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An SITR Analysis of Treatment Model of Hepatitis B Epidemic

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Abstract

This research article focuses on the formulation of a treatment model of hepatitis epidemic of type B. The dynamics of the model were studied and the local stability analyses of the equilibrium points of the model were investigated. Lyapunov functions were defined for the equilibrium points and their global stabilities were performed. It was shown that the global dynamics is determined by the basic reproduction ratio R_0. Thus, the disease-free is globally stable when $R_0 < 1$ and the endemic equilibrium is globally stable when $R_0 > 1$.
KEYWORDS: Next-generation matrix, Lyapunov function, Hepatitis B, Basic Reproduction ratio

1. INTRODUCTION

Disease modeling has brought many important underlying ideas in control intervention of infectious diseases to light ([8], [9], [10], [11], [13], [14]). One basic underlying idea is the estimation of the threshold parameter R_0 which tells us whether an invading epidemic into a susceptible population would be a failure to develop or develop. Hepatitis B virus (HBV), since its surfacing, has been steadily increasing over the last seven years and has become a major global health problem [3]. The hepatitis B virus is present in bodily fluids and is regarded to be easily acquired with a higher degree of infectiousness than the Human immunodeficiency virus (HIV). The virus incubation period is estimated to be about 90 days on the average, but can vary from about 30 to 180 days [18]. HBV may be detected 30 to 60 days after infection and persist for widely several period of time. (WHO, 2014), estimated that about 240 million people worldwide are infected with HBV, and about one third of this have chronic HBV infection and about 780,000 die each year from the HBV-related liver disease [23].

Hepatitis can be prevented with a vaccine. Vaccination against HBV infection provides long-term protection against infection and is ninety five percent effective in preventing infection and the development of chronic disease and liver cancer due to hepatitis B , and

therefore becomes safer and effective [4].

HBV modeling has increasingly attracted the attention of mathematical modelers and several works in that regards have been considered ([19], [20], [21], [22]). However, most of these works have focused on vaccination. Thus, often, vaccination of HBV is considered for children and adults in the susceptible class and the exposed periods.

This research focuses on the formulation of a treatment model for hepatitis epidemic of type B, in order to understand the epidemic phenomenon and to investigate the effect of treatment on the infective class. Treatment here refers to the process of offering the HBV infected individual with antiretroviral treatment. We define a lyapunov function to investigate the global stabilities of the disease-free equilibrium and the endemic equilibrium. The model is developed in section 2. The basic reproduction ratio is deduced and shown to be a threshold parameter by using the next-generation matrix. The section 3 investigates the global stability of the disease free and the endemic equilibrium. The section 4 provides the simulation, discussion and the concluding remarks.

2. The Model Formulation

A treatment model in a constant population where birth rate equal death rate is considered in a mixing homogeneous population. The total population is categorized into four compartments namely susceptible $S(t)$, infective , $I(t)$, treated class, $T(t)$, and removed class, $R(t)$. Here, there is an influx of newly recruited to the susceptible class at a rate of μ. Infection invades the susceptible class at a rate of β. It is assumed that only a fraction of the population seeks medical attention, and hence represents the treated class. Treatment here is defined as the process of offering the Hepatitis of type B infected person with a life prolonging medicine known as antiretroviral (ARV) drug or treatment (ART). Recruitment into the treated class occur at a rate of λ. Again, infected individuals are recruited into the removed class at a rate of γ, while treated individuals also move to the removed class at a rate of δ. At the same time, natural death occur at the different compartments.

Hence the flowchart of the SITR model underlying the given assumption is as shown below.

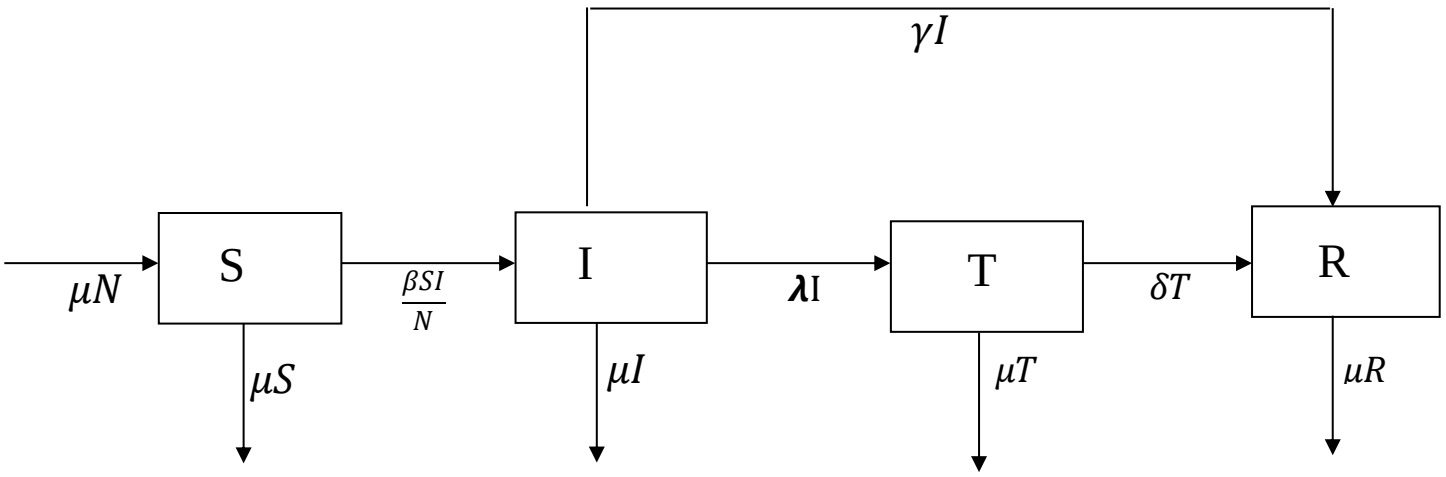

Figure 1: Schematics of the susceptible –Infected-Treated-Removed (SITR) model

The non-linear system of differential equations describing the model are given by

$$\frac{ds}{dt} = \mu N - \mu S - \beta \frac{SI}{N} \quad (1)$$

$$\frac{dI}{dt} = \beta \frac{SI}{N} - \mu I - \gamma I - \lambda I \quad (2)$$

$$\frac{dT}{dt} = \lambda I - \mu T - \delta T \quad (3)$$

$$\frac{dR}{dt} = \gamma I + \delta T - \mu R \quad (4)$$

where $(0) = S_0 \geq 0$, $I(0) = I_0 \geq 0$, , $T(0) = T_0 \geq 0$, , $R(0) = R_0 \geq 0$for every $t \geq 0$.

The total population, N for the model is given by

$$N = S + I + T + R \quad (5)$$

Dividing equation (5) by N and substituting the fractional variables $s = \frac{S}{N}$, $i = \frac{I}{N}$, $z = \frac{T}{N}$, $r = \frac{R}{N}$ into equations (1-4) gives:

$$\frac{ds}{dt} = \mu - \mu s - \beta si \quad (6)$$

$$\frac{di}{dt} = \beta si - \mu i - \gamma i - \lambda i \quad (7)$$

$$\frac{dz}{dt} = \lambda i - \mu z - \delta z \quad (8)$$

$$\frac{dr}{dt} = \gamma i + \delta z - \mu r \quad (9)$$

Since $r = 1 - s - i - z$, we can ignore equation (9) and the resulting reduced system becomes

$$\frac{ds}{dt} = \mu - \mu s - \beta si \qquad (10)$$

$$\frac{di}{dt} = \beta si - (\mu + \gamma + \lambda)i \qquad (11)$$

$$\frac{dz}{dt} = \lambda i - (\mu + \delta)z \qquad (12)$$

2.1 Model Equilibria

The derivatives $\frac{ds}{dt}$, $\frac{di}{dt}$ and $\frac{dz}{dt}$ of the equations (10-12) are set to zero and then solved to find the two equilibriums points. Hence the disease-free equilibrium (DFE) point of the model is

$E_0 = (S_0, i_0, z_0) = (1,0,0)$ and the endemic equilibrium point is

$$E_1 = (s^*, i^*, z^*) = \left(\frac{(\mu+\gamma+\lambda)}{\beta}, \frac{\mu(\mu+\gamma+\lambda)-\beta\mu}{\beta(\mu+\gamma+\lambda)}, \lambda\left(\frac{\mu(\mu+\gamma+\lambda)-\beta\mu}{\beta(\mu+\delta)(\mu+\gamma+\lambda)}\right)\right).$$

2.2 Basic Reproduction Ratio (R_0)

One question of importance in epidemiology is to estimates a threshold parameter that determines whether an invading infection into a susceptible population will spread or would be failure to spread. It is defined as new infections from a single infected person introduced into a population originally free of infection. According to Driessche and Diekmann ([1], [2], [15], [16]), the basic reproduction ratio can be defined as

$$R_0 = \rho(FV^{-1}) \qquad (13)$$

where ρ is defined as the spectral radius of the Next Generation Matrix (FV^{-1}), F is the rate of invading of new infections in compartment i and V is the transfer of individuals out of compartment i by death and recovery.

When the DFE is determined, R_0 is derived as the largest eigenvalue of the matrix of partial derivative

$$\left[\frac{\partial \mathcal{F}_i(E_0)}{\partial X_j}\right]\left[\frac{\partial \mathcal{V}_i(E_0)}{\partial X_j}\right]^{-1}. \qquad (14)$$

Furthermore, if the reproduction number $R_0 = \rho(FV^{-1})$ is consistent with the differential equation model, then it should follow that the disease-free equilibrium is asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$. Hence the basic reproduction ratio could be seen as a ‘‘pilot ’’ of disease spread in epidemiology.

Applying the Next generation method to systems (10-12), we only need to consider the

infective differential equations $\frac{di}{dt}$ and $\frac{dz}{dt}$. Thus

$$\frac{di}{dt} = \beta si - (\mu + \gamma + \lambda)i \quad (15)$$

$$\frac{dz}{dt} = \lambda i - (\mu + \delta)z \quad (16)$$

Hence $\mathcal{F} = \begin{bmatrix} \beta si \\ 0 \end{bmatrix}$ and $\mathcal{V} = \begin{bmatrix} (\mu + \gamma + \lambda)i \\ -\lambda i + (\mu + \delta)z \end{bmatrix}$.

This implies $F = \begin{bmatrix} \frac{\partial}{\partial i}(\beta si) & \frac{\partial}{\partial z}(\beta si) \\ \frac{\partial}{\partial i}(0) & \frac{\partial}{\partial z}(0) \end{bmatrix}$

$$F = \begin{bmatrix} \beta s & 0 \\ 0 & 0 \end{bmatrix}$$

Evaluating F at the disease –free equilibrium E_0 gives

$$F(E_0) = F(1,0,0) = \begin{bmatrix} \beta & 0 \\ 0 & 0 \end{bmatrix}$$

Again, the matrix of transfer between compartments (V) becomes

$$V = \begin{bmatrix} \frac{\partial}{\partial i}(\mu + \gamma + \lambda)i & \frac{\partial}{\partial z}(\mu + \gamma + \lambda)i \\ \frac{\partial}{\partial i}(-\lambda i + z(\mu + \delta)) & \frac{\partial}{\partial z}(-\lambda i + z(\mu + \delta)) \end{bmatrix}$$

$$V = \begin{bmatrix} (\mu + \gamma + \lambda) & 0 \\ -\lambda & (\mu + \delta) \end{bmatrix}$$

Evaluating V at the disease –free equilibrium E_0 gives

$$V(E_0) = V(1,0,0) = \begin{bmatrix} (\mu + \gamma + \lambda) & 0 \\ -\lambda & (\mu + \delta) \end{bmatrix}$$

$$V^{-1} = \begin{bmatrix} \frac{1}{(\mu+\gamma+\lambda)} & 0 \\ \frac{\lambda}{(\mu+\delta)(\mu+\gamma+\lambda)} & \frac{1}{(\mu+\delta)} \end{bmatrix}$$

But from (14), $R_0 = \rho(FV^{-1})$, hence

$$FV^{-1} = \begin{bmatrix} \frac{\beta}{(\mu+\gamma+\lambda)} & 0 \\ 0 & 0 \end{bmatrix}$$

Hence the spectral radius of the next generation matrix is

$$R_0 = \frac{\beta}{(\mu+\gamma+\lambda)} \quad (17)$$

3. Local stability of the Disease- free Equilibrium (DFE)

The disease-free equilibrium has no presence of infection. Hence it follows that $I = 0$ at this stage. The stability analysis of the disease-free equilibrium is investigated by using linearization approach.

Lemma 3 : If $R_0 < 1$, then the disease–free equilibrium is locally asymptotically stable. The lemma is proved by the Hartman-Grobmann theorem ([17]).

Proof: The linearization of the system of equations of the model is given by

$$J = \begin{bmatrix} -\mu - \beta i & -\beta s & 0 \\ \beta i & \beta s - (\mu + \gamma + \lambda) & 0 \\ 0 & \lambda & -(\mu + \delta) \end{bmatrix}$$

Evaluating the Jacobian matrix at the disease–free equilibrium point $E_0 = (S_0, i_0, z_0) = (1,0,0)$ gives

$$J(1,0,0) = \begin{bmatrix} -\mu & -\beta & 0 \\ 0 & \beta - (\mu + \gamma + \lambda) & 0 \\ 0 & \lambda & -(\mu + \delta) \end{bmatrix}$$

Evidently, the eigenvalues of the disease-free equilibrium DFE are given by
$P_1 = -\mu$, $P_2 = \beta - (\mu + \gamma + \lambda)$, $P_3 = -(\mu + \delta)$.
Clearly, the two eigenvalues $P_1 = -\mu$ and $P_3 = -(\mu + \delta)$ are negatives since $\mu,\ \delta > 0$. The disease-free equilibrium would then be stable if
$P_2 = \beta - (\mu + \gamma + \lambda) < 0$,
otherwise unstable. If $P_2 < 0$ then

$$\beta - (\mu + \gamma + \lambda) < 0 \qquad (18)$$
$$\Rightarrow \beta < (\mu + \gamma + \lambda)$$
$$\Rightarrow \frac{\beta}{(\mu+\gamma+\lambda)} < 1$$

Hence $R_o < 1$. However, if $R_o < 1$, it could be deduced that the inequality (18) holds and hence lemma 3 is proved. Imperatively, $R_o < 1$, corresponds to the stability of the disease-free equilibrium and hence suggests the failure of epidemic to develop.

3.1 Global stability of the Disease- free equilibrium (DFE)

Lemma 3.1: The disease-free equilibrium $E_0 = (S_0, i_0, z_0) = (1,0,0)$ is globally asymptotically stable in R^3 if $R_0 < 1$.

Proof: We construct a Lyapunov function $L(s,i,z): R^3 \to R^+$ as $L(s,i,z) = vi$ for every $v \geq 0$ for the disease-free equilibrium $E_0 = (S_0, i_0, z_0) = (1,0,0)$.

Differentiating $L(s,i,z)$ with respect to time gives $\frac{dL}{dt}(s,i,z) = v\frac{di}{dt}$. Substituting the equations (10-12) gives

$$\frac{dL}{dt}(s,i,z) = v(\beta si - (\mu + \gamma + \lambda)i)$$

$$= v(\beta s - (\mu + \gamma + \lambda))i$$
$$= v(\beta - (\mu + \gamma + \lambda))i \quad \text{since} \quad s = 1 \quad \text{at} \quad t_0$$
$$= v(\mu + \gamma + \lambda)\left(\frac{\beta}{(\mu+\gamma+\lambda)} - 1\right)i$$

But $R_0 = \frac{\beta}{(\mu+\gamma+\lambda)}$, setting $v = \frac{1}{(\mu+\gamma+\lambda)}$ gives

$$\frac{dL}{dt}(s,i,z) = (R_0 - 1)i \leq 0 \qquad (19)$$

From (19), when $i = 0$, $\frac{dL}{dt}(s,i,z) = 0$, substituting $i = 0$ into equations (11)-(13) for $\frac{ds}{dt}$ and $\frac{dz}{dt}$ gives $s \to 1$ and $z \to 0$ as $t \to \infty$. It follows that ([2], [5]), the maximum invariant set in $\{(s,i,z) \in \tau | \frac{dL}{dt}(s,i,z) \leq 0)\}$ is the singleton set $\{E_0\}$.

Hence, from LaSalle's invariance principle (Lasalle,1976) , $E_0 = (S_0, i_0, z_0) = (1,0,0)$ is globally stable when $R_0 < 1$.

3.2 Local stability of the endemic equilibrium (EE)

Lemma 3.2: If $R_0 > 1$, then the endemic equilibrium is locally asymptotically stable.

Proof: The Jacobain matrix for the systems of equations is given by

$$J = \begin{bmatrix} -\mu - \beta i & -\beta s & 0 \\ \beta i & \beta s - (\mu + \gamma + \lambda) & 0 \\ 0 & \lambda & -(\mu + \delta) \end{bmatrix}$$

At the endemic equilibrium $E_1 = (s^*, i^*, z^*) = \left(\frac{(\mu+\gamma+\lambda)}{\beta}, \frac{\mu(\mu+\gamma+\lambda)-\beta\mu}{\beta(\mu+\gamma+\lambda)}, \lambda\left(\frac{\mu(\mu+\gamma+\lambda)-\beta\mu}{\beta(\mu+\delta)(\mu+\gamma+\lambda)}\right)\right)$.

$$J(s^*, i^*, z^*) = \begin{pmatrix} \mu - \frac{\beta(\mu(\mu+\gamma+\lambda)-\beta\mu))}{\beta(\mu+\gamma+\lambda)} & \frac{-\beta(\mu+\gamma+\lambda)}{\beta} & 0 \\ \frac{\beta(\mu(\mu+\gamma+\lambda)-\beta\mu))}{\beta(\mu+\gamma+\lambda)} & \frac{\beta(\mu+\gamma+\lambda)}{\beta} - (\mu + \gamma + \lambda) & 0 \\ 0 & \lambda & -(\mu + \delta) \end{pmatrix}$$

$$J(s^*, i^*, z^*) = \begin{pmatrix} R_0\mu & (\mu + \gamma + \lambda) & 0 \\ \mu(1 - R_0) & 0 & 0 \\ 0 & \lambda & -(\mu + \delta) \end{pmatrix}.$$

Hence $|A - \lambda I| = det \begin{bmatrix} R_0\mu - \lambda & (\mu + \gamma + \lambda) & 0 \\ \mu(1 - R_0) & -\lambda & 0 \\ 0 & \lambda & -(\mu + \delta) - \lambda \end{bmatrix}$.

Hence the characteristic equation is therefore given by

$$a_0\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0 \qquad (20)$$

where

$a_0 = 1 \ , \quad a_1 = \big((\mu+\delta) - R_0\mu\big)\big) \ ,$

$a_2 = \big(\big(\mu(1-R_0)(\mu+\gamma+\lambda) - R_0\mu(\mu+\delta)\big)\big)$ and

$a_3 = \mu(\mu+\delta)(1-R_0)(\mu+\gamma+\lambda)$

By Hurwitz criterion ([5], [6]), the necessary and sufficient conditions of the characteristic equation of the cubic polynomial (20) to have a negative real part is
$a_0 > 0, \ a_1 a_2 > a_3 > 0.$ Hence the endemic equilibrium is locally asymptotically stable if the conditions are satisfied, otherwise unstable.

3.3 Global stability of the endemic equilibrium (EE)

Lemma 3.3: If $s = s^*, \ i = i^*$ and $z = z^*$, then the system (10-12) is said to be globally asymptotically stable if $R_0 > 1$ and unstable when $R_0 < 1.$

Proof : A Lyapunov function

$$L(s^*, i^*, z^*) = u_1\left(s - s^* - s^* \ln\left(\frac{s}{s^*}\right)\right) + u_2\left(i - i^* - i^* \ln\left(\frac{i}{i^*}\right)\right) +$$

$$u_3\left(z - z^* - z^* \ln\left(\frac{z}{z^*}\right)\right),$$

for $u_1 > 0, \ u_2 > 0 \ , u_3 > 0$ in $L(s^*, i^*, z^*)$: $R^3 \to R^+$ is defined for the endemic equilibrium

$$E_1 = (s^*, i^*, z^*) = \left(\frac{(\mu+\gamma+\lambda)}{\beta}, \frac{\mu(\mu+\gamma+\lambda)-\beta\mu}{\beta(\mu+\gamma+\lambda)}, \lambda\left(\frac{\mu(\mu+\gamma+\lambda)-\beta\mu}{\beta(\mu+\delta)(\mu+\gamma+\lambda)}\right)\right)$$

By direct calculation, we obtained;

$$\frac{dL}{dt} = u_1\left(\frac{s-s^*}{s}\right)\frac{ds}{dt} + u_2\left(\frac{i-i^*}{i}\right)\frac{di}{dt} + u_3\left(\frac{z-z^*}{z}\right)\frac{dz}{dt}$$

Hence

$$\frac{dL}{dt} = u_1\left(\frac{s-s^*}{s}\right)(\mu - \mu s - \beta s i) + u_2\left(\frac{i-i^*}{i}\right)\big(\beta s i - i(\mu+\gamma+\lambda)\big) + u_3\left(\frac{z-z^*}{z}\right)\big(\lambda i -$$

$$z(\mu+\delta)\big)$$

$$\frac{dL}{dt} = u_1\left(\frac{s-s^*}{s}\right)\big(\mu - \mu(s-s^*) - (\beta)(s-s^*)(i-i^*)\big) + u_2\left(\frac{i-i^*}{i}\right)\big(\beta(s-s^*)(i-i^*) -$$

$$(i-i^*)(\mu+\gamma+\lambda)\big) + u_3\left(\frac{z-z^*}{z}\right)\big(\lambda(i-i^*) - (z-z^*)(\mu+\delta)\big)$$

This implies

$$\frac{dL}{dt} = u_1\left(\mu\left(\frac{s-s^*}{s}\right) - \mu\left(\frac{(s-s^*)^2}{s}\right) - \beta\left(\frac{(s-s^*)^2}{s}\right)(i-i^*)\right) + u_2\left(\beta(s-s^*)\left(\frac{(i-i^*)^2}{i}\right) -\right.$$

$$\left.\left(\frac{(i-i^*)^2}{i}\right)(\mu+\gamma+\lambda)\right) + u_3\left(\lambda\left(\frac{z-z^*}{z}\right)(i-i^*) - \left(\frac{(z-z^*)^2}{z}\right)(\mu+\delta)\right) \qquad (21)$$

Grouping the negatives and positive terms and setting $u_1 = u_2 = u_3 = 1$ gives

$\frac{dL}{dt} = T_1 - T_2$

where

$T_1 = \mu + \beta i\left(\frac{(s-s^*)^2}{s}\right)^* + \beta s\left(\frac{(i-i^*)^2}{i}\right) + \lambda i + \frac{\lambda i^* z^*}{z^*}$

$T_2 = \frac{\mu s^*}{s} + \mu\left(\frac{(s-s^*)^2}{s}\right) + \beta i\left(\frac{(s-s^*)^2}{s}\right) + \beta s\left(\frac{(i-i^*)^2}{i}\right) + \left(\frac{(i-i^*)^2}{i}\right)(\mu+\gamma+\lambda) + \frac{\lambda i z^*}{z} + \lambda i^* + \left(\frac{(z-z^*)^2}{z}\right)(\mu+\delta)$

It could be verified that $T_1 < T_2$. This yields $\frac{dL}{dt} \leq 0$ when $T_1 < T_2$.

Hence, it could be deduced that $\frac{dL}{dt} = 0$ if and only if $s = s^*,\ i = i^*,\ z = z^*$. This implies that the largest compact invariant set $\left\{(s^*, i^*, z^*)\epsilon\tau : \frac{dL}{dt} = 0\right\}$ is a singleton $\{{E_1}^*\}$, where ${E_1}^*$ is the endemic equilibrium. From ([2], [5] ,[6]) LaSalle's invariant principle, ${E_1}^*$ is globally asymptotically stable in τ if $T_1 < T_2$.

4. Numerical Simulations

The system (10-12) is simulated for various sets of parameter values using Matlab, in order to comprehend the dynamic of the model. The simulated results display a significant rise in the infective class during the early stages of the epidemic, and slowly decreases before it maintain its equilibrium. To investigate the effect of treatment on the dynamics of the model, we simulated the model over a different set of values of the treatment rates. Our results indicate that an increase in the treatment rate has the effect of reducing the number of disease infections in the treated class. Hence, it has effect on the number of successive cases in a hepatitis B epidemic.

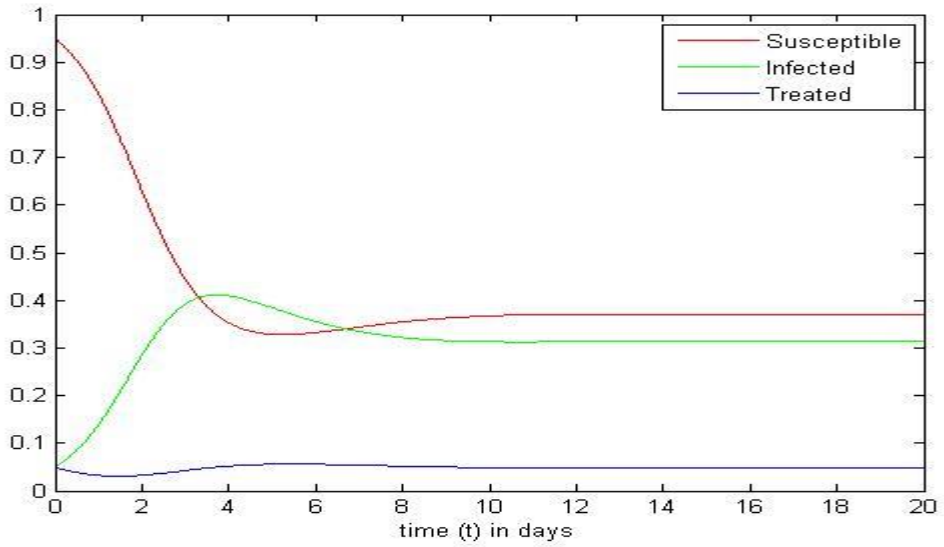

Figure 1 Solutions of the SIT model using the parameter values $\beta = 1.95$, $\delta = 0.3$, $\lambda = 0.1$, $\mu = 0.36$, $\gamma = 0.26$

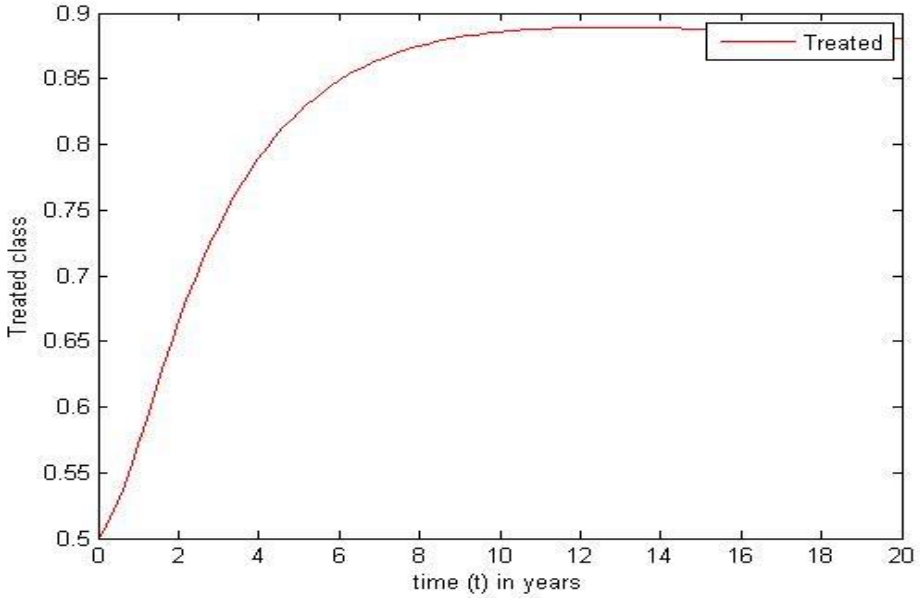

Figure 2 Disease infections in the treated class with a treatment rate $\delta = 0.001$

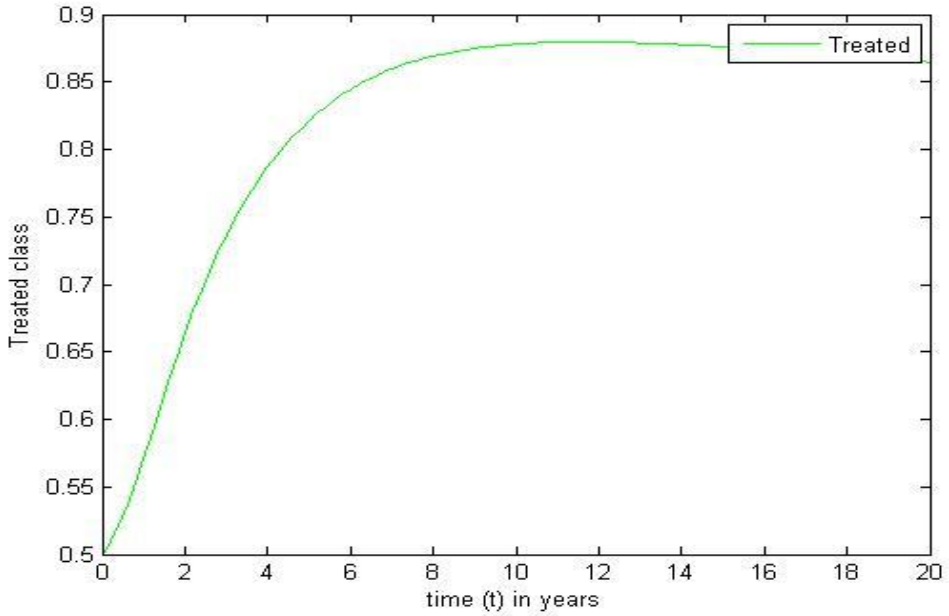

Figure 3 Disease infections in the treated class with a treatment rate $\delta = 0.002$

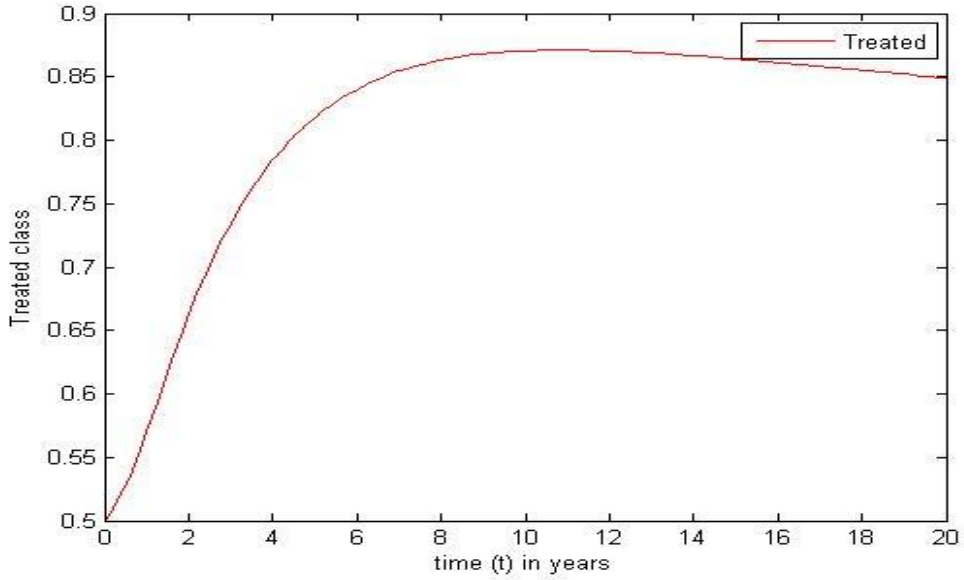

Figure 4 Disease infections in the treated class with a treatment rate $\delta = 0.003$

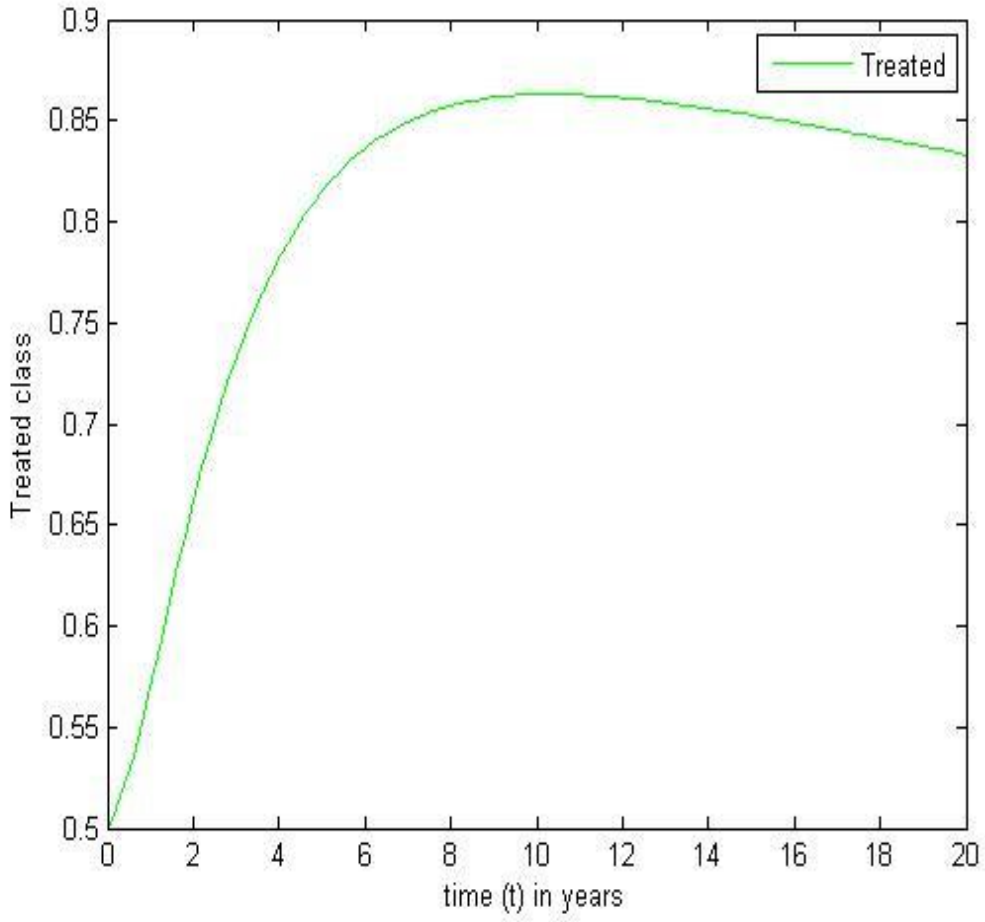

Figure 5 Disease infections in the treated class with a treatment rate $\delta = 0.004$

4.1 Conclusion

As already mentioned, our primary purpose in this research was to formulate and study a mathematical model for hepatitis disease of type B in order to understand the epidemic phenomenon and suggests intervention strategies for the control for the epidemic in general. The local and the global qualitative analysis of both the disease-free and the endemic equilibrium were carried out. In regards to the basic reproduction ratio

$R_0 = \frac{\beta}{(\mu+\gamma+\lambda)}$, the analysis showed that when $R_0 < 1$, the disease-free equilibrium is globally stable, and the endemic equilibrium is globally stable when $R_0 > 1$.

To understand the effect of treatment on the model, we simulated the model over different parameter values of the treatment rate. The results showed that increasing the treatment rate decreases the disease infection in the treated class as compared in figures 2, 3, 4 and 5. We conclude that treatment intervention strategy, though it leads to drug resistance, should be encouraged since it helps to reduce the proportion of the infected and prolongs the lives of all infected individuals.

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