infected erythrocytes with malaria (merozoites) $C(t)$; and CTL response to infected erythrocytes with merozoites , $Z_{MB}(t)$. The total population is :

$$N(t) = x(t) + y_H(t) + z_H(t) + y_M(t) + z_M(t) + y_{HM}(t) + B(t) + C(t) + z_{MB}(t) \quad (2.4)$$

2.4 Positivity analysis of solution

For system (2.3) to be epidemiologically meaningful, it is important to prove that the feasible solution sets for all time $t \geq 0$. In other words, solution of system (2.3) with positive initial data remain positive for all time t.

Theorem 2.1: The region$\Gamma \in \mathbb{R}_+^9$ is positively invariant with respect to the system of equation (2.3) and a non- negative solution exists for all $0 < t < \infty$.

Proof: if $\pi_1 = \pi_2 = \pi_3 = 0 \; and \; x(0) = x_0 > 0, y_H(0) = y_{H0} > 0, z_H(0) = z_{H0} > 0, y_M(0) = y_{M0} > 0,$
$z_M(0) = z_{M0} > 0, y_{HM}(0) = y_{HM0} > 0, B(0) = B_0 > 0, C(0) = C_0 > 0 \; and \; z_{MB}(0) = z_{MB0} > 0$ are the non negative initial conditions, the solution $x(t), y_H(t), z_H(t), y_M(t), z_M(t), y_{HM}(t), B(t), C(t), and \; z_{MB}(t)$ of system (2.3) are all non negative for $t > 0$ and if not, let there exist a time $\bar{t}$ such that $x(\bar{t}) = 0$, $x'(\bar{t}) \leq 0$ and
$x(t) > 0, y_H(t), z_H(t) > 0, y_H(t) > 0, z_M(t) > 0, y_{HM}(t) > 0, B(t) > 0, C(t) > 0 \; and \; z_{MB}(t) > 0$
for $0 < t < \bar{t}$. Suppose there exist a time $\hat{t}$ such that $x(\hat{t}) = 0, x'(t) \leq 0, x(t) > 0, y_H(t) > 0, z_H(t) > 0, y_M(t) > 0, z_M(t) > 0, y_{HM}(t) > 0, B(t) > 0, C(t) > 0, and \; z_{MB}(t) > 0 \; for \; 0 < t < \hat{t}$.

This approach was used by Magombedze et al [27]. This can be verified as follows. Suppose for example the variable z_H becomes zero for some time $\bar{t} > 0 \; i.e., z(\bar{t}) = 0$ while other variables are non negative. Then, from the z_H equation we have

$$\frac{dz_H(\bar{t})}{dt} = \gamma_1 + a_5 y_H z_H - b_4 z_H$$
$$= \gamma_1 > 0 \qquad (2.5)$$

which is a contradiction. For the latter case, from y_H equation we have

$$\frac{dy_H(\hat{t})}{dt} = \zeta_1 y_H + (1-\pi)\left[\frac{\beta a_3}{\mu} + \sigma\right] x y_H - a_1 y_H - (b_1 + a_2) y_H z_H - (1-\pi_1)\frac{\tau \eta b_3 y_M}{\Lambda}$$
$$= (1-\pi_1)\frac{\tau \eta b_3 y_M}{\Lambda} \geq 0 \qquad (2.6)$$

This is true if $y_M(\hat{t}) = 0$ or $y_M(\hat{t}) > 0$ and it follows that the solution $z_H(\hat{t}) \geq 0$ and $y_H(\hat{t}) \geq 0$ are positive at any given time. Similarly, it can be shown that the variables $x(t), y_M(t), z_M(t), y_{HM}(t) B(t), C(t) \; and \; z_{MB}(t)$ remain positive for all $t > 0$.Thus the solutions of the system of equation (2.3) remains non negative for all time$t > 0$.

2.5 Mathematical analysis of the HBV and Malaria sub model

2.5.1 HBV-only sub model

We begin by analyzing the HBV only sub model (obtained by setting $y_M = z_M = y_{HM} = B = C = z_{MB} = 0$) in equation (2.3) given by

$$\left.\begin{aligned} \frac{dx}{dt} &= \psi + b_1 y_H z_H - a_1 x - (1-\pi)\left[\frac{\beta a_3}{\mu} + \sigma\right] x y_H \\ \frac{dy_H}{dt} &= \zeta_1 y_H + (1-\pi)\left[\frac{\beta a_3}{\mu} + \sigma\right] x y_H - a_1 y_H - (a_2 + b_1) y_H z_H \\ \frac{dz_H}{dt} &= \gamma_1 + a_5 y_H z_H - b_4 z_H \end{aligned}\right\} \quad (2.7)$$

2.5.2 Positivity and boundedness of solutions of HBV-only sub model

To validate our model, we show that all cells and HBV contractions are non-negative and bounded.
Theorem 2.2: All solutions of system (2.7) starting from positive initial value (x_0, y_{H0}, z_{H0}) remain bounded and positive for all $t > 0$. Moreover, we have

$$(i) \qquad H(t) \le H(0) + \frac{\varphi}{a_1}$$

$$(ii) z_H(t) \le z_{H0} + \frac{\gamma_1}{b_4} + \frac{a_5}{a_2 + b_1}\left[\frac{\psi}{a_1} + x_0 + y_{H0} + \Omega_1 \|x\|_\infty + \Omega_2 \|y_H\|_\infty\right],$$

where $H = x + y_H$ that represents the total hepatocytes $\xi = min(a_1, a_2)\Omega_1 = \max\left\{0, 1 - \frac{a_1}{b4}\right\}$ $and\ \Omega_2 = \max\left\{0, 1 - \frac{a_2}{b4}\right\}$.

Proof: we first show that any solution starting in the $\mathbb{R}^3_+ = \left\{\left(x, y_{H,} z_H\right) \in \mathbb{R}^3_+ : x \ge 0, y_H \ge 0, z_H \ge 0\right\}$ stays in$\mathbb{R}^3_+$. In fact, for $(x(t), y_H(t), z_H(t) \in \mathbb{R}^3_+)$, we have

$$\left.\begin{aligned} \frac{dx}{dt}|_{x=0} &= \psi + b_1 y_H z_H \ge 0 \\ \frac{dy_H}{dt}|y_{H=0} &= f(x,0) y_H) \ge 0 \\ \frac{dz_H}{dt}|z_{H=0} &= \gamma_1 \ge 0 \end{aligned}\right\} \quad (2.8)$$

This instantly showed that all solutions of system (2.7) with initial conditions $(x_0, y_{H0}, z_{H0}) \in \mathbb{R}^3_+$ stay in $\mathbb{R}^3_+$. We now show the boundedness of solutions. Let $\frac{dH}{dt} = \psi - a_1 H$. Then,

$$H(t) \le H(0) e^{-a_1 t} + \frac{\varphi}{a_1}(1 - e^{-a_1 t}) \quad (2.9)$$

Since $0 \le e^{-a_1 t} \le 1\ and\ 1 - e^{-a_1 t} \le 1$ we have
From the third equation of (2.7), we have that

$$\frac{dz_H}{dt} + b_4 z_H \leq \gamma_1 + a_5 y_H z_H \qquad (2.10)$$

Hence

$$\frac{dz_H}{dt} + b_4 z_H \leq \gamma_1 + \frac{a_5}{a_2 + b_1}[\psi - \left(\frac{dx}{dt} + a_1 x\right) - (\frac{dy_H}{dt} + a_1 y_H)] \qquad (2.11)$$

$$\frac{dz_H}{dt} e^{b_4 t} - z_{H0} \leq \left(\frac{\gamma_1}{b_4} + \frac{a_5 \psi}{b_4(a_2 + b_1)}\right)(e^{b_4 t} - 1) - \frac{a_5}{a_2 + b_1}\int_0^t e^{(b_4 - a_1)\theta} \frac{d}{d\theta}\left(x(\theta)e^{a_1\theta}\right)d\theta - \frac{a_5}{a_2 + b_1}\int_0^t e^{(b_4 - a_1)\theta} \frac{d}{d\theta}\left(y_H(\theta)e^{a_1\theta}\right)d\theta \qquad (2.12)$$

Integrating by parts, we have

$$\left.\begin{aligned} \int_0^t e^{(b_4 - a_1)\theta} \frac{d}{d\theta}\left(x(\theta)e^{a_1\theta}\right)d\theta &= \left[x(\theta)e^{b_4\theta}\right]_0^t - (b_4 - a_1)\int_0^t x(\theta)e^{b_4\theta}\, d\theta \\ \int_0^t e^{(b_4 - a_1)\theta} \frac{d}{d\theta}\left(y_H(\theta)e^{a_1\theta}\right)d\theta &= \left[y_H(\theta)e^{b_4\theta}\right]_0^t - (b_4 - a_1)\int_0^t y_H(\theta)e^{b_4\theta}\, d\theta \end{aligned}\right\} \qquad (2.13)$$

Thus,

$$z(t) \leq \left[\frac{a_5}{a_2 + b_1}(x_0 + y_{H0}) + z_{H0}\right]e^{-b_4 t} + \left(\frac{\gamma_1}{b4} + \frac{a_5\psi}{b_4(a_2 + b_1)}\right)\left(1 - e^{b_4(t)}\right) + \frac{a_5}{a_2 + b_1}\left[\int_0^t [(b_4 - a_1)x(\theta) + (b_4 - a_1)y_H(\theta)]e^{b_4(\theta - t)}d\theta - x(t) - y_H(t)\right] \qquad (2.14)$$

Next is to find an upper bound to this integral and it is done be studying the following cases:

if $b_4 - a_1 \leq 0\ and\ b_4 - a_1 \leq 0$, then

$$z_H(t) \leq z_{H0} + \frac{\gamma_1}{b_4} + \frac{a_5}{a_2 + b_1}\left(\frac{\psi}{b_4} + x_0 + y_{H0}\right) \qquad (2.15)$$

If $b_4 - a_1 \leq 0\ and\ b_4 - a_2 \leq 0$, then

$$z_H(t) \leq z_{H0} + \frac{\gamma_1}{b_4} + \frac{a_5}{a_2 + b_1}\left(\frac{\psi}{b_4} + x_0 + y_{H0} + \left(1 - \frac{a_2}{b_4}\right)||y_H||_\infty\right) \qquad (2.16)$$

If $b_4 - a_1 \leq 0\ and\ b_4 - a_2 \leq 0$, then

$$z_H(t) \leq z_{H0} + \frac{\gamma_1}{b_4} + \frac{a_5}{a_2 + b_1}\left(\frac{\psi}{b_4} + x_0 + y_{H0} + \left(1 - \frac{a_1}{b_4}\right)||x||_\infty\right) \qquad (2.17)$$

If $b_4 - a_1 \leq 0\ and\ b_4 - a_2 \leq 0$, then

$$z_H(t) \leq z_{H0} + \frac{\gamma_1}{b_4} + \frac{a_5}{a_2 + b_1}\left(\frac{\psi}{b_4} + x_0 + y_{H0} + \left(1 - \frac{a_1}{b_4}\right)||x||_\infty + \left(1 - \frac{a_2}{b_4}\right)||y_H||_\infty\right) \quad (2.18)$$

From (2.15) to (2.18), we can conclude (ii), that is,

$$z_H(t) \leq z_{H0} + \frac{\gamma_1}{b_4} + \frac{a_5}{a_2 + b_1}\left[\frac{\psi}{a_1} + x_0 + y_{H0} + \Omega_1\|x\|_\infty + \Omega_2\|y_H\|_\infty\right]$$

2.5.3 Basic reproduction number and stability of equilibrium

The disease free and endemic equilibria are obtained by setting the rates of change or the left hand side of the equations of system (2.7) to zero and also set the infected class to zero and solving the resulting systems at steady state, we have the disease free equilibrium DFE as

$$E_H = \left(\frac{\psi}{a_1}, 0, \frac{\gamma_1}{b_4}\right) \quad (2.19)$$

Then we define the basic reproduction number of system (2.7) as follows

$$R_{0H} = \left[\frac{\psi(1-\pi)(\beta a_3 + \sigma\mu) + \mu a_1\zeta_1}{\mu a_1}\right]\left[\frac{b_4}{\gamma_1(a_2 + b_1) + a_1 b_4}\right] \quad (2.20)$$

Which can be rewritten as

$$R_{0H} = \frac{b_4(\psi(1-\pi)(\mu\sigma + \beta a_3) + \mu a_1\zeta_1)}{\mu a_1[\gamma_1(a_2 + b_1) + a_1 b_4]} \quad (2.21)$$

Expressing the endemic equilibrium point explicitly in HBV only, the parameters of the model is mathematically tractable. The components of the endemic equilibrium point (x^*, y_H^*, z_H^*) are related through the following equations:

$$\left.\begin{gathered} x^* = \frac{[(a_2 + b_1)\gamma_1 + a_1(b_4 - a_5 y_H^*) - \mu_1(b_4 - a_5)y_H^*]\mu}{(b_4 - a_5 y_H^*)(1-\pi)(\beta a_3 + r\mu)} \\ z^* = \frac{\gamma_1}{(b_4 - a_5 y_H^*)} \\ and \\ a_5(1-\pi)(\beta a_3 + \sigma\mu)[a_1 - \zeta_1]y_H^{*2} \\ +\left[(1-\pi)(\,(\beta a_3 + \sigma\mu)\left[\gamma_1\left(b_1 - (a_5 + b_1)\right) - b_4(a_1 - \zeta_1) - \psi a_5\right] - \mu a_1 a_5(a_1 - \zeta_1)\right]y_H^* \\ +\varphi b_4(1-\pi)(\beta a_3 + \sigma\mu) - \gamma_1 a_1\mu(a_2 + b_1) - \mu a_1^2 b_4 + a_1 b_4\mu\zeta_1 = 0 \end{gathered}\right\} \quad (2.22)$$

The third equation of (2.22) can be written as

$$P_2 y_H^{*2} + P_1 y_H^* + P_0 = 0 \quad (2.23)$$

were

$$\left.\begin{aligned} P_2 &= a_5(1-\pi)(\beta a_3+\sigma\mu)[a_1-\zeta_1] \\ P_1 &= (1-\pi)(\,(\beta a_3+\sigma\mu)\big[\gamma_1\big(b_1-(a_5+b_1)\big)-b_4(a_1-\zeta_1)-\psi a_5\big]-\mu a_1 a_5(a_1-\zeta_1) \\ P_0 &= \frac{\psi}{\mu a_1}(1-\pi)(\beta a_3+\sigma\mu)+\zeta_1-\frac{\gamma_1}{b_4}(a_2+b_1)-a_1 \end{aligned}\right\} \quad (2.24)$$

Also P_0 can be rewritten in the form

$$\frac{b_4(\psi(1-\pi)(\mu\sigma+\beta a_3)+\mu a_1\zeta_1)}{\mu a_1[\gamma_1(a_2+b_1)+a_1 b_4]}-1 \Rightarrow R_H-1 \quad (2.25)$$

From system (2.25) we observe that $P_0>0$ whenever $R_H>1$ and $P_0<0$ whenever $R_H<1$. There will always be stability with respect to perturbations in x, y_H, z_H. The equation $\zeta_1+\frac{\varphi}{\mu a_1}(1-\pi)(\beta a_3+\sigma\mu)$ represents the ability of HBV. ζ_1 Represents the multiplication ability of infected hepatolytes, a_1 represents the death rate of both infected and uninfected hepatolytes, a_3 represents the production ability of HBV from infected hepatocytes, β represents the infectivity ability of HBV, μ represents the death rate of HBV, ψ represents the production ability (recruitment) of uninfected hepatolytes and σ represents infectivity rate of Hepatocytes by free virus, while $1-\pi$ represents the probability of not effectively treating HBV infection.

Also, the equation $\frac{\gamma_1}{b_4}(a_2-b_1)-a_1$ represents the ability of the immune system, b_1 represents the ability of CTL to cure HBV infection without destroying the infected hepatolytes (non lytic ability) and a_2 represents the ability of CTL to destroy both the HBV and the infected hepatolytes (lytic ability). Also $\frac{\gamma_1}{b_4}$ is the initial value of CTL while a_1 represents the death rate both infected and uninfected hypatolytes. If $\zeta_1+\frac{\varphi}{a_1}(1-\pi)(\beta a_3+r\mu)<a_1+\frac{\gamma_1}{b_4}(a_2+b_1)$ then the immune system is strong enough to control the infection. But if $\zeta_1+\frac{\varphi}{a_1}(1-\pi)(\beta a_3+\sigma\mu)>a_1+\frac{\gamma_1}{b_4}(a_2+b_1)$ then, there will always be instability. In other words, HBV can invade the hepatocyte and exist for a long time. Likewise, if $\pi\geq 1$, then the treatment option will be able to control HBV infection and if $\pi<1$, then the infection will persist and may lead to chronic infection.

2.5.3 Malaria - only sub model

Here we consider the malaria only model (obtained by setting $y_H=z_H=y_{HM}=0$) in system (2.7) and we have

$$\left.\begin{aligned}
\frac{dx}{dt} &= \psi + b_2 y_M z_M - a_1 x - (1-\pi_1)\frac{\eta b_3 x y_M}{\Lambda} \\
\frac{dy_M}{dt} &= \zeta_2 y_M + (1-\pi_1)\frac{\eta b_3 x y_M}{\Lambda} - (b_2 + a_6) y_M z_M - a_1 y_M - k y_M \\
\frac{dz_M}{dt} &= \gamma_2 + a_4 y_M z_M - b_4 z_M \\
\frac{dB}{dt} &= \varphi + d_1 C z_{M\beta} - k_1 B - (1-\pi_2)\frac{\alpha B k C}{k_2} \\
\frac{dC}{dt} &= (1-\pi_2)\frac{\alpha k B C}{k_2} + d_3 C - k_1 C - (d_1 + d_2) C z_{MB} \\
\frac{dz_{MB}}{dt} &= \gamma_3 + d_4 C z_{M\beta} - b_4 z_{MB}
\end{aligned}\right\} \qquad (2.26)$$

Note that the malarial model is an extension of the model by Chinebu et al, [12], and it is necessary we point out that since the hepatocyte population is free of HBV, that is, there is no HBV infected hepatolyte that can transmit HBV infection to susceptible hypatocytes.

2.5.4 Disease free equilibrium and basic reproduction numbers

The malaria only sub-model (2.26) has a disease free equilibrium (DFE), given by

$$E_M = (x, y_M, z_M, B, C, z_{MB}) = \left(\frac{\psi}{a_1}, O, \frac{\gamma_2}{b_4}, \frac{\varphi}{k_1}, 0, \frac{\gamma_3}{b_4}\right) \qquad (2.27)$$

The basic Reproduction number, that is, the linear stability of E_M can be established using the next generation operator [42] on the system (2.26). We thus have

$$R_{0M} = \left[\frac{\Lambda a_1 \zeta_2 + (1-\pi_1)\eta b_3 \psi}{\Lambda a_1}\right]\left[\frac{b_4}{\gamma_2(b_2 + a_6) + b_4(a_1 + k)}\right] + \left[\frac{d_3 k_1 k_2 + (1-\pi_2)\alpha k \varphi}{k_1 k_2}\right]\left[\frac{b_4}{\gamma_3(d_1 + d_2) + b_4 k_1}\right] \qquad (2.28)$$

which can further be simplified into

$$R_{0M} = \frac{b_4(\Lambda a_1 \zeta_2 + (1-\pi_1)\eta b_3 \psi)}{\Lambda a_1[\gamma_2(b_2 + a_6) + b_4(a_1 + k)]} + \frac{b_4(d_3 k_1 k_2 + (1-\pi_2)\alpha k \varphi)}{k_1 k_2[\gamma_3(d_1 + d_2) + b_4 k_1]} \qquad (2.29)$$

From system (2.29), $\frac{\psi \eta b_3 (1-\pi)}{\Lambda a_1} + \zeta_2$ is the multiplication ability of sporozoite (malaria infection) on the hepatocytes and the ability that the hepatocytes will produce sufficient merozoite that will eventually infect the erythrocytes. $(b_2 + a_6)\frac{\gamma_2}{b_4} - a_1 + k$ is the ability of the immune system in controlling sporozoites in the hepatocytes before merozoite are released to invade the erythrocytes,

$(1-\pi_3)\frac{\alpha k\varphi}{k_1k_2}+d_3$ is the multiplication ability of merozoites in the erythrocytes and the probability that the erythrocytes will produce sufficient gametocytes that will be ingested by mosquitoes during blood meal, $(d_1+d_2)\frac{\gamma_3}{b_4}+k_1$is the ability of the immune system in controlling the infection at the RBC stage. With this analysis, we have the basic reproduction number R_{0M} as

$$R_{0M}=R_{0M_H}+R_{0M_R} \tag{2.30}$$

where

$$R_{0M_H}=\frac{b_4(\Lambda a_1\zeta_2+(1-\pi_1)\eta b_3\psi)}{\Lambda a_1[\gamma_2(b_2+a_6)+b_4(a_1+k)]} \tag{2.31}$$

$$and$$

$$R_{0M_R}=\frac{b_4(d_3k_1k_2+(1-\pi_2)\alpha k\varphi)}{k_1k_2[\gamma_3(d_1+d_2)+b_4k_1]} \tag{2.32}$$

Therefore, R_{0M_H} describes the expected member of hypatocytes that will be infected by one infectious hepatocyte where as R_{0M_R} describes the average number of infected erythrocytes by one infectious erythrocyte.

2.5.5 Local stability of equilibria

In this section, we describe the local stability of both equilibria of malaria only sub model system (2.26). Note that the Jacobian matrix of (2.26) is given by

$$J:=\begin{pmatrix} -a_1 & A & 0 & 0 & 0 & 0 \\ 0 & D & 0 & 0 & 0 & 0 \\ 0 & a_4\cdot z_M & -b_4 & 0 & 0 & 0 \\ 0 & 0 & 0 & -k & G & 0 \\ 0 & 0 & 0 & 0 & Q & 0 \\ 0 & 0 & 0 & 0 & d_4\cdot z_{MB} & -b_4 \end{pmatrix} \tag{2.33}$$

where,

$$A=b_2z_m-(1-\pi_1)\frac{\eta b_3x}{\Lambda},\qquad D=\varsigma_1+\frac{(1-\pi_1)\eta b_3X}{\Lambda}-(b_2+a_6)z_M-a_1-k$$

$$G=d_1z_{MB}-(1-\pi_1)\frac{\alpha kB}{k_2}\,and\;Q=(1-\pi)\frac{\alpha kB}{k_2}+d_3-k_1-(d_1+d_2)z_{MB}$$

First, we get the following results.

Theorem 2.3: The infection free equilibrium E_M is locally asymptotically stable if $R_{0M} < 1$ and unstable if $R_{0M} > 1$.

Proof: Evaluating system(2.33)at E_M, we obtain

$$J(E_M) := \begin{pmatrix} -a_1 & A_1 & 0 & 0 & 0 & 0 \\ 0 & D_1 & 0 & 0 & 0 & 0 \\ 0 & \frac{a_4 \cdot \gamma_2}{b_4} & -b_4 & 0 & 0 & 0 \\ 0 & 0 & 0 & -k & G_1 & 0 \\ 0 & 0 & 0 & 0 & Q_1 & 0 \\ 0 & 0 & 0 & 0 & \frac{d_4 \cdot \gamma_3}{b_4} & -b_4 \end{pmatrix} \tag{2.34}$$

where

$$A_1 = \frac{b_2\gamma_2}{b_4} - \frac{(1-\pi_1)\eta b_3\psi}{\Lambda a_1}, \qquad D_1 = \zeta_2 + \frac{(1-\pi_1)\eta b_3\varphi}{\Lambda a_1} - (b_2 + a_6)\frac{\gamma_2}{b_4} - a_1 - k$$
$$G_1 = \frac{d_1\gamma_3}{b_4} + \frac{(1-\pi_2)\alpha k\psi}{k_1k_2} \quad and \quad Q_1 = \frac{(1-\pi)\alpha k\psi}{k_1k_2} + d_3 - k_1 - (d_1 + d_2)\frac{\gamma_3}{b_4}$$

Then the characteristics equation at E_M is given by

$$(\boldsymbol{\lambda}_4 + a_1)(\boldsymbol{\lambda}_5 + D_1)(\boldsymbol{\lambda}_6 + b_4)(\boldsymbol{\lambda}_7 + k)(\boldsymbol{\lambda}_8 + Q_1)(\boldsymbol{\lambda}_9 + b_4) = 0 \tag{35}$$

Hence, the roots of $(2.35)$are$\lambda_4 = -a_1$, $\lambda_5 = R_{0M_H} - 1$, $\lambda_6 = -b_4$, $\lambda_7 = -k$, $\lambda_8 = R_{0M_R} - 1$ and $\lambda_9 = -b_4$. Clearly λ_4, λ_6 , λ_7 and λ_9 are negative. However, λ_5 and λ_8 are respectively negative if $R_{0M_H} < 1$ and $R_{0M_R} < 1$ and respectively positive if $R_{0M_H} > 1$and $R_{0M_R} > 1$. Therefore, E_M is locally asymptotically stable if $R_{0M_H} < 1$ and $R_{0M_R} < 1$ and unstable if $R_{0M_H} > 1$and $R_{0M_R} > 1$.

Next, we focus on the local stability of the endemic equilibrium $E_M{}^*$. This is the point where the disease cannot be totally eradicated but remains in the population of both the hepatocytes and erythrocytes.

Theorem 2.4: The endemic equilibrium $E_M{}^*$ is locally asymptotically stable if $R_{0M} > 1$i.e $R_{0M_H} > 1$and $R_{0M_R} > 1$.

Proof: To calculate the endemic equilibrium point, we have

$$E_M{}^* = (X^*, y_m{}^*, Z_m{}^*, B^*, C^*, Z_{MB}{}^*) \neq 0$$

From equation (2.27) we have

$$\left.\begin{aligned} x^* &= \frac{\Lambda[(b_2 + a_6)\gamma_2 + (b_4 - a_4 y_M{}^*)(a_1 + k - \zeta_2)]}{\eta b_3(1-\pi_1)(b_4 - a_4 y_M{}^*)} \\ z_m{}^* &= \frac{\gamma_2}{b_4 - a_1 y_M{}^*} \\ B^* &= \frac{k_2[(d_1 + d_2)\gamma_3 + (k_1 - d_3)(b_4 - d_4 C^*)]}{\alpha k(1-\pi_3)(b_4 - d_4 C^*)} \\ z_{MB}{}^* &= \frac{\gamma_3}{b_4 - d_4 C^*} \end{aligned}\right\}$$

$y_M{}^*$is obtained as

$$\left.\begin{aligned} &\eta b_3 a_4(1-\pi_1)(a_1 + k - \zeta_2) y_M{}^{*2} \\ &+\left[\begin{matrix} b_2 b_3 \gamma_3 \eta + \Lambda a_1 a_4(a_1 + k - \zeta_2) - \psi\eta a_4 b_3(1-\pi) - \eta b_3 \gamma_2(1-\pi_1)(b_4 + a_6) \\ -\eta b_3 b_4(1-\pi_1)(a_1 + k - \zeta_2) \end{matrix}\right] y_M{}^* \\ &+b_4\psi\eta b_3(1-\pi_1) - \Lambda a_1[\gamma_2(b_4 + a_6) + b_4(a_1 + k - \zeta_2)] = 0 \end{aligned}\right\} \quad (2.36)$$

While C^* is obtained as

$$\left.\begin{aligned} &d_4\alpha k(1-\pi_2)(k_1 - d_3) C^{*2} \\ &+\left[\begin{matrix} d_1\gamma_3\alpha k(1-\pi_2) + k_1 k_2 d_4(k_1 - d_3) - b_4\alpha k(1-\pi_2)(k_1 - d_3) \\ -k_1 k_2 b_4(k_1 - d_3) - \varphi\alpha k d_4(1-\pi_2) \end{matrix}\right] C^* \\ &+\varphi\alpha k b_4(1-\pi_2) - k_1 k_2[\gamma_3(d_1 + d_2) + b_4(k_1 - d_3)] = 0 \end{aligned}\right\} \quad (2.37)$$

Equations (2.36) and (2.37) can be rewritten as

$$P_{MH_2} y_M{}^{*2} + P_{MH_1} y_M{}^* + P_{MH_0} = 0 \quad (2.38)$$

and

$$P_{MR_2} C_M{}^{*2} + P_{MR_1} C^* + P_{MR_0} = 0 \quad (2.39)$$

where

$$\left.\begin{aligned} P_{MH_2} &= \eta b_3 a_4(1-\pi_1)(a_1 + k - \zeta_2) \\ P_{MH_1} &= b_2 b_3 \gamma_2 \eta + \Lambda a_1 a_4(a_1 + k - \zeta_2) - \psi\eta a_4 b_3(1-\pi_1) - \eta b_3 \gamma_2(1-\pi_1)(b_4 + a_6) \\ &\quad -\eta b_3 b_4(1-\pi_1)(a_1 + k - \zeta_2) \\ P_{MH_0} &= R_{0M_H} - 1 \end{aligned}\right\} \quad (2.40)$$

and

$$\left.\begin{aligned} P_{MR_2} &= d_4\alpha k(1-\pi_2)(k_1-d_3) \\ P_{MR_1} &= d_1\gamma_3\alpha k(1-\pi_2) + k_1k_2d_4(k_1-d_3) - b_4\alpha k(1-\pi_2)(k_1-d_3) - \alpha k\gamma_3(1-\pi_2)(d_1+d_2) \\ &\quad -k_1k_2d_4(k_1-d_3) - \varphi\alpha k d_4(1-\pi_2) \\ P_{MR_0} &= R_{0M_R} - 1 \end{aligned}\right\} \quad (2.41)$$

It is worth noting that the coefficient P_{MH_0} and P_{MR_0} are always positive if and only if $R_{0M_H} > 1$and $R_{0M_R} > 1$ respectively and negative if and only if $R_{0M_H} < 1$ and $R_{0M_R} < 1$ respectively.

2.6 Analysis of the full HBV-Malaria model

Having analysed the dynamics of the two sub-models that is HBV only and malaria only models, The full HBV-malaria model (2.3) is now considered.

2.6.1 Local Stability of the Disease Free Equilibrium

The HBV-malaria model (2.3) has a DFE given by

$$E_{0HM} = (x_0, 0, Z_{H0}, 0, Z_{M0}, 0, B_0, 0\ Z_{MB0})$$

where$x_0 = \frac{\psi}{a_1}, z_{H0} = \frac{y_1}{b_4}, z_{M0} = \frac{y_2}{b_4}, B_0 = \frac{\varphi}{k_1}$ and $z_{MB0} = \frac{y_3}{b_4}$

The spectra radii of the next generation matrix FV^{-1} are independent and given in terms of HBV and malaria – only associated reproduction members, in which that of the malaria comprises the Hepatocytes and erythrocytes stages. It is therefore evident that the associated reproduction member for the full HBV – malaria model is given by

$$R_{0HM} = Max\{R_{0H}, R_{0M}\}, \quad (2.42)$$

where

$$R_{0H} = \frac{b_4(\psi(1-\pi)(\mu\sigma+\beta a_3)+\mu a_1\zeta_1)}{\mu a_1[\gamma_1(a_2+b_1)+a_1b_4]}$$

$$R_{0M} = \frac{b_4(\Lambda a_1\zeta_2 + (1-\pi_1)\eta b_3\psi)}{\Lambda a_1[\gamma_2(b_2+a_6)+b_4(a_1+k)]} + \frac{b_4(d_3k_1k_2+(1-\pi_2)\alpha k\varphi)}{k_1k_2[\gamma_3(d_1+d_2)+b_4k_1]}$$

R_{0H} Gives the number of secondary HBV infection cases produced by a HBV infectious hepatocytes during its effective infectious period when introduced in a population of mostly HBV susceptible. R_{0M} is the malaria reproduction number in the absence of HBV which gives the number of secondary malaria infections produced by a malaria infectious cell (either hepatocytes and/or erythrocytes) but not infected with HBV, during its infectious period when introduced in a population of malaria susceptible hepatocyte and/or erythrocytes that have no HBV.

A threshold condition for endemicity is given by $R_{0HM} = 1$: The disease dies out if $R_{0HM} < 1$, and becomes endemic if $R_{0HM} > 1$. Then, we can claim the following result.

Theorem 2.5: The disease free equilibrium with treatment effects of HBV – malaria infection exists anis locally asymptotically stable if $R_{0H\pi} < 1, R_{0MH\pi_1} < 1$ and $R_{0MR\pi_2} < 1$ and unstable if $R_{0H\pi} > 1$, $R_{0MH\pi_1} > 1$ and $R_{0MR\pi_2} > 1$.

Proof: A partial differentiation of $R_{0H\pi}, R_{0MH\pi_1}$ and $R_{0MR\pi_2}$ with respect to π, π_1 and π_2 respectively, and obtain:

$$\frac{dR_{0H\pi}}{d\pi} = -\frac{\psi b_4(\mu\sigma + \beta a_3)}{\mu a_1[\gamma_1(a_2 + b_1) + a_1 b_4]} < 0$$

$$\frac{dR_{0MH\pi_1}}{d\pi_1} = -\frac{b_4 \eta b_3 \psi}{\Lambda a_1[\gamma_2(b_2 + a_6) + b_4(a_1 + k)]} < 0$$

$$\frac{dR_{0MR\pi_2}}{d\pi_2} = -\frac{b_4 \alpha k \varphi}{k_1 k_2[\gamma_3(d_1 + d_2) + b_4 k_1]} < 0$$

This means that that the values of $R_{0H\pi}, R_{0MH\pi_1}$ and $R_{0MR\pi_2}$ decreases as π, π_1 and π_2 increase. $R_{0H\pi}, R_{0MH\pi_1}, R_{0MR\pi_2} < 1 < R_{0HM}$ Whenever, the partial derivatives $\frac{dR_{0H\pi}}{d\pi}, \frac{dR_{0MH\pi_1}}{d\pi_1}$ and $\frac{dR_{0MR\pi_2}}{d\pi_2}$ are less than zero. it is also evident that treatment is effective as π, π_1 and π_2 approach 1.Therefore, a highly effective drug administered to infected individuals in the asymptomatic stage can lead to effective disease control if lim $R_{0H\pi}, R_{0MH\pi_1}, R_{0MR\pi_2} \to 0$ and $R_{0H\pi}, R_{0MH\pi_1}, R_{0MR\pi_2}$<1.
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3 Numerical results

Numerical simulate of the intracellular co-infection model of HBV and malaria were conducted having the initial conditions for the state variables as:$x = 1$,$y_H = 0.01$, $z_H = 0.01$, $y_M = 0.01$, $z_M = 0.02$, $y_{HM} = 0.01$, $B = 30$, $C = 10$, and $z_{MB} = 0.02$. We use a set of logical parameter values. The basic reproduction number of HBV/malaria co-infection model when control is effective is given as $(R_{0H}, R_{0M_H}, R_{0M_R}) = (0.3457,\ 0.0213, 0.9595)$ and when control is not effective is given as $(R_{0H}, R_{0M_H}, R_{0M_R}) = (4.3333,\ 1.2041, 22.9791)$. Graphical results are displayed in figures 2 to 7 and all the parameters with their values are shown in table 3 and 4. The simulations of model systems (2.3), (2.7) and (2.26) are performed with time 180 days. The simulations were in the presence of immune response and treatment.

Table 3: Parameter Value

Parameters	Value	***Parameters***	Value
ψ	3	γ_3	0.25
a_1	0.02	τ	0.00000001
β	1	a_6	0.002
μ	0.58	a_4	0.41
a_3	2	b_4	0.2
σ	0.01	φ	0.83

b_3	0.181	k_1	0.0083
Λ	48	d_1	0.0035
η	0.04	b_2	0.056
a_2	5	ρ	0.00000001
b_1	1	d_4	0.5
a_5	0.1	k_2	48
γ_1	1	k	0.16
γ_2	0.3	α	0.002

Table 4: Model parameter value for control

Parameters	Effective Control Value	Ineffective Control Value
ζ_1	0.004	0.4
ζ_2	0.0003	0.3
ζ_3	0.001	0.01
d_2	0.24	0.0024
d_3	0.3	0.98
π	0.98	0.75
π_1	0.98	0.05
π_2	0.98	0.05
ω	0.0004	0.4

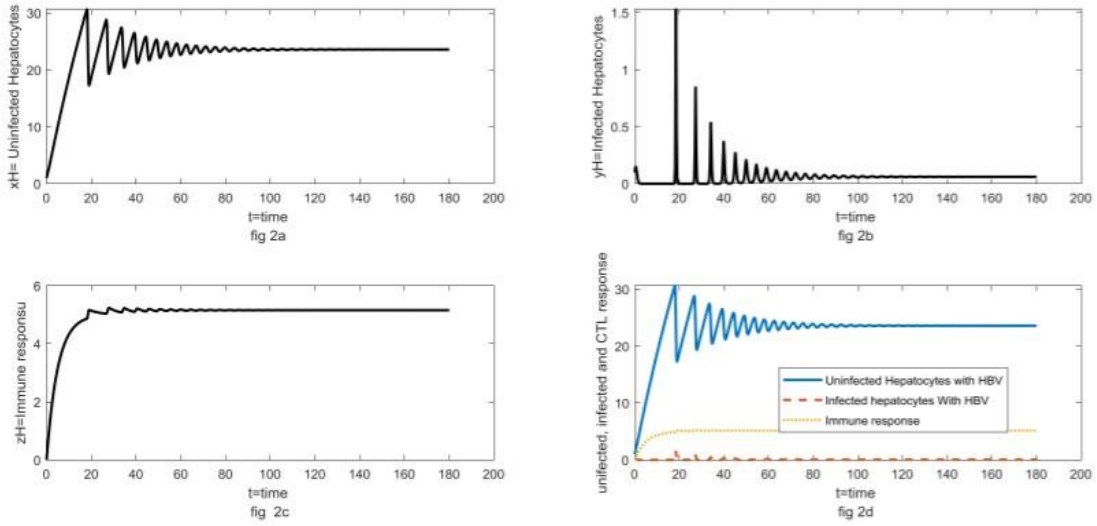
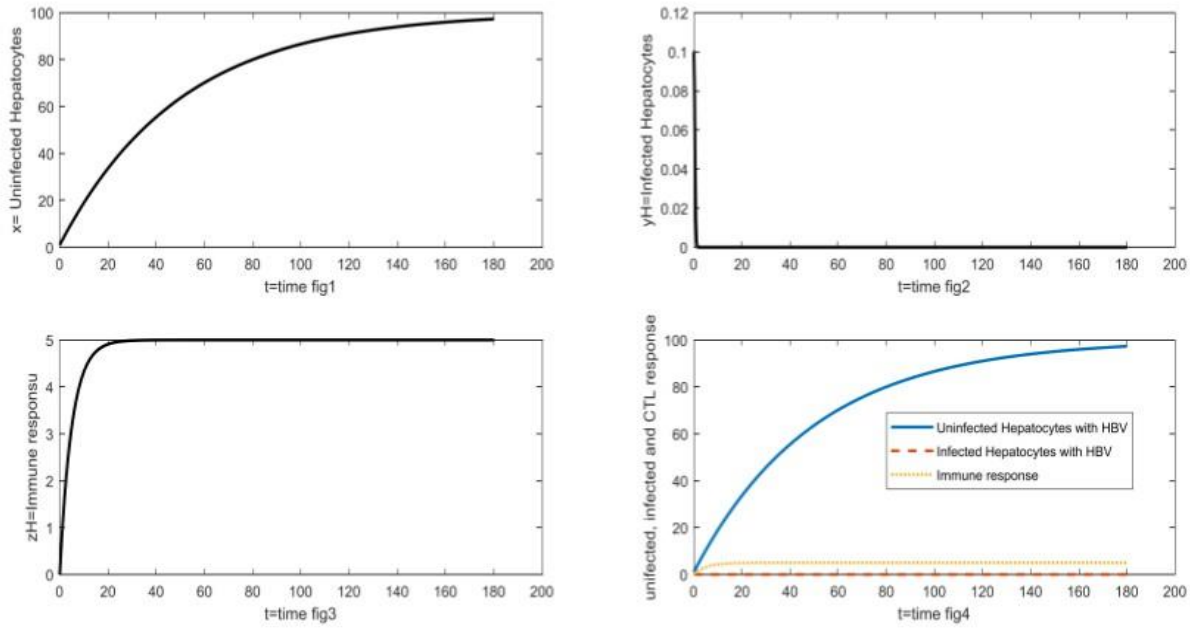
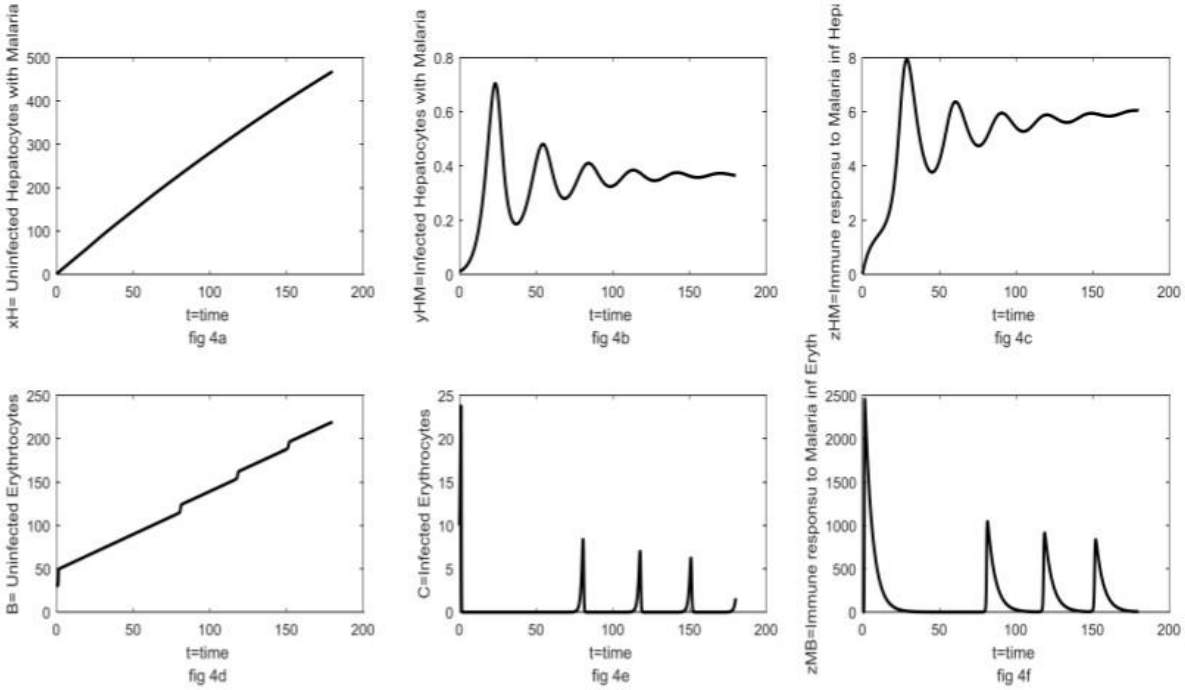


Figure 2(a-d): Simulation of HBV only model of system (2.7) where the proliferation rate of HBV infected hepatocytes is high, immune response is low and treatment rate is not effective.



Figures 3(a – d): Simulation of HBV only model of system (2.7) where the proliferation rate of HBV infected hepatocytes is slow and weak, immune response fast and strong, while treatment rate is effective.



Figures 4(a – f): Simulation of malaria only model of system (2.26) where the proliferation rate of malaria infected hepatocytes and erythrocytes is high and strong, immune response to both infected hepatocytes and erythrocytes is slow and weak with ineffective treatment rate.

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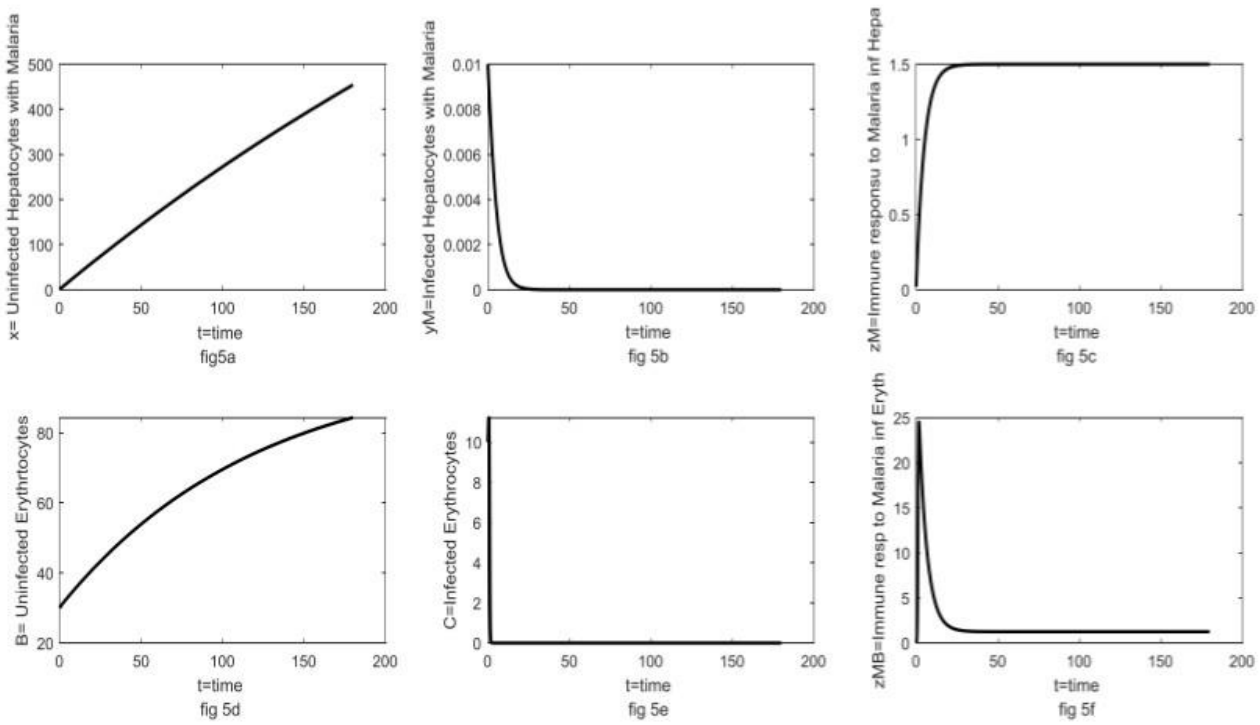
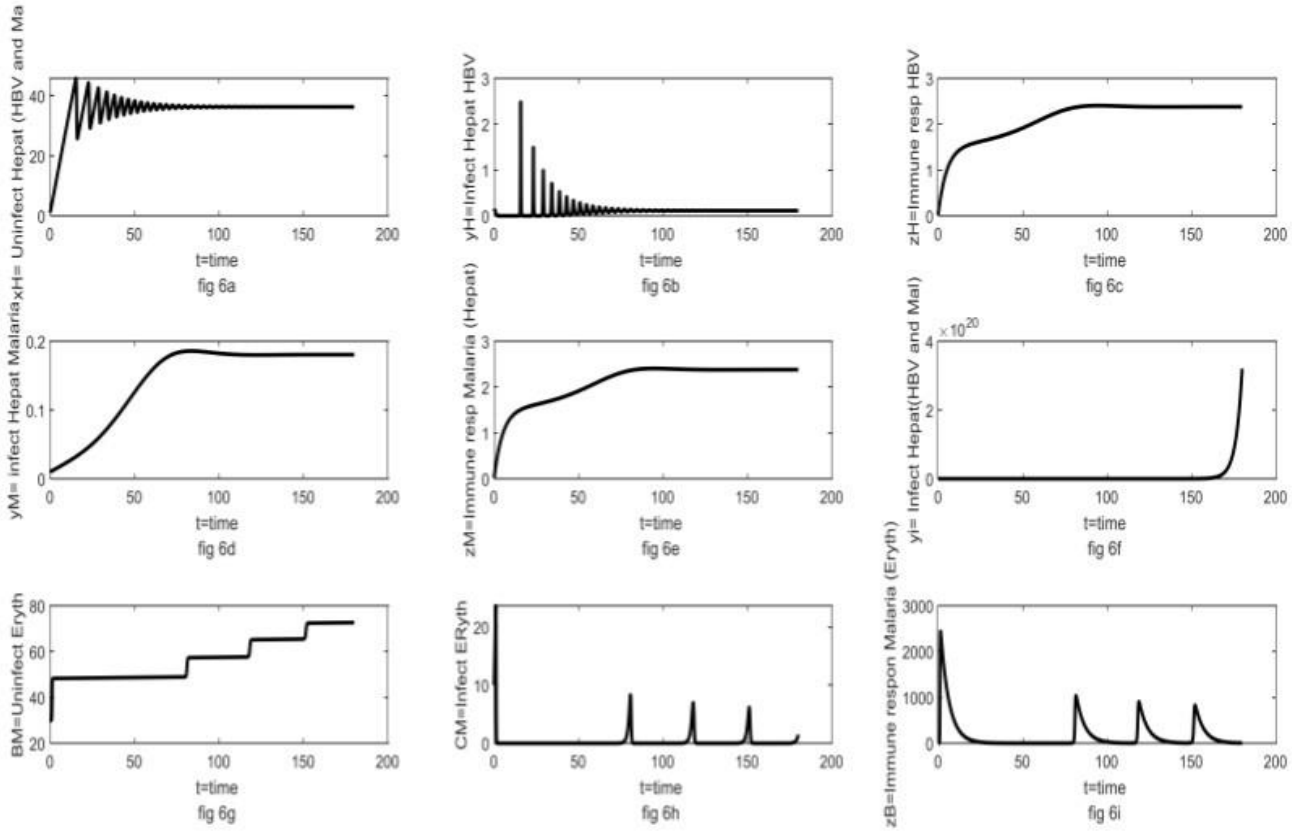
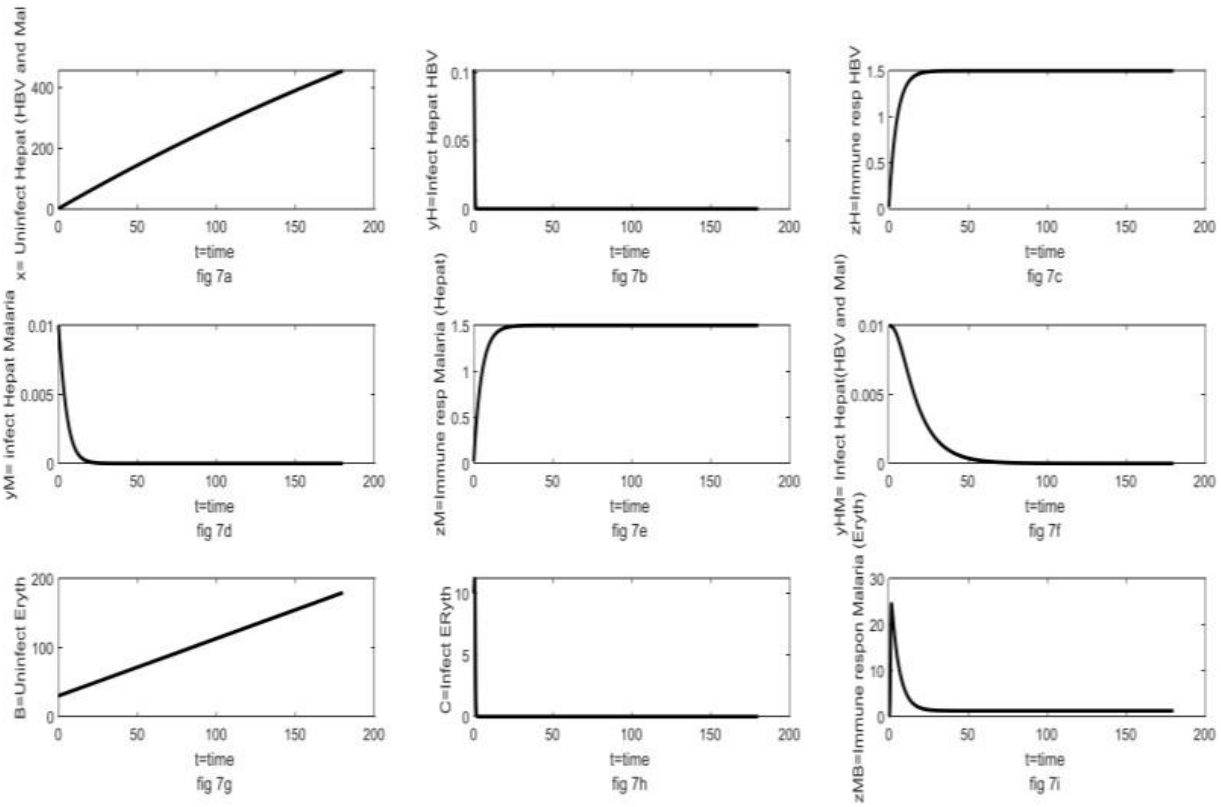


Figures 5(a – f): Simulation of malaria only model of system (2.26) where the proliferation rate of malaria infected hepatocytes and erythrocytes is slow and weak, immune response to both infected hepatocytes and erythrocytes is high and strong with effective treatment rate.



Figures 6(a – i): Simulation of HBV-malaria co-infection model of system (2.3) where the proliferation rate of malaria infected hepatocytes, erythrocytes and co-infected hepatocytes is strong, immune response to both infected hepatocytes, erythrocytes and co-infected hepatocytes is weak with ineffective treatment rate.



Figures 7(a – i): Simulation of HBV-malaria co-infection model of system (2.3) where the proliferation rate of malaria infected hepatocytes, erythrocytes and co-infected hepatocytes is weak, immune response to both infected hepatocytes, erythrocytes and co-infected hepatocytes is strong with effective treatment rate.

4 Discussion

From the simulation of BHV only model of system (2.7), we shall notice that HBV infection will persist in the cell population if treatment rate is not effective, immune response is slow and proliferation of HBV infected hepatocytes is high as displayed in figure 2(a-d). We observe the effect of immune response and treatment via the drastic reduction of the infected hepatocytes in figure 3(a-d). As expected, both the uninfected hepatocytes and immune response increases and this imply that with effective treatment and adequate immune response, HBV only infection can be controlled in the liver. Also, it is shown in figures 2 (a-d) that the infected hepatocytes with HBV oscillated for some time before becoming constant continually implying that the treatment and immune response are inadequate and this can lead to chronic HBV.

From the simulation of malaria only model of system (2.26) which was represented in figures 4(a-f), we observe the effect of immune response and treatment both in the hepatocytes and erythrocytes. The simulation results showed that treatment is ineffective within sufficient immune response and this is responsible for the increase in malaria infected hepatocytes and erythrocytes. Figure 5(a-f)

showed that malaria can be controlled in the heaptocytes and erythrocytes, that is, if immune response is fast and strong enough to slow the proliferation rate of both malaria infected hepatocytes and erythrocytes, and with effective treatment stop more cells from being infected. We also noticed that the level of malaria infected hepatocytes and erythrocytes were to a great extent diminished, whereas the uninfected hepatocytes and erythrocytes with malaria and immune responses increases.

Figures 6(a-i) denoted the simulation of HBV-malaria co-infection of model system (3) and it indicates that the rate of HBV-malaria co-infection in the hepatcytes continues to increase. The immune response and treatment control of HBV only infection was inadequate as the infected hepatocytes oscillated before becoming constant. But this is not the same with the immune response and treatment of malaria only infected hepatocytes because they are drastically reduced. This is why Kolawole and Kana [22] stated that individuals with HBV and malaria co-infection tend to have higher level of changes in their disease conditions compared to those with mono-infections. This simply implies that the presence of HBV and malaria co-infection in the hepatocytes and erythrocytes significantly affect the liver function and hematological parameters if not properly controlled in the cell population. Finally, figure 7(a-i) specifies that HBV and malaria co-infection can be controlled via reducing the rate at which hepatocytes are infected by both infections, rate of proliferation of co-infected hepatocytes and rate at which erythrocytes are infected with effectual treatment and fast and strong immune response.

5 Conclusion

In this paper, we considered the immune response and treatment effects hepatitis B Virus and malaria model with intracellular transmission. By the basic reproduction number R_{0H} for HBV in the hepatocytes and R_{0M} for malaria both in the hepatocytes and erythrocytes, which we respectively denoted by R_{0MH} and R_{0MR} were obtained using the next generation matrix.

In the proposed model, the modes of transmission of both infections with their processes were modeled using different functions. Firstly, the existence, positivity and boundedness of solutions of the problem that helps in guaranteeing the wellposedness of the co-infection model were proved. The locally asymptotic stability of both HBV only free and endemic equilibria and malaria only free and endemic equilibria were considered. By analyzing the effect of treatment on both HBV and malaria, we have from theorem 2.5 that the disease free equilibrium with treatment effects of HBV-malaria co-infection exists and is locally asymptotically stable if $R_{0H\pi} < 1, R_{0MH\pi_1} < 1$ and $R_{0MR\pi_2} < 1$ and unstable if $R_{0H\pi} > 1, R_{0MH\pi_1} > 1$ and $R_{0MR\pi_2} > 1$.

We observe from the analysis that if the cellular immune response for HBV only infection satisfies $\frac{\psi}{\mu a_1}(1-\pi)(\beta a_3 + \sigma\mu) + \zeta_1 < \frac{\gamma_1}{b_4}(a_2 + b_1) + a_1$,then the immune system and treatment is strong enough to eliminate the infection. But if $\frac{\psi}{\mu a_1}(1-\pi)(\beta a_3 + \sigma\mu) + \zeta_1 > \frac{\gamma_1}{b_4}(a_2 + b_1) + a_1$,chronic hepatitis appears because the immune system cannot clear the infection. Thus, if β and a_3 are large,

strong fast, then most of the hepatocytes will be infected with HBV and this will be eventually result to massive liver necrosis due to strong immune response.

Similarly, if the cellular immune response for HBV only infection satisfies $\varsigma_2 + \frac{(1+\pi_1)\eta b_3 \psi}{\Lambda a_1} < (b_2 + a_6)\frac{\gamma_2}{b_4} + a_1 + k$, then the immune response and treatment is capable of stopping the multiplication of sporozoites and subsequently eradicate them from the liver thereby preventing the production of merozoites that can infect the erythrocytes. $\varsigma_2 + \frac{(1+\pi_1)\eta b_3 \psi}{\Lambda a_1} > (b_2 + a_6)\frac{\gamma_2}{b_4} + a_1 + k$, then sufficient merozoite that can infect the erythrocytes would be produced. Also, if $\frac{(1-\pi_2)\alpha k \varphi}{k_1 k_2} + d_3 < k_1 + (d_1 + d_2)\frac{\gamma_3}{b_4}$, the immune response and treatment can control malaria in the erythrocytes. But if $\frac{(1-\pi_2)\alpha k \varphi}{k_1 k_2} + d_3 > k_1 + (d_1 + d_2)\frac{\gamma_3}{b_4}$, then there would be maximum damage caused to the erythrocytes and maximum concentration of merozoites which can be ingested by mosquito during blood meal.

Finally, if $\max\left\{\frac{\psi}{\mu a_1}(1-\pi)(\beta a_3 + \sigma\mu) + \zeta_1, \varsigma_2 + \frac{(1+\pi_1)\eta b_3 \psi}{\Lambda a_1} + \frac{(1-\pi_2)\alpha k \varphi}{k_1 k_2} + d_3\right\} < max\left\{\frac{\gamma_1}{b_4}(a_2 + b_1) + a_1, (b_2 + a_6)\frac{\gamma_2}{b_4} + a_1 + k + k_1 + (d_1 + d_2)\frac{\gamma_3}{b_4}\right\}$, then HBV-Malaria co-infection can be eradicated from the hepatocytes and erythrocytes by the combined effect of immune response and treatment. But if otherwise, the HBV-malaria co-infection will persist in the hepatocyte and erythrocyte population thereby causing serious damage to the co-infected individual.

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