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Mathematical Modelling of Spread and Control of the Hepatitis C Virus

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Abstract: ***In this research paper, we developed and analysis a mathematical model of hepatitis C virus transmission we formulated and investigated using ordinary differential equations and a Susceptible-Infected- Removed model with partitioned population across disease risk factors. The feasible region of the model was verified and the positivity of the solutions was shown. The Disease Free Equilibrium and the Endemic Equilibrium are obtained. The basic reproduction numbers of the model are computed and analysed and both the local and global stability of the disease free and endemic equilibrium are shown. The model was implemented and verified with simulation across various population partitions.***

Keywords: Modeling, Hepatitis C virus, Control, Equilibrium, Stability, Spread

1. Introduction

"Hepatitis C is the disease caused by the hepatitis C virus (HCV). The infection causes acute and chronic infection, running in seriousness from a gentle disease enduring half a month to a genuine, long lasting sickness" [8]. Hepatitis C infection (HCV) is a typical reason for liver sickness and a significant general medical issue around the world. More than two decades ago, HCV was recognized and the chance of screening blood items for sullying with hepatitis C emerged [4].

The Hepatitis C virus is a problem found across the world. Hepatitis C is a blood- borne disease that can be contracted whenever there is an exposure to a contaminated blood. Globally about 170 million people are infected by the disease [1]. Transmission of hepatitis C infection occurs by introduction to the blood stream of contaminated blood or body liquids containing blood. "The major route of transmissions includes unprotected sexual contact, blood transfusions, re-utilization of tainted needles and syringes, and vertical transmission from mother to child amid labor" [4]. The World Health Organization (WHO) indicates that the "most affected regions are the WHO Eastern Mediterranean Region and the WHO European Region, with an estimated prevalence in 2015 of 2.3% and 1.5% respectively" [8]. Mathematical modeling and scientific visualization helps characterize issues, under- stand information, impart and evaluate comprehension, and forecast outcomes. Use of a deterministic compartmental model provides methods for exploring elements of viral trans- mission and its control among the various susceptible and infected population subgroups. A deterministic compartmental model thus serves as a research tool for development of epidemiological information. A particular epidemiological parameter of interest is the "energy of contamination". This is the normal rate at which susceptible people become infected. In an open populace where people are tracked after initial infection with HCV disease and when they become chronic, the energy of contamination can be determined.

Over the last two decades, numerous mathematicians have investigated numerical models on the transmission and control of hepatitis C infection. This includes Dontwi *et al.*[4], Lemon and Brown [5], Nowak *et al.* [6], and Hickman [7], who have utilized a variety of numerical models to assess and control the spread of hepatitis C infection.

2. Model Formulation

In this model develops and analyses a mathematical model of transmission dynamics of hepatitis C infection. Before the formulation of the model, the population is subdivided into the following epidemiological classes or subgroups namely: susceptible $S(t)$, acutely infected $A(t)$, chronically infected $C(t)$, and recovered $R(t)$; where susceptible is the group of individuals in the total population who are not yet infected by the disease, acutely infected are the group of individuals infected but are not yet highly infectious, chronically infected are the individuals infected by the disease and are very infectious, and recovered are individuals who have respond to treatment and are cured. Thus the total population $N(t)$s given by $N(t)=S(t)+A(t)+C(t)+R(t)$. The susceptible individuals are recruited into the population through birth and migration at a constant rate π.A susceptible individual becomes exposed to the hepatitis C virus after coming into contact with an infected persons and transfer to the acute infected state at a rate βC, where βC is the product of the effective contact rate and probability per

contact with an infectious person. A susceptible individual can die of a cause unrelated to HCV at the rate μ After a while the initially infected (exposed) but not symptomatic individual may show symptoms and move to infected (symptomatic) chronic class at a rate ϕ or may be treated and move to the recovered class at a rate γ. Individuals in this class can die naturally at a constant rate μ. Individuals in the chronic infected and symptomatic class will either die of the disease at the rate δ or die naturally at the rate μ or get treated and recover from the disease at the rate τ and move into recovered class. The corresponding mathematical equations of the schematic diagram can be described by a system of ordinary differential equations given below:

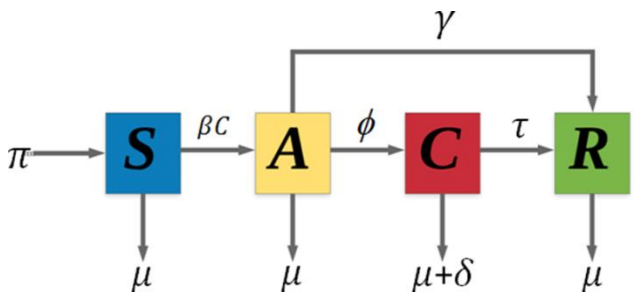


Figure 1: The Flow Diagram

Table 3.1: Notation and definition of variables and parameter

Symbol	Description
$S(t)$	Susceptible individuals at time, t
$A(t)$	Acutely infected individuals at time, t
$C(t)$	Chronically infected individuals at time, t
$R(t)$	Recovered individuals at time, t
$N(t)$	Total population at time, t
π	Constant recruitment rate
β	Contact rate at which susceptible become infected
μ	Death removal rate due to other causes other than HCV
δ	Death rate due to HCV
γ	The rate at which acutely infected recover
τ	Treatment rate for chronically infected
ϕ	The rate at which acutely infected becomes chronic.

2.1 The Model Equations

From the assumptions and the dynamics between the compartments shown in the model compartments in figure 1, the effect of immunization on the epidemiology of hepatitis C virus is modeled by the following system of ordinary differential equations;

$$\left.\begin{aligned}\frac{dS}{dt}&=\pi-(\beta C+\mu)S\\ \frac{dA}{dt}&=\beta CS-(\phi+\gamma+\mu)A\\ \frac{dC}{dt}&=\phi A-(\tau+\delta+\mu)C\\ \frac{dR}{dt}&=\gamma A+\tau C-\mu R\end{aligned}\right\} \quad (1)$$

Analysis of the Model Equations

Theorem 1: (Invariant Region) The following biological feasible region of the model equations (1)

$$\Omega=\{(S,A,C,R)\in\Re_+^4 : S(t)+A(t)+C(t)+R(t)\le\frac{\pi}{\mu}\} \quad (2)$$

Is positively invariant.

Proof: Adding all the equations model in (1) we have

$$\frac{dN}{dt}=\frac{dS}{dt}+\frac{dA}{dt}+\frac{dC}{dt}+\frac{dR}{dt} \quad (3)$$

$$\frac{dN}{dt}=\pi-(S+A+C+R)-\delta C \quad (4)$$

So that

$$\frac{dN}{dt}\le\pi-\mu N \quad (5)$$

It follows from the Gronwall inequality

$$N(t)\le N(0)e^{-\mu(t)}+\frac{\pi}{\mu}\left(1-e^{-\mu(t)}\right) \quad (6)$$

Hence $N(t)\le\frac{\pi}{\mu}$ if $N(0)\le\frac{\pi}{\mu}$ (7)

Thus Ω is positively invariant, and therefore the model equation (1) is epidemiologically and mathematically well posed.

Theorem 2: (Positivity of the solution for the model) If we let $t_0>0, S(0)>0, A(0)>0, C(0)>0$ and $R(0)>0$ then the solutions $S(t), A(t), C(t)$ and $R(t)$ of the model equations in (1) are positive for every $t\ge 0$

Proof: We will prove $S(t), A(t), C(t)$ and $R(t)$ a repositive in $\Re_+^4$ for all $t\in[0,t_0]$.

Note that all model parameters are positive. It follows from the first equation in (1) that

$$\frac{dS}{dt}=\pi-\beta SC-\mu S\ge-(\beta C+\mu)S \quad (8)$$

So that we have

$$S(t)\ge S(0)e^{-\int(\beta C+\mu)dt}\ge 0. \quad (9)$$

Also we can show from the second equation in (1) that is

$$\frac{dA}{dt} = \beta SC - (\phi + \gamma + \mu)A \geq -(\phi + \gamma + \mu)A \quad (10)$$

So that

$$A(t) \geq A(0)e^{-\int(\phi+\gamma+\mu)dt} \geq 0. \quad (11)$$

Similarly, it can be verified that the rest of the equations are positive for all $t > 0$, since $e^{\omega} > 0 \forall \omega \in \Re$.

3.3 Disease Free Equilibrium State

The disease-free equilibrium of the model (1) is obtained by setting

$$\frac{dS}{dt} = \frac{dA}{dt} = \frac{dC}{dt} = \frac{dA}{dt} = 0 \quad (12)$$

n this case there is no disease: $A = C = R = 0$. Hence, the DFE of our equation is given by:

$$E^0 = (S^0, A^0, C^0, R^0) = \left(\frac{\pi}{\mu}, 0, 0, 0\right) \quad (13)$$

3.4 Basic Reproduction Number R_0,

Diekmann *et. al.* [3] defines the basic reproduction number, R_0, as the average number of secondary infections caused by an infectious individual during his or her entire life as an infectious person. Using the next generation operator technique described by Diekmann and Heesterbeek [3], we obtained the basic reproduction number, R_0 of the model in Equations (1) which is the spectral radius (ρ) of the next generation matrix, K, that is $R_0 = \rho(K)$, where $K = FV^{-1}$.We define F to be matrix of the rate of appearance of new infections and V to be the matrix of the rate of other transitions between other compartments and the infected compartments.

The matrices F (for the new infection terms) and V (of the transition terms) are obtained from the infected classes (i. e., A and C) at HCV-free equilibrium and are given by

Where $K_1 = (\phi + \gamma + \mu), K_2 = (\tau + \delta + \mu)$ and $K_3 = \mu$

$$F = \begin{bmatrix} 0 & \beta S^0 \\ 0 & 0 \end{bmatrix} \text{ and } V = \begin{bmatrix} K_1 & 0 \\ -\phi & K_2 \end{bmatrix} \quad (14)$$

with

$$V^{-1} = \frac{1}{K_1 K_2}\begin{bmatrix} K_1 & 0 \\ -\phi & K_2 \end{bmatrix} = \begin{bmatrix} \frac{1}{K_1} & 0 \\ \frac{\phi}{K_1 K_2} & \frac{1}{K_2} \end{bmatrix} \quad (15)$$

Thus, we have

$$K = FV^{-1} = \begin{bmatrix} \frac{\phi\beta S^0}{K_1 K_2} & \frac{\beta S^0}{K_2} \\ 0 & 0 \end{bmatrix} \quad (16)$$

To get the highest eigen value ρ, we find the characteristic polynomial of K

$$\begin{vmatrix} \frac{\phi\beta S^0}{K_1 K_2} - \lambda_1 & \frac{\beta S^0}{K_2} \\ 0 & 0 - \lambda_2 \end{vmatrix} = 0 \quad (17)$$

Therefore, the basic reproduction number $R_0 = \rho(FV^{-1})$ = spectra radius of FV^{-1} and hence

$$R_0 = \frac{\phi\beta\pi}{\mu K_1 K_2} \quad (18)$$

3.5 Local Stability Analysis of Disease Free Equilibrium State.

Theorem 3: The disease-free equilibrium, E^* of (18) is locally asymptotically stable (LAS) in D if $R_0 < 1$ and unstable if otherwise $R_0 > 1$.

Proof: We shall use Jacobean stability technique to carry out the local stability analysis of the disease disease-free equilibrium.

Jacobean matrix of the system of equations at disease-free equilibrium is:

At DFE point $E^0 = (S^0, 0, 0, 0)$, then we have

$$J = \begin{bmatrix} -\mu & 0 & -\beta S^0 & 0 \\ 0 & -K_1 & \beta S^0 & 0 \\ 0 & \phi & -K_2 & 0 \\ 0 & \gamma & \tau & -\mu \end{bmatrix} \quad (19)$$

Next applying Gaussian elimination with a series of elementary row operations on (19) we obtain the row equivalent matrix

$$J = \begin{vmatrix} -\mu & 0 & -\beta S^0 & 0 \\ 0 & -K_1 & \beta S^0 & 0 \\ 0 & 0 & \frac{-K_1 K_2 - \beta S^0 \phi}{K_1} & 0 \\ 0 & 0 & 0 & -\mu \end{vmatrix} \quad (20)$$

Determinant gives

Therefore $\lambda_3 < 0$ if and only if $\frac{K_1 K_2 - \beta S^0 \phi}{K_1} < 0$. This yields

$$\beta S^0 \phi < K_1 K_2 \quad (21)$$

Dividing both side of (21) by $K_1 K_2$, we have

$$\frac{\beta S^0 \phi}{K_1 K_2} < 1 \quad (22)$$

But $R_0 = \frac{\beta S^0 \phi}{K_1 K_2}$, since we acquired $R_0 < 1$ and all the other three eigen values were all negative, it shows that the disease free equilibrium is LAS

3.5 Global Stability of Disease Free Equilibrium

Theorem 5: The HCV-free equilibrium (DFE) is globally asymptotically stable (GAS) if $R_0 \leq 1$.

Proof: One common approach in studying the global asymptotic stability of the DFE is to construct a Lyapunov function in proving this theorem.

Consider the Lyapunov function

$$L = \phi A + K_1 C \tag{23}$$

Then taking its derivative along the solutions of the model equation, we have

$$\begin{aligned} L' &= \phi A' + K_1 C' \\ &= \phi\left(\beta SC - K_1 A\right) + K_1\left(\phi A - K_2 C\right) \\ &= \phi\beta SC - K_1 K_2 C \\ &= K_1 K_2 C\left(\frac{\phi\beta S^0}{K_1 K_2} - 1\right) \end{aligned} \tag{24}$$

But since $S^0 > S$ we have

$$\begin{aligned} L' &\leq K_1 K_2 C\left(\frac{\phi\beta S^0}{K_1 K_2} - 1\right) \\ &\leq K_1 K_2 C\left(R_0 - 1\right) \end{aligned} \tag{25}$$

Since all the model parameters are nonnegative, it follows that when $R_0 \leq 1, L' \leq 0.$ This implies that the equality $L' = 0$ holds when $R_0 = 1$. Hence this proves the theorem and shows that HCV will be under control.

3.7 Existence of Endemic Equilibrium Point in Terms of force of Infection

$E^* = \left(S^*, A^*, C^* R^*\right) \neq \left(0,0,0,0\right)$ To obtain the endemic equilibra, we see that from the third of equation (13)

$$A^* = \frac{K_2 C}{\phi} \tag{26}$$

But if we consider the fact that in an endemic equilibrium $C \neq 0$, then from the second equation of (), we see that

$$\begin{aligned} S^* &= \frac{K_1 A^*}{\beta C^*} \\ &= \frac{K_1 K_2}{\beta\phi} \end{aligned} \tag{27}$$

Which implies

$$S^* = \frac{K_1 K_2}{\beta\phi} \tag{28}$$

However, from the first equation of (1), we see that

$$\begin{aligned} C^* &= \frac{\pi}{\beta S^*} - \frac{\mu}{\beta} \\ &= \frac{\mu}{\beta}\left(\frac{\pi}{\mu S^*} - 1\right) \end{aligned} \tag{29}$$

Putting (27) into (29) and simplifying it we have

$$C^* = \frac{\mu}{\beta}\left(\frac{\beta\phi\pi}{\mu K_1 K_2} - 1\right) \tag{30}$$

Hence

$$C^* = \frac{\phi\pi}{K_1 K_2} - \frac{\mu}{\beta} \tag{31}$$

As a result of this and by putting (31) into (26)

$$A^* = \frac{\pi}{K_1} - \frac{K_2 \mu}{\beta\phi} \tag{32}$$

Then from the fourth equation of (1) and by substituting (32) and (1) respectively into it, we see that

$$R^* = \frac{\gamma\pi}{\mu K_1} - \frac{\gamma K_2}{\phi\beta} + \frac{\tau\phi\pi}{\mu K_1 K_2} - \frac{\tau}{\beta} \tag{33}$$

3. Numerical Simulation

It is difficult to get reliable data on disease transmission, so we estimated some of the parameter values based on the available data from the World Health Organization (WHO) [8] and reliable literature [5]. Values for β variables marked Estimated in Table 4.1 were chosen to proportionally represent across the disease transmission risk differences between the population groups and were set at a level to permit the disease to spread relative to treatment rates. For the numerical simulations, a interval of 30 months was used. Considering the average time of 3-6 months for an acutely infected person to shift to being chronically infected and the 12 week course of treatment with DAA, 30 months was sufficient to illustrate the disease dynamics. As the population will not greatly increase or decrease in this relatively short time interval, we held the population constant and thus did not include births or deaths, so $\pi = \mu = \delta = 0$ Table 4.1 details selected parameters values for disease dynamics

Table 4.1: Table of population parameters

Parameters and variables	Value	Source
$\beta_1 = \beta_{IV}$	0.08	Estimated
$\beta_2 = \beta_{STD}$	0.05	Estimated
$\beta_3 = \beta_{IV} + \beta_{STD}$	0.10	Estimated
$\beta_4 = \beta_{Other}$	0.01	Estimated
ϕ	0.60	WHO [8]
τ	0.071	WHO [8]
α	0.10	WHO [8]
γ	0.45	WHO [8]

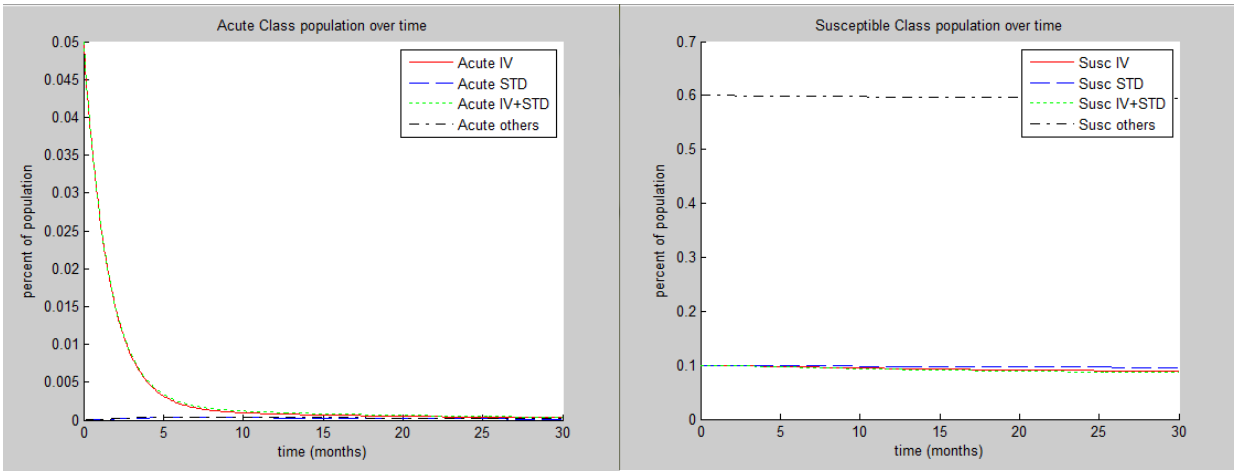
Table 4.2 shows initial conditions for populations expressed in percentages for each class that was used for testing and the first set of model simulations. To allow simulation results to show the progression of infection across different demographic groups, the initial infection was given only to intravenous drug users in the acute class, with 10% of the population infected and assigned equally to the A_{IV} and $A_{IV} + A_{STD}$ classes. To provide for simple visualization of impact on disease dynamics resulting from changes to the treatment and infection rates, no one was initially assigned to any of the chronic or recovered categories. The total of susceptible population was set at 90%, with the majority of the population in the S_{Other} category (60%). An with equal amounts of population assigned to the susceptible groups that have disease transmission risk factors (10% each). An additional set of simulations was also completed with population proportions set to more realistically reflect real-world initial conditions and is detailed at the end of this section.

Table 4.2: Table of initial population proportions

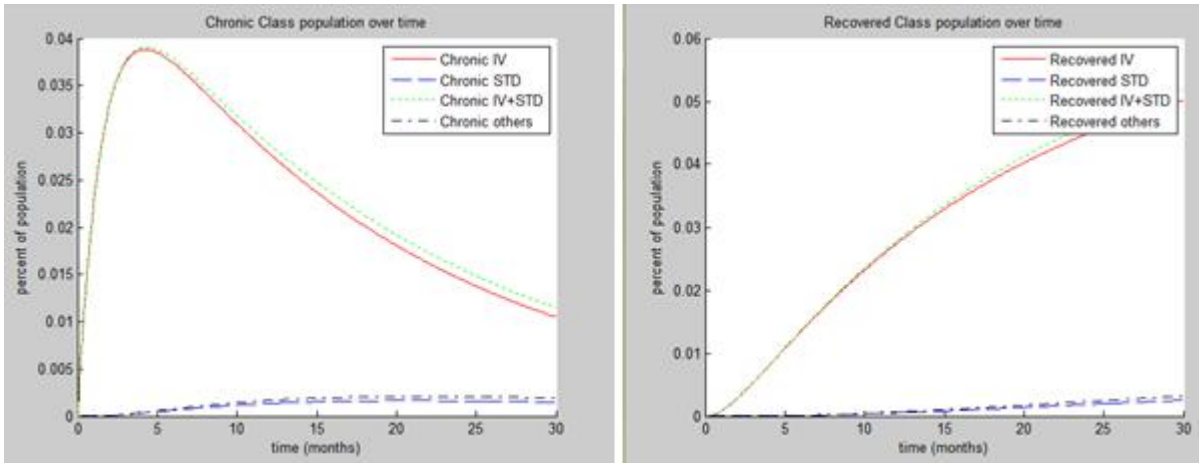
Population proportion	Value
S_{IV}	0.10
S_{STD}	0.10
$S_{IV} + S_{STD}$	0.10
S_{Other}	0.60
A_{IV}	0.05
A_{STD}	0
$A_{IV} + A_{STD}$	0.05
A_{Other}	0
C_{IV}	0
C_{STD}	0
$C_{IV} + C_{STD}$	0
C_{Other}	0
R_{IV}	0
R_{STD}	0
$R_{IV} + R_{STD}$	0
R_{Other}	0

4.1 Graphical Representation of the Improved Model

The graphical representations are from the numerical solutions of the improved model equations. The Matlab simulation of the improved model assumes the initial conditions of the population proportion when there is no government policy or proper education with little or low treatment available. As a result of this, it can be seen from the graphs in Figure4.1that over a period of time in (a) the susceptible population begin to slightly reduce especially the IV and IV + STD susceptible groups, in (b) the acutely infected population moves faster to the chronic class over the period of time, and in (c) the chronically infected proportion from the IV and IV+STD population increases over a long period of time.

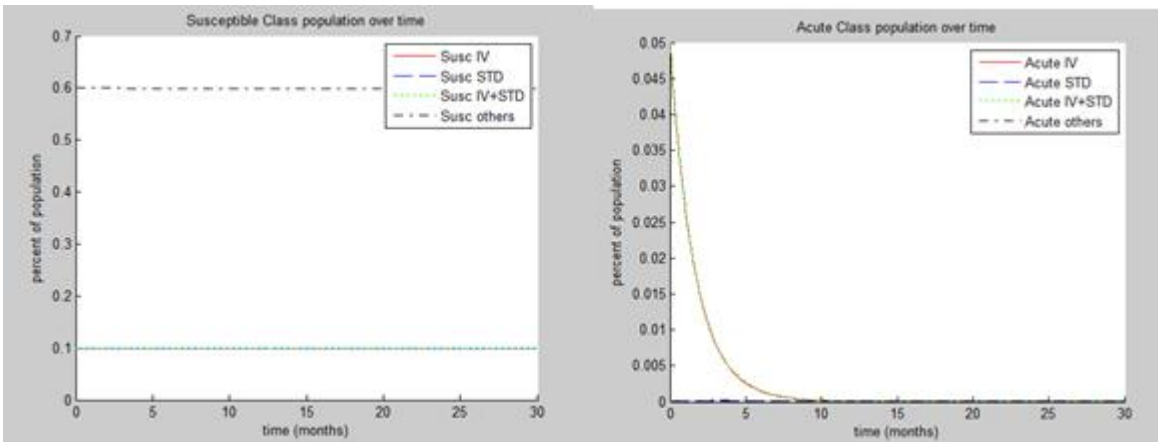


(a) (b)

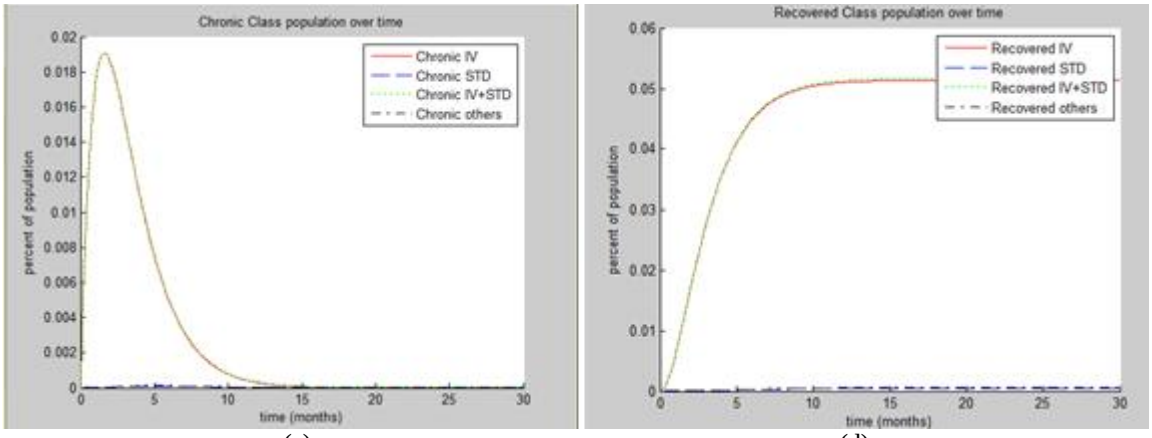


(c) (d)

Figure 4.1: The graph of time series plots showing the effect of high contact rates on the population over a period of time with the assumed initial conditions from Table 4.2 when there is little or no treatment

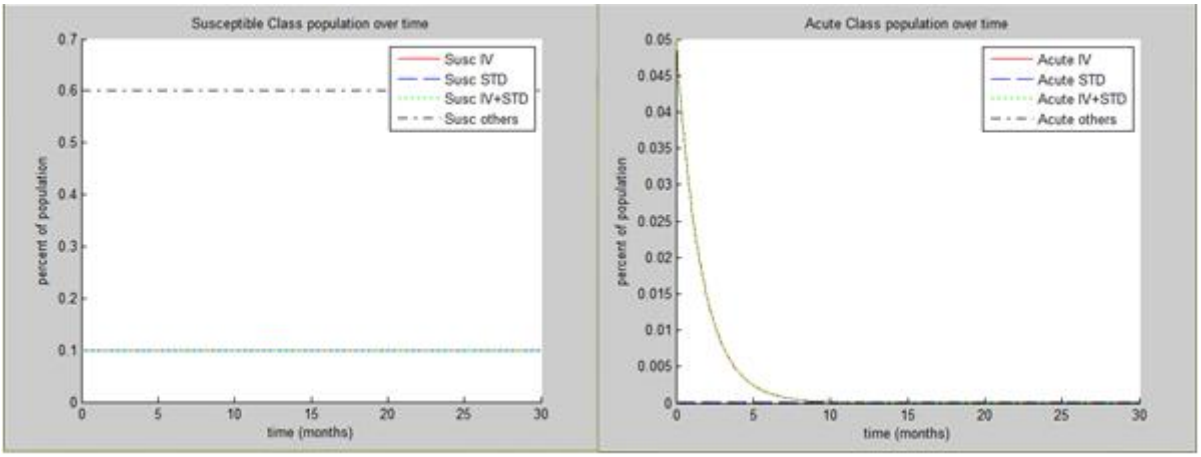


(a) (b)



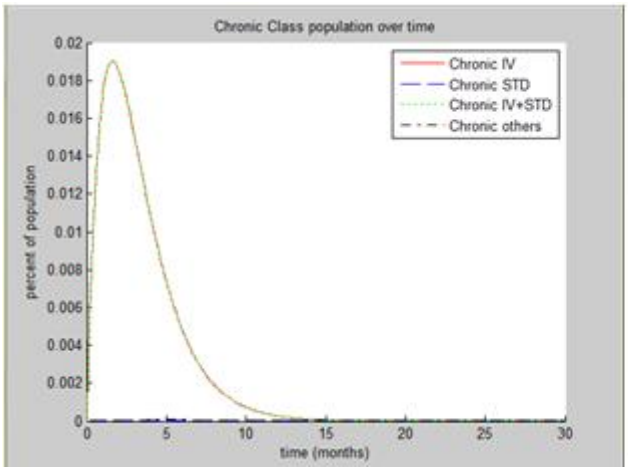
(c) (d)

Figure 4.2: The graph of time series plots showing the effect of high contact rates on the population over a period of time with the assumed initial conditions from Table 4.2 with an increased rate of treatment

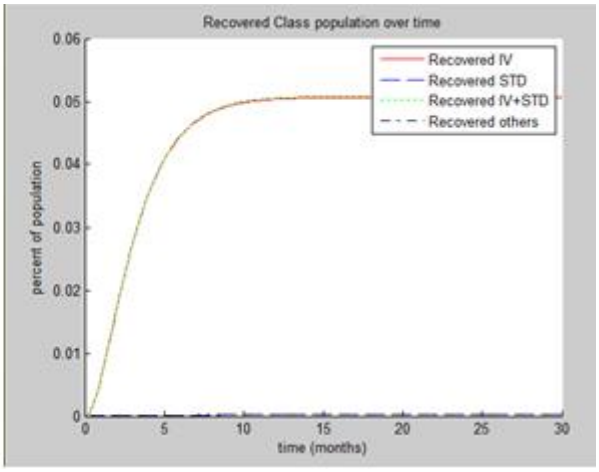


(a)

(b)



(c)



(d)

4. Discussion

The simulation done in Figure 4.2 shows the effect of increasing treatment rate on the population with high contact rate.As it can be seen from (a) that the Susceptible class is slightly decreasing with time because of the increased contact rate and in (b) the rate of transfer from the acute class to the chronic class is faster as well. However, (c) show the population proportion of the IV and IV + STD chronically infected grows and decreases so quickly over time, while (d) show the infected class are recovering faster because of the effect of high treatment rate.

Figure 4.3: The graph of time series plots showing the effect of low contact rates on the population over a period of time with the assumed initial conditions from Table 4.2 when there is little or no treatment

The graph of Figure 4.3 depicts the effect of low contact rate on the population when there is government policy in place and public enlightenment and proper education on how to use condoms to prevent sexually transmitted diseases and education on drug use. From (a) we can see that it takes time for people to move from the susceptible class to acute, and (b) shows that people leave the acute stage quickly. In (c) the chronically population recovers well and completely in the first few months. Then (d) shows a lot of individuals recovering from the IV and IV+STD chronically infected.

5. Concluding Remarks

In this study, a mathematical model for the spread and transmission dynamics of hepatitis C virus infection is developed and analyzed using a system of first order ordinary differential equations. Treatment and other control measures were incorporated and analysis carried out on the developed model by considering the different modes of transmitting the disease. The basic or effective reproduction number of the model was computed and the equilibrium states(points) were obtained and analyzed for their stability relatively to the effective reproduction number. The result shows that, the disease free equilibrium was stable and the criteria for stability of the endemic equilibrium were established. It is shown that the model's infectious and disease free equilibria are locally and globally a symptotically stable if $R<1$, and it is endemic equilibrium or unstable if $R>1$.Numerical simulations of the model show that the hepatitis C virus will be eradicated or reduced to the minimum from the proposed population in consideration if there is proper education, adequate awareness, and proper intensive treatment given at the initial phase of the disease outbreak with the proposed interventions of the model in due time.

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