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OPTIMAL CONTROL STRATEGIES AND COST-EFFECTIVENESS ANALYSIS OF HCV MODEL IN TANZANIA

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Abstract—The aim of this paper is to investigate the effectiveness and cost-effective of two HCV preventive measures i.e. (i) education, health care and immunization (ii) treatment. The local and global stability of the disease free equilibrium is established. It is noted that the disease-free equilibrium point is locally stable whenever basic reproduction number. Also, the model has a unique HCV-persistent equilibrium whenever, implying the persistence of endemic disease in the community. As with many models, the model presented in this article should be treated with circumspection because of the assumptions made and the difficulty in the estimation of the model parameters. Pontryagin's Maximum Principle is used to derive necessary conditions for the optimal control of the disease. The Infection Averted ratio and the Incremental Cost-Effectiveness Ratio (ICER) are calculated to investigate the cost-effectiveness of all possible combinations of the two control measures. Results revealed among others that the most cost-effective strategy for HCV control is the treatment of infected individuals. Therefore, more efforts from policy-makers on the provisions of treatment of infectives would go a long way to combat the HCV epidemic.

Keywords— HCV disease, stability, basic reproductive number, validation, optimal control, cost-effectives.

I. INTRODUCTION

The main reason for taking protective and control measures against HCV is to reduce the prevalence of the disease and, if possible, eradicate it completely. That is, reducing the level of susceptibility of healthy individuals against the infection and the number of infectious individuals. As reported in World Health Organization [1], an estimated 170 million people worldwide (3% of the world's population) are now thought to be HCV chronic carriers. In Africa the prevalence is estimated to be 5.3% [1]. Symptomatic acute infection occurs in estimated 1-3 cases per 100,000 persons annually but the actual incidence of new HCV infection is higher as the majority of cases are asymptomatic [2]. According to recent population based studies, approximately 40% of the cases of chronic liver disease are HCV-related, resulting in 8,000-10,000 deaths per annum [2].

The model to be consider in this paper is an extension of the model proposed by [3] in which the effect of treatment and Infected immigrants is considered by the inclusion of model validation, optimal control and cost effective analysis of the model without the inflow of infected immigrants. Very little has been done in the area of applying optimal control theory to study and analyse the

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dynamics of HCV. [4] used optimal control to examine the role of chemotherapy in controlling the virus reproduction in a HIV patient. [5] used optimal control theory to determine the optimal timing and intensity of a HCV antiviral treatment programme for active injecting drug users (IDUs) with a variety of policy objectives, budget constraints, and prevalence settings. [6], [7], [8] and [9] used optimal control to minimize the costs of both the diseases and treatment. Furthermore, [9] and [10] were used optimal control to investigate the best strategy for educational campaigns during the outbreak of an epidemic and at the same time minimizing the number of infective humans. [11] investigated the effectiveness and cost-effectiveness of three malaria preventive measures (use of treated bed nets, spray of insecticides and a possible treatment of infective humans that blocks transmission to mosquitoes). The main outputs of this work will be minimum spread of HCV disease, costs, contribution to the design of public health policy, suggestion on future research and decision framework for programme implementation in Tanzania. The paper is intended to use optimal control theory to study the effectiveness and cost effectiveness of all possible combinations of two HCV preventive measures, namely (i) education, health care and immunization and (ii) treatment model without the inflow of infected immigrants in the community.

II. MODEL FORMULATION

The model sub-divides the total human population at time t, denoted by $N(t)$, into sub-populations of susceptible individuals $(S(t))$, exposed individuals (infected but not infectious) $(E(t))$, individuals with acute infection (initially infected) $(A(t))$, chronic infected individuals (infectious individuals) $(C(t))$ and recovered individuals $(R(t))$. Total population at time t is given by

$$N(t)=S(t)+E(t)+A(t)+C(t)+R(t). \quad (1)$$

The interaction between the classes will be assumed as follows: Susceptible individuals' contacts with acute and chronic infected individuals at rates $\beta_i(i=1,2)$ respectively. Infected individuals move to the exposed group at a rate $\frac{(\beta_1 A+\beta_2 C)}{N}$. The exposed individuals develop to acute infected group at a rate θ while acute infective develop to chronic group at a rate k_1 and exposed individuals move to chronic class at the rate k_1. The infectious individuals recovered at a rate ρ, and recovered individual loses immunity and become immediately susceptible again at a rate σ. Acute and chronic infected individuals undergo death due to the disease at the rates a and d respectively.

It is assumed that the rate of contact of susceptibles with chronic individuals is much less than acute infectives $(\beta_2 \le \beta_1)$ because on chronic stage people become aware of their infection and may choose to use control measures and change their behaviour and thus may contribute little in spreading the infection.

Taking into account the above considerations, we have the following schematic flow diagram:

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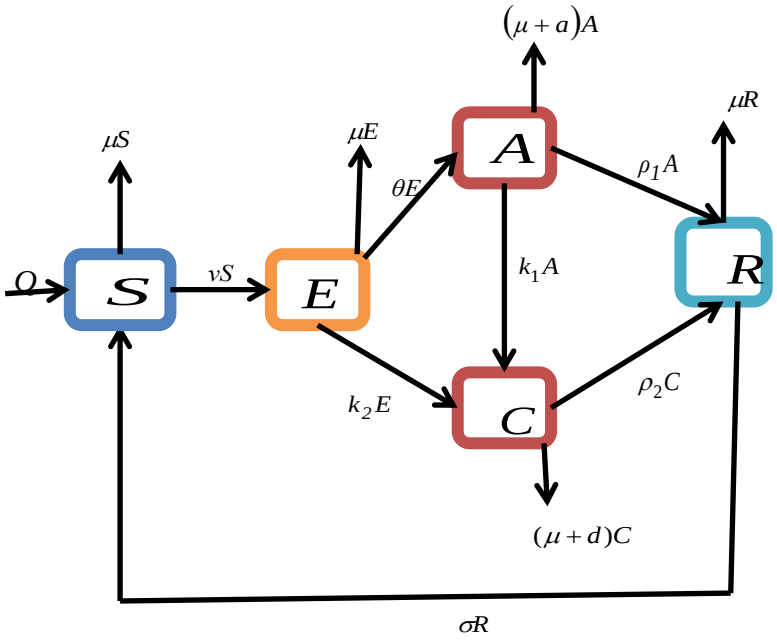

Figure 1: Model Flow Chart

Thus, from the above flow chart and with the force of infection

$$v = \frac{(\beta_1 A + \beta_2 C)}{N}$$

where $N = S + E + A + C + R$ is the total population size the model will be governed by the following system of equations:

$$\begin{aligned}
\frac{dS}{dt} &= Q - \upsilon S + \sigma R - \mu S \\
\frac{dE}{dt} &= \upsilon S - (\theta + k_2 + \mu) E \\
\frac{dA}{dt} &= \theta E - (k_1 + \rho_1 + a + \mu) A \\
\frac{dC}{dt} &= k_2 E + k_1 A - (\rho_2 + d + \mu) C \\
\frac{dR}{dt} &= \rho_1 A + \rho_2 C - (\sigma + \mu) R
\end{aligned} \tag{2}$$

with nonnegative initial conditions and $N(0) > 0$.

$\beta_i \, (i = 1, 2)$ are the effective contact rate of individuals with acute and chronic hepatitis C respectively, Q is the recruitment rate, θ is the rate of progression to acute infected class from exposed class, $k_i \, (i = 1, 2)$ are the rates at which acute and exposed infective develop chronic respectively, $\rho_i \, (i = 1, 2)$ are the rates at which acute and chronic individuals recovered respectively, a is the death rate of acute infected group due to the disease, σ is the rate at which infectious humans after recovery become immediately susceptible again, μ is the natural death rate, d is the death rate of chronic infected group due to the disease and μ is the natural death rate.

III. POSITIVITY AND BOUNDEDNES OF SOLUTIONS

Since the model system of equation (2) is HCV model dealing with human population, it is assumed that all state variables and parameters of the model are positive for all $t \geq 0$. The model will be analysed in a suitable feasible region where all state variables are positive.

Theorem 1: *The solutions of the system (2) are feasible for all* $t > 0$ *if they enter the invariant region* Ω .

Proof :

Let $\Omega = (S,E,A,C,R) \in R^5_+$ be a solution of the system (2) with non-negative initial conditions. From equation (2), in the absence of the disease, $d = 0$, $a = 0$, system (2) becomes,

$$\dot{N} \leq Q - \mu N$$

$$\Rightarrow \dot{N} + \mu N \leq Q \,. \tag{3}$$

The integrating factor is (IF) = $e^{\int \mu dt} = e^{\mu t}$.

Then

$$e^{\mu t} N + \mu N e^{\mu t} \leq Q e^{\mu t}$$

$$\Rightarrow \frac{d}{dt}\left(N e^{\mu t} \right) \leq Q e^{\mu t}$$

Integrating on both sides gives

$$N e^{\mu t} \leq \frac{Q}{\mu} e^{\mu t} + c \,.$$

where c is a constant of integration. Therefore

$$N \leq \frac{Q}{\mu} + c e^{-\mu t} \,.$$

Using the initial conditions that when $t = 0, N(0) = N_0$, then

$$N_0 - \frac{Q}{\mu} \leq c$$

$$N \leq \frac{Q}{\mu} + \left(N_0 - \frac{Q}{\mu} \right) e^{-\mu t} \,. \tag{4}$$

As $t \to \infty$ in (4), the population size, $N \to \frac{Q}{\mu}$, which implies that $0 \leq N \leq \frac{Q}{\mu}$. Thus, the feasible solutions set of (1) enter and remain in the region

$$\left\{ \Omega = (S,\ E,\ A,\ C,\ R) \in R^5_+ \,\middle|\, S > 0,\ E \geq 0,\ A \geq 0,\ C \geq 0,\ R \geq 0,\ N \leq \frac{Q}{\mu} \right\}$$

In this case, whenever $N > \frac{Q}{\mu}$, then $\dot{N} < 0$ which means that the population decreases asymptotically to the carrying capacity and whenever $N \leq \frac{Q}{\mu}$, every solution with initial condition in Ω remains in that region for $t > 0$, so the model is well posed in Ω . Thus, the region is positively invariant (i.e. solutions remain positive for all times, t). Therefore, the basic model is well posed epidemiologically and mathematically. Hence, it is sufficient to study the dynamics of the basic model in Ω .

IV. STEADY STATE

In this section the model system (2) is qualitatively analysed by deriving the equilibrium states.

Let $\left(S^*,E^*,A^*,C^*,R^*\right)$ be the equilibrium point of the system (2). Then, setting the right hand side of system (2) to zero, we obtain

$$Q-v^*S^*+\sigma R^*-\mu S^*=0 \quad (5)$$

$$v^*S^*-(\theta+k_2+\mu)E^*=0 \quad (6)$$

$$\theta E^*-(k_1+\rho_1+a+\mu)A^*=0 \quad (7)$$

$$k_2E^*+k_1A^*-(\rho_2+d+\mu)C^*=0 \quad (8)$$

$$\rho_1A^*+\rho_2C^*-(\sigma+\mu)R^*=0 \quad (9)$$

All state variables of HCV are computed in terms of the force of infection v^*. From (6) we have

$$E^*=\frac{v^*S^*}{\theta+k_2+\mu} \quad (10)$$

By making A^*, C^* and R^* the subjects of equations (7), (8) and (9) respectively we have

$$A^*=\frac{\theta E^*}{k_1+\rho_1+a+\mu} \quad (11)$$

$$C^*=\frac{k_2E^*+k_1A^*}{\rho_2+d+\mu} \quad (12)$$

and

$$R^*=\frac{\rho_1A^*+\rho_2C^*}{\sigma+\mu} \quad (13)$$

Substituting (10) in (11), we obtain

$$A^*=\frac{\theta v^*S^*}{r_1} \quad (14)$$

Substituting (10) and (11) in (12), we obtain

where $r_1=(\theta+k_2+\mu)(k_1+\rho_1+a+\mu)$

$$C^*=\frac{r_2v^*S^*}{r_3} \quad (15)$$

with, $r_2=\left[k_2+k_1\theta(\theta+k_2+\mu)\right]$

and

$$r_3=(\theta+k_2+\mu)(\rho_2+d+\mu)$$

Substituting (14) and (15) in (13), we obtain

$$R^*=r_4v^*S^* \quad (16)$$

$$r_4=\frac{\left[\frac{\rho_1\theta}{r_1}+\frac{\rho_2r_2}{r_3}\right]}{(\delta+\mu)}$$

By making S^* the subjects of equations (5) we have

$$S^* = \frac{Q + \sigma R^*}{v^* + \mu} \tag{17}$$

Substituting (16) in (17), we obtain

$$S^* = \frac{Q}{r_5 v^* + \mu} \tag{18}$$

where $r_5 = (1 - r_4\delta)$

Substituting (18) in (10), (14), (15) and (16) respectively, we obtain

$$E^* = \frac{v^* Q}{(r_5 v^* + \mu)(\theta + k_2 + \mu)} \qquad A^* = \frac{\theta v^* Q}{r_1 (r_5 v^* + \mu)} \qquad C^* = \frac{r_2 v^* Q}{r_3 (r_5 v^* + \mu)}$$

$$R^* = \frac{r_4 Q v^*}{(r_5 v^* + \mu)}$$

Thus the state variables of our HCV model as follows,

$$S^* = \frac{Q}{r_5 v^* + \mu} \qquad E^* = \frac{v^* Q}{(r_5 v^* + \mu)(\theta + k_2 + \mu)} \qquad A^* = \frac{Q\theta v^*}{r_1 (r_5 v^* + \mu)} \tag{19}$$

$$C^* = \frac{Q r_2 v^*}{r_3 (r_5 v^* + \mu)} \qquad R^* = \frac{Q r_4 v^*}{(r_5 v^* + \mu)}$$

where $\nu^* = \frac{(\beta_1 A + \beta_2 C)}{N}$

Substituting the expression of A^* and C^* into expression of ν^* , we obtain

$$\nu^* \left[N r_1 r_3 (r_5 \nu^* + \mu) + \beta_1 \theta Q r_3 + \beta_2 Q r_2 r_1 \right] = 0 \tag{20}$$

We thus have $\nu^* = 0$ or

$$N r_1 r_2 (r_5 \nu^* + \mu) + \beta_1 \theta Q r_3 + \beta_2 Q r_2 r_1 = 0 \tag{21}$$

4.1 THE DISEASE FREE EQUILIBRIUM POINT (DFE) Δ_0

This solution $\nu^* = 0$, leads to the disease-free equilibrium point given by

$$\Delta_0 = (S^*, E^*, A^*, C^*, R^*) = \left(\frac{Q}{\mu}, 0, 0, 0, 0 \right) \tag{22}$$

This represents the state in which there is no infection and is known as the disease-free equilibrium point.

4.2 THE BASIC REPRODUCTIVE NUMBER R_0

The basic reproduction number R_0 is calculated by using the next generation operator approach of [12]. It is obtained by taking the largest (dominant) Eigen value, (spectral radius) of

$$\left[\frac{\partial F_i(\epsilon_0)}{\partial X_j} \right] \cdot \left[\frac{\partial V_i(\epsilon_0)}{\partial X_j} \right]^{-1}, \tag{23}$$

where F_i is the rate of appearance of new infection in compartment i, V_i is the transfer of individuals out of the compartment i by all other means and Δ_0 is the disease free equilibrium. Therefore,

$$\mathbf{F}_i = \begin{pmatrix} \frac{(\beta_1 A + \beta_2 C)}{N} S \\ 0 \\ 0 \end{pmatrix} \tag{24}$$

and

$$\mathbf{V}_i = \begin{pmatrix} (\theta + k_2 + \mu)E \\ (k_1 + \rho_1 + a + \mu)A - \theta E \\ (\rho_2 + d + \mu)C - k_2 E - k_1 A \end{pmatrix} \tag{25}$$

The partial derivatives if (24) and (25) with respect to E, A and C gives

$$\mathbf{F} = \begin{pmatrix} 0 & \frac{\beta_1 S}{N} & \frac{\beta_2 S}{N} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \tag{26}$$

and

$$\mathbf{V} = \begin{pmatrix} \theta + k_2 + \mu & 0 & 0 \\ -\theta & k_1 + \rho_1 + a + \mu & 0 \\ -k_2 & -k_1 & \rho_2 + d + \mu \end{pmatrix} \tag{27}$$

In the absence of the disease and when $N = \frac{Q}{\mu}$, the matrix (26) becomes;

$$\mathbf{F} = \begin{pmatrix} 0 & \beta_1 & \beta_2 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \tag{28}$$

Now, taking the inverse of matrix (27) leads to

$$\mathbf{V}^{-1} = \begin{pmatrix} H1 & H2 & H3 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \tag{29}$$

where

$$H1 = \frac{\beta_1 \theta}{(\theta + k_2 + \mu)(k_1 + \rho_1 + a + \mu)} + \frac{\beta_2 (\theta k_1 + k_1 k_2 + k_2 \rho_1 + k_2 a + k_2 \mu)}{(\theta + k_2 + \mu)(k_1 + \rho_1 + a + \mu)(\rho_2 + d + \mu)}$$

$$H2 = \frac{\beta_1}{(k_1 + \rho_1 + a + \mu)} + \frac{\beta_2 k_1}{(k_1 + \rho_1 + a + \mu)(\rho_2 + d + \mu)}$$

$$H2 = \frac{\beta_2}{(\rho_2 + d + \mu_C)}$$

The spectral radius (dominant eigenvalue) of the matrix $\mathbf{FV}^{-1}$ is

$$\frac{\beta_1\theta}{\left(\theta+k_2+\mu\right)\left(k_1+\rho_1+a+\mu\right)}+\frac{\beta_2\left(\theta k_1+k_1k_2+k_2\rho_1+k_2a+k_2\mu\right)}{\left(\theta+k_2+\mu\right)\left(k_1+\rho_1+a+\mu\right)\left(\rho_2+d+\mu\right)}$$

Hence, the basic reproduction number of the model system (2) is given by

$$R_0=\frac{\beta_1\theta}{\left(\theta+k_2+\mu\right)\left(k_1+\rho_1+a+\mu\right)}+\frac{\beta_2\left(\theta k_1+k_1k_2+k_2\rho_1+k_2a+k_2\mu\right)}{\left(\theta+k_2+\mu\right)\left(k_1+\rho_1+a+\mu\right)\left(\rho_2+d+\mu\right)} \quad (30)$$

The basic reproduction number R_0 measures the average number of new infections generated by a typical infectious individual in a community with no inflow of infected immigrants when education, health care, immunization and treatment strategies are in place.

Theorem 2: *The disease free equilibrium of the model system (2) is locally asymptotically stable if* $R_0<1$ *and unstable if* $R_0>1$.

4.3 LOCAL STABILITY OF DISEASE FREE EQUILIBRIUM (DFE)

Local stability of disease free equilibrium Δ_0, can be determined by the variational matrix $\boldsymbol{J}_0$ of the model system (2) corresponding to Δ_0. The Jacobian matrix is computed by differentiating each equation in the system (2) with respect to the state variables *S, E, A, C* and *R*. The system is re-defined as;

Local stability of disease free equilibrium Δ_0, can be determined by the variational matrix $\boldsymbol{J}_0$ of the model system (2) corresponding to Δ_0. The Jacobian matrix is computed by differentiating each equation in the system (2) with respect to the state variables *S, E, A, C* and *R*. The system is re-defined as;

$$\begin{aligned}
H &= Q-vS+\sigma R-\mu S\\
G &= vS-(\theta+k_2+\mu)E\\
K &= \theta E-(k_1+\rho_1+a+\mu)A\\
Y &= k_2E+k_1A-(\rho_2+d+\mu)C\\
P &= \rho_1A+\rho_2C-(\sigma+\mu)R
\end{aligned} \quad (31)$$

It follows that

$$\boldsymbol{J}_0=\begin{pmatrix}
\frac{\partial H(\epsilon_0)}{\partial S} & \frac{\partial H(\epsilon_0)}{\partial E} & \frac{\partial H(\epsilon_0)}{\partial A} & \frac{\partial H(\epsilon_0)}{\partial C} & \frac{\partial H(\epsilon_0)}{\partial R}\\
\frac{\partial G(\epsilon_0)}{\partial S} & \frac{\partial G(\epsilon_0)}{\partial E} & \frac{\partial G(\epsilon_0)}{\partial A} & \frac{\partial G(\epsilon_0)}{\partial C} & \frac{\partial G(\epsilon_0)}{\partial R}\\
\frac{\partial K(\epsilon_0)}{\partial S} & \frac{\partial K(\epsilon_0)}{\partial E} & \frac{\partial K(\epsilon_0)}{\partial A} & \frac{\partial K(\epsilon_0)}{\partial C} & \frac{\partial K(\epsilon_0)}{\partial R}\\
\frac{\partial Y(\epsilon_0)}{\partial S} & \frac{\partial Y(\epsilon_0)}{\partial E} & \frac{\partial Y(\epsilon_0)}{\partial A} & \frac{\partial Y(\epsilon_0)}{\partial C} & \frac{\partial Y(\epsilon_0)}{\partial R}\\
\frac{\partial P(\epsilon_0)}{\partial S} & \frac{\partial P(\epsilon_0)}{\partial E} & \frac{\partial P(\epsilon_0)}{\partial A} & \frac{\partial P(\epsilon_0)}{\partial C} & \frac{\partial P(\epsilon_0)}{\partial R}
\end{pmatrix} \quad (32)$$

Hence the variational matrix of the model system (2) at steady states is given by

$$\boldsymbol{J}_0 = \begin{bmatrix} -\mu & 0 & -\beta_1 & -\beta_2 & 0 \\ 0 & -(\theta+k_2+\mu) & \beta_1 & \beta_2 & 0 \\ 0 & \theta & -(k_1+\rho_1+a+\mu) & 0 & 0 \\ 0 & k_2 & k_1 & -(\rho_2+d+\mu) & 0 \\ 0 & 0 & (\rho_{1+a}) & \rho_2 & -(\delta+\mu) \end{bmatrix} \quad (33)$$

Then, the stability of the DFE is determined by the Eigen values of the matrix (33). It is clear that the first column has diagonal entry, so, this diagonal entry –μ is an eigenvalue. Hence, removing this column and the row corresponding to it, the Jacobian matrix $\boldsymbol{J}_0$ is then reduced to the following:

$$\boldsymbol{J}_{0_1} = \begin{bmatrix} -(\theta+k_2+\mu) & \beta_1 & \beta_2 & 0 \\ \theta & -(k_1+\rho_1+a+\mu) & 0 & 0 \\ k_2 & k_1 & -(\rho_2+d+\mu) & 0 \\ 0 & (\rho_{1+a}) & \rho_2 & -(\delta+\mu) \end{bmatrix} \quad (34)$$

We therefore calculate the eigenvalues of the reduced matrix. Solving the eigenvalues of $\boldsymbol{J}_{0_1}$, requires that $det\left(\boldsymbol{J}_{0_1} - \Lambda\right) = 0$,

This, leads to the following characteristic polynomial,

$$\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 \quad (35)$$

Here,

$$a_1 = (\partial + 2\mu + \rho_2 + d + k_1 + \rho_1 + a + \theta - k_2)$$

$$a_2 = (\theta k_1 - k_2 k_1 - k_2\rho_1 - k_2 a + \rho_2 k_1 + \rho_2\rho_1 + \rho_2 a + \rho_2\theta - \rho_2 k_2 + dk_1 + d\rho_1 + da + d\theta$$
$$-dk_2 + \theta\rho_1 + \theta a - \theta\beta_1 - k_2\beta_2 + \delta\rho_2 + \delta d + \delta k_1 + \delta\rho_1 + \delta a + \delta\theta - \delta k_2 + \mu\rho_2$$
$$+\mu d + \mu k_1 + \mu\rho_1 + \mu a + 3\mu\theta - 3\mu k_2 + \delta\mu)$$

$$a_3 = (\theta k_1\rho_2 + \theta k_1 d + \theta\rho_1\rho_2 + \theta\rho_1 d + \theta a\rho_2 + \theta ad - k_2 k_1\rho_2 - k_2 k_1 d - k_2\rho_1\rho_2 - k_2\rho_1 d - k_2 a\rho_2 - k_2 ad + 2\mu\theta a$$
$$+2\mu\theta\rho_1 + 2\mu d\theta - 2\mu dk_2 + 2\mu\rho_2\theta - 2\mu\rho_2 k_2 - 2\mu k_2 a + 2\mu\theta k_1 - 2\mu k_2 k_1 - 2\mu k_2\rho_1 - \delta\theta\beta_1 - \delta k_2\beta_2 + \delta\theta\rho_1$$
$$+\delta\theta a - \delta dk_2 + \delta da + \delta d\theta + \delta dk_1 + \delta d\rho_1 + \delta\rho_2\theta - \delta\rho_2 k_2 + \delta\rho_2 k_1 + \delta\rho_2\rho_1 + \delta\rho_2 a - \delta k_2\rho_1 - \delta k_2$$
$$+\delta\theta k_1 - \delta k_2 k_1 - d\theta\beta_1 - \rho_2\theta\beta_1 - k_2\beta_2 k_1 - k_2\beta_2\rho_1 - k_2\beta_2 a - k_1\theta\beta_2 - 2\mu\theta\beta_1 - 2\mu k_2\beta_2$$
$$-\rho_2\mu^2 - d\mu^2 - \mu^2 k_1 - \mu^2\rho_1 - \mu^2 a + 3\mu^2\theta - 3\mu^2 k_2 - \delta\mu^2 + 2\delta\mu\theta - 2\delta\mu k_2 - 2\mu^3)$$

$$a_4 = -(\delta+\mu)(-\theta k_1\rho_2 - \theta k_1 d - \theta\rho_1\rho_2 - \theta\rho_1 d - \theta a\rho_2 - \theta ad + k_2 k_1\rho_2 + k_2 k_1 d + k_2\rho_1\rho_2 + k_2\rho_1 d + k_2 a\rho_2$$
$$+k_2 a d - \mu\theta a - \mu\theta\rho_1 - \mu d\theta + \mu d k_2 + \mu d k_1 + \mu d\rho_1 + \mu da - \mu\rho_2\theta + \mu\rho_2 k_2 + \mu\rho_2\rho_1 + \mu\rho_2 a + \mu k_2 a + \mu\rho_2 k_1$$
$$-\mu\theta k_1 + \mu k_2 k_1 + \mu k_2\rho_1 + d\theta\beta_1 + \rho_2\theta\beta_1 + k_2\beta_2 k_1 + k_2\beta_2\rho_1 + k_2\beta_2 a + k_1\theta\beta_2 + \mu\theta\beta_1$$
$$+\mu k_2\beta_2 + \rho_2\mu^2 + d\mu^2 + \mu^2 k_1 + \mu^2\rho_1 + \mu^2 a - u^2\theta + \mu^2 k_2 + \mu^3)$$

Hence the characteristic equation corresponding to $\boldsymbol{J}_{0_1}$ is

$$f(\lambda)=(\lambda+\mu)\left(\lambda^4+a_1\lambda^3+a_2\lambda^2+a_3\lambda+a_4\right) \quad (36)$$

By applying the Routh-Hurwitz stability conditions, we establish the following for the polynomial; $a_1>0,\ a_2>0,\ a_3>0,\ a_4>0$ and

$$H_1=a_1>0$$
$$H_2=a_1a_2-a_3>0$$
$$H_3=a_3\left(a_1a_2-a_3\right)-a_1a_4>0 \text{ and } H_4=a_4H_3>0$$

Consequently, using Maple 13 it is found that $H_1>0$, $H_2>0$ $H_3>0$ and $H_4>0$ which shows that the eigenvalues of the Jacobian matrix, $\boldsymbol{J}_{0_1}$, are all having negative real parts whenever $R_0<1$. But if $R_0>1$, clearly we can see that $a_4<0$. Moreover, having, $a_1>0,\ a_2>0,\ a_3>0,\ a_4>0$ shows that not all the roots of the polynomial will have negative real parts. This means that whenever $R_0>1$, the disease- free equilibrium point is unstable, that is, it is not stable.

4.4 GLOBAL STABILITY OF DISEASE FREE EQUILIBRIUM (DFE)

In this section, the global stability of the disease-free equilibrium point is analysed by applying the [13] approach.

The model system (2) is written in the form of

$$\begin{cases}\dfrac{d\mathbf{X}_s}{dt}=\mathbf{A}\left(\mathbf{X}_s-\mathbf{X}_{DFE,s}\right)+\mathbf{A}_1\mathbf{X}_i\\ \dfrac{d\mathbf{X}_i}{dt}=\mathbf{A}_2\mathrm{X}_i\end{cases} \quad (37)$$

where $\mathbf{X}_s$ is the vector representing the non-transmitting compartments and $\mathbf{X}_i$ is the vector representing the transmitting components. The DFE is globally asymptotically stable if $\mathbf{A}$ has real negative eigenvalues and $\mathbf{A_2}$ is a Metzler matrix (i.e. the off-diagonal elements of $\mathbf{A_2}$ are non-negative).

From system (2) we have: $\mathbf{X}_i=\left(E,A,C\right)^T$,$\mathbf{X}_s=\left(S,R\right)^T$

$$X_s-X_{DFE,s}=\begin{bmatrix}S\\R\end{bmatrix}-\begin{bmatrix}\dfrac{Q}{\mu}\\0\end{bmatrix}=\begin{bmatrix}S-\dfrac{Q}{\mu}\\R\end{bmatrix} \quad (38)$$

We need to check whether a matrix $\mathbf{A}$ for the non-transmitting compartments has real negative eigenvalues and that $\mathbf{A_2}$ is a Metzler matrix.

From the equation for non-transmitting compartments in (2) we have:

$$\mathbf{A}=\begin{bmatrix}-\mu & 0\\ 0 & -(\delta+\mu)\end{bmatrix} \quad (39)$$

$$\mathbf{A}_1=\begin{bmatrix}0 & \dfrac{\beta_1S}{N} & \dfrac{\beta_2S}{N}\\ 0 & \rho_1 & \rho_2\end{bmatrix} \quad (40)$$

$$\text{and } \mathbf{A_2} = \begin{bmatrix} -(\theta + k_2 + \mu) & \frac{\beta_1 S}{N} & \frac{\beta_2 S}{N} \\ 0 & -(k_1 + \rho_1 + a + \mu) & 0 \\ k_2 & k_1 & -(\rho_2 + d + \mu) \end{bmatrix} \quad (41)$$

A direct computation shows that, the eigenvalues of $\mathbf{A}$ are real and negative. This implies that the system $\frac{d\mathbf{X_s}}{dt} = A(\mathbf{X}_s - \mathbf{X}_{DFE,s}) + \mathbf{A}_1\mathbf{X}_i$ is globally asymptotically stable at DFE and also $\mathbf{A_2}$ a Metzler matrix. Thus, the DFE is globally asymptotically stable.

Theorem 3. *The disease-free equilibrium point is globally asymptotically stable if* $R_0 < 1$ and unstable if $R_0 > 1$.

4.5. EXISTENCE OF ENDEMIC EQUILIBRIUM POINT Δ^*

Endemic equilibrium point Δ is a steady state solution in which the disease persists in the population (i.e. $\nu^* = 0$). In this case, the following solution is considered

$$N^* r_2 r_5 (r_9 \nu^* + \mu) + \beta_1 \theta r_8 r_5 + \beta_2 r_4 r_8 r_2 = 0 \quad (42)$$

The total population size is given by

$$N^* = S^* + E^* + A^* + C^* + R^* \quad (43)$$

Substituting the expression of S^*, E^*, A^*, C^* and R^* in (31), we obtain

$$N^* = \frac{r_8}{r_9 v^* + \mu} + \frac{v^* r_8}{(r_9 v^* + \mu)(\theta + k_2 + \mu)} + \frac{\theta v^* r_8}{r_2 (r_9 v^* + \mu)} + \frac{r_4 v^* r_8}{r_5 (r_9 v^* + \mu)} + \frac{r_7 r_8 v^*}{(r_9 v^* + \mu)} \quad (44)$$

Substituting (44) in (42), we obtain leads to

$$f(\nu^*) = A(\nu^*)^2 + B(\nu^*) + C = 0 \quad (45)$$

Where

$A = r_1 r_3 r_5 r_7$

$B = r_8 + r_9 R_0$

$C = r_{10} + r_{11} R_0$

$r_6 = Q r_1 r_3 (\theta + k_2 + \mu)$

$r_7 = Q r_1 r_3 - Q r_3 (\theta + k_2 + \mu)\theta - Q r_1 r_2 (\theta + k_2 + \mu) - Q r_1 r_3 r_4 (\theta + k_2 + \mu)$

$r_8 = r_1 r_3 r_7 \mu + r_1 r_3 r_5 r_6$

$r_9 = Q r_1 r_3 r_5 (\theta + k_2 + \mu)^4 (k_1 + \rho_1 + a + \mu)^2 (\rho_2 + d + \mu) R_0$

$r_{10} = r_1 r_3 r_6 \mu$

$r_{11} = Q r_1 r_3 \mu (\theta + k_2 + \mu)^4 (k_1 + \rho_1 + a + \mu)^2 (\rho_2 + d + \mu)$

THEOREM 4

(a) If $B > 0$, *then the model (2) has forward bifurcation at* $R_0 = 1$.

(b) If $B < 0$, *then the model (2) undergoes backward bifurcation at* $R_0 = 1$ (Hussaini, 2010)

Since the model parameters are non-negative, it is clear that $A>0$. However it is important to note that B is positive only if $R_0>1$ and C is positive only if $R_0>1$

4.6. GLOBAL STABILITY OF THE ENDEMIC EQUILIBRIUM POINT Δ^*

The global stability of the endemic equilibrium Δ^* is analysed using the following constructed Lyapunov function by [14].

Theorem 4: *If* $R_0>1$, *the endemic equilibrium* Δ^* *of the model* (2) *is globally asymptotically stable.*

Proof: To establish the global stability of the endemic equilibrium Δ^*, we construct the following Lyapunov function:

$$V=\left(S-S^*\ln S\right)+\left(E-E^*\ln E\right)+\left(A-A^*\ln A\right)+\left(C-C^*\ln C\right)+\left(R-R^*\ln R\right)$$

By direct calculating the derivative of V along the solution of (2) we have;

$$\frac{dV}{dt}=\left(\frac{S-S^*}{S}\right)\frac{dS}{dt}+\left(\frac{E-E^*}{E}\right)\frac{dE}{dt}+\left(\frac{A-A^*}{A}\right)\frac{dA}{dt}+\left(\frac{C-C^*}{C}\right)\frac{dC}{dt}+\left(\frac{R-R^*}{R}\right)\frac{dR}{dt}$$

which gives

$$\frac{dV}{dt}=P\text{-}Q \tag{46}$$

where,

$$P=\left(\frac{\left(S-S^*\right)^2}{S}\right)\left[\left(\frac{(\beta_1A+\beta_2C)}{N}\right)-\mu\right]+\sigma R+\frac{S^*}{S}\delta R^*+\left(\frac{(\beta_1A+\beta_2C)}{N}\right)S$$

$$+\left(\frac{(\beta_1A^*+\beta_2C^*)}{N}\right)S^*+\theta E+\frac{A^*}{A}\theta E^*+k_2E+k_1A+\frac{C^*}{C}k_2E^*+\frac{C^*}{C}k_1A^*+\rho_1A+\rho_2C$$

$$+\frac{R^*}{R}(\rho_1+a)A^*+\frac{R^*}{R}\rho_2C^*+Q$$

$$Q=\text{-}\delta R^*-\frac{S^*}{S}\delta R-\left(\frac{\left(E-E^*\right)^2}{E}\right)\left[\theta+k_2+\mu\right]\text{-}\left(\frac{(\beta_1A+\beta_2C)}{N}\right)S^*-\frac{S^*}{S}Q$$

$$-\left(\frac{(\beta_1A^*+\beta_2C^*)}{N}\right)S-\left(\frac{\left(A-A^*\right)^2}{A}\right)\left[k_1+\rho_1+a+\mu\right]-\theta E^*-\frac{A^*}{A}\theta E$$

$$-\left(\frac{\left(C-C^*\right)^2}{C}\right)\left[\rho_2+d+\mu\right]-k_2E\text{-}k_1A^*\text{-}\frac{C^*}{C}k_2E-\frac{C^*}{C}k_1A$$

$$-\left(\frac{\left(R-R^*\right)^2}{R}\right)[\delta+\mu]-\rho_1 A^*-\rho_2 C^*-\frac{R^*}{R}\rho_1 A-\frac{R^*}{R}\rho_2 C$$

Thus if $P<Q$ then $\frac{dV}{dt}\leq 0$; Noting that $\frac{dV}{dt}=0$ if and only if $S=S^*$; $E=E^*$; $A=A^*$; $C=C^*; R=R^*$:

Therefore, the largest compact invariant set in $\left\{\left(S^*,E^*,A^*,C^*,R^*\right)\in\Omega: \frac{dV}{dt}=0\right\}$ is the singleton $\left\{\Delta^*\right\}$ where Δ^* is the endemic equilibrium of the system (2). By LaSalle's invariant principle, it implies that Δ^* is globally asymptotically stable in Ω if $P<Q$.

V. MODEL FITTING

According to [15], the prevalence of HCV alone, observed study was 13.8%, which is significantly higher than 7.1%, which was reported by [16]. Regarding HCV in Tanzania, females are more affected 17(21.5%) than males 8(9%) a finding that is consistent with a study done by [16] (Prevalence of Hep B and C among children transfused with anti-HIV negative donor blood at MNH in 2000) (unpublished data).

The model is applied to data on HCV in the Tanzania. The data is collected by Muhimbili National Hospital (MNH) for individuals from different regions by referral cases. MNH is a public and tertiary hospital located in Dar es Salaam, the largest commercial city of Tanzania. The data for the HCV infected individuals in the Tanzania is given as follows: 2000 = 0, 2001=1, 2002=1, 2003=2, 2004=3, 2005=3, 2006=4, 2007=8, 2008=12, 2009=15, 2010=19, 2011=18, 2012=26, 2013=32, 2014=53. This includes HCV infected individuals in Tanzania for the period of fifteen years consecutively. Because of the unavailability of data on transmission and progression rates, we estimated most of the parameters, which makes the setting of initial conditions difficult. Many parameters are known to lie within limits. Only a few parameters are known exactly and it is thus important to estimate the others. The estimation process attempts to find the best accordance between the computed and observed data. The estimation can be carried out by 'trial and error' or by the use of software programs that are designed to find parameters that give the best fit. A Matlab18 code was used where unknown parameter values were given a lower and upper bound from which the set of parameter values that produced the best fit were obtained. The parameter values obtained from the fitting are as follows:

$\beta_1=0.9865, \beta_2=0.1745, \theta=0.0984, k_1=0.3875, k_2=0.3350, \rho_1=0.0635, \rho_2=0.0698,$

$\sigma=0.1814, a=0.0199, d=0.2809$

In Figure 2, the model fits well with the data where by the continuous line shows the fit from the model and circles represent the actual data. The equations of the system (2) are integrated by the Runge- Kutta numerical scheme in Matlab.

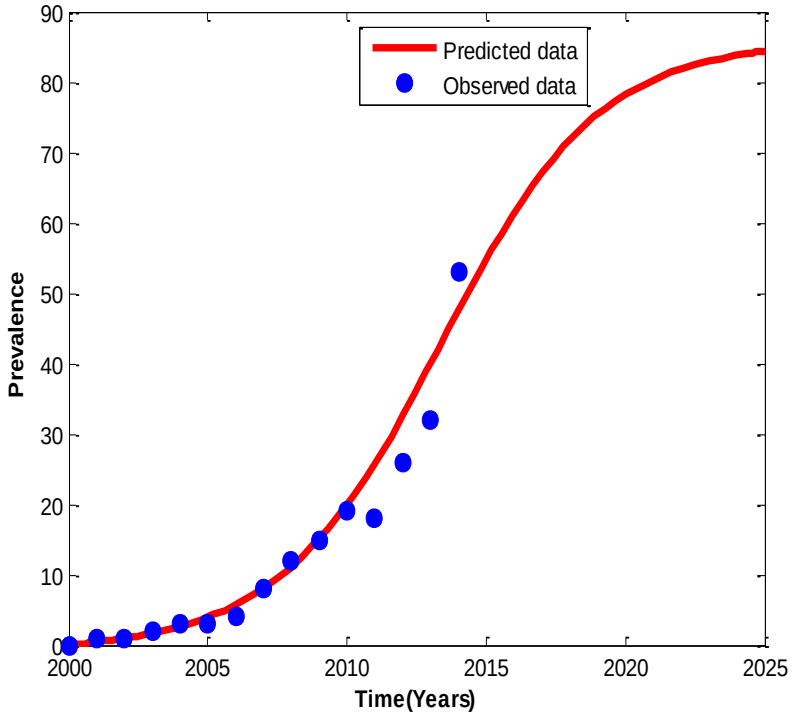

Figure. 2: Shows the change in the population of HCV infected individuals.

As can be observed in Figure 2, the model fits very closely to the data. The continuous line represents the model's prediction of the actual data (represented by the blue dots). It is observed that Mathematical model validation determined the degree to which a computer model is an accurate representation of the real world from the model applications.

For planning and management of interventions, it is important to project the prevalence of the HCV epidemic over a number of years. In our case, we chose 25 years. The projected prevalence over 25 years to 2025 is shown in Figure 3.

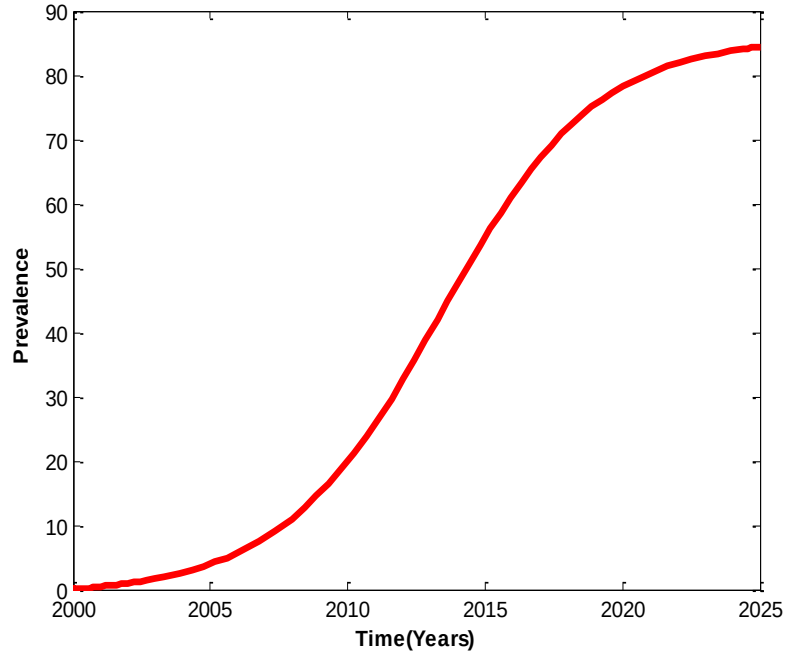

Figure. 3. The projection of the prevalence of HCV disease in a community to 2025.

The model projection shows that there will be an increase in prevalence. For the given parameter values, the prevalence population increases to the peak over a period of 25 years. This estimation, of course, assumes that the dynamics remain the same over the entire period in Tanzania. Carrying capacity is also observed in the graph.

VI. ANALYSIS OF OPTIMAL CONTROL

From the previous section, we show that effective control of the disease may be too costly when constant controls are considered as it requires treatment at higher levels for all time. For effective control to be achievable in a finite time, we need to consider time dependent controls. When the control is time dependent, the disease free equilibrium no longer exists [17]. We then proceed by applying Pontryagins maximum principle to determine the conditions for effective control in finite time. We introduce into the model (2), time dependent preventive (u_1,u_2) efforts as controls to minimize the spread of the disease. We wish to minimize the spread of HCV disease, as well as minimizing the cost associated with control strategies. For effective control to be achievable in a finite time, we need to consider time dependent controls. We introduce into the model (2), education, health care, immunization (u_1) and treatment (u_2) as time dependent controls to curtail the spread of HCV disease. The model (2) becomes

$$\begin{aligned}
\frac{dS}{dt} &= Q-(1-u_1)\upsilon S+\sigma R-\mu S\\
\frac{dE}{dt} &= (1-u_1)\upsilon S-(\theta+k_2+\mu)E\\
\frac{dA}{dt} &= \theta E-(k_1+u_2\rho_1+a+\mu)A\\
\frac{dC}{dt} &= k_2E+k_1A-(u_2\rho_2+d+\mu)C\\
\frac{dR}{dt} &= u_2\rho_1A+u_2\rho_2C-(\sigma+\mu)R
\end{aligned} \tag{47}$$

Here,

$$\upsilon=\frac{(\beta_1A+\beta_2C)}{N}$$

where, $0\le u_1\le 1$ is the control on education, healthcare and immunization and $0\le u_2\le 1$, is the treatment control for $t\in[0,T]$. To investigate the optimal level of efforts that would be needed to control the disease, we form the objective function J, which is to minimize the spread of the disease and the cost of applying the control u_1 and u_2.

$$J=\min\int_0^T\left(B_1A+B_2C+\frac{A_1{u_1}^2}{2}+\frac{A_2{u_2}^2}{2}\right)dt \tag{48}$$

where B_1,B_2,A_1 and A_2 are positive weights. The terms $A_1{u_1}^2$ and $A_2{u_2}^2$ are the costs associated with u_1 (education, health care and immunization) and u_2 (treatment). With the given objective function $J(u_1,u_2)$, our goal is to minimize the spread of the disease, while minimizing the cost of controls $u_1(t)$ and $u_2(t)$. We thus seek an optimal control triple ${u_1}^*$ and ${u_2}^*$ such that

$$J({u_1}^*,{u_2}^*)=\min\{J(u_1,u_2)\,|\,u_1,u_2\in\boldsymbol{U}\}. \tag{49}$$

Here $u=\{u_1,u_2\}$ such that u_1,u_2 are measurable with $0\le u_1\le 1$ and $0\le u_2\le 1$ for $t\in[0,T]$ is the control set. The necessary conditions that an optimal control problem must satisfy come from Pontryagin's maximum principle [18]. This principle converts (45)-(48) into a problem of minimizing pointwise a Hamiltonian H , with respect to u_1 and u_2

$$\begin{aligned}H = {} & B_1A+B_2C+\frac{A_1{u_1}^2}{2}+\frac{A_2{u_2}^2}{2}\\ & +\lambda_S\{Q-(1-u_1)\upsilon S+\sigma R-\mu S\}\\ & +\lambda_E\{(1-u_1)\upsilon S-(\theta+k_2+\mu)E\}\\ & +\lambda_A\{\theta E-(k_1+u_2\rho_1+a+\mu)A\}\\ & +\lambda_C\{k_2E+k_1A-(u_2\rho_2+d+\mu)C\}\\ & +\lambda_R\{u_2\rho_1A+u_2\rho_2C-(\sigma+\mu)R\}\end{aligned} \tag{50}$$

where the λ_S, λ_E, λ_A, λ_C and λ_R are the adjoint variables or co-state variables. By applying Pontryagin's maximum principle [18] and the existence result for the optimal control [19], we obtain

Proposition 1. *For optimal control triple u_1^* and u_2^* that minimizes $J(u_1,u_2)$ over u , then there exist adjoint variables λ_S, λ_E, λ_A, λ_C and λ_R satisfying.*

$$\begin{aligned}-\frac{d\lambda_S}{dt} &= ((1-u_1)\upsilon+\mu)\lambda_s-(1-u_1)\upsilon\lambda_E\\ -\frac{d\lambda_E}{dt} &= -\beta_1+(\theta+k_2+\mu)\lambda_E-\theta\lambda_A-k_2\lambda_C\\ -\frac{d\lambda_A}{dt} &= -\beta_2+(k_1+u_2\rho_1+a+\mu)\lambda_A-k_1\lambda_C-u_2\rho_1\lambda_R\\ &\quad +(1-u_1)\frac{\beta_1}{N}S\lambda_S-(1-u_1)\frac{\beta_1}{N}S\lambda_E\\ -\frac{d\lambda_C}{dt} &= -\beta_3+(u_2\rho_2+d+\mu)\lambda_C+(1-u_1)\frac{\beta_2}{N}S\lambda_S\\ &\quad -(1-u_1)\frac{\beta_2}{N}S\lambda_E-u_2\rho_2\lambda_R\\ -\frac{d\lambda_R}{dt} &= -\sigma\lambda_S+(\sigma+\mu)\lambda_R\end{aligned} \tag{51}$$

and with transversality conditions

$$\lambda_S(T)=\lambda_E(T)=\lambda_A(T)=\lambda_C(T)=\lambda_R(T)=0 \tag{52}$$

and by optimality conditions

$$u_1^*=\max\{0,\min(1,\bar{u}_1)\} \text{ and } u_2^*=\max\{0,\min(1,\bar{u}_2)\}.$$

To find $\bar{u}_1$, $\bar{u}_2$ and $\bar{u}_3$ we first solve the optimality conditions given by

$$\frac{\partial H}{\partial u_1}=0 \text{ and } \frac{\partial H}{\partial u_2}=0 \tag{53}$$

We differentiate equestion (50) with respect to u_1 and u_2 to get

$$\frac{\partial H}{\partial u_1}=A_1u_1+\lambda_s\left(\frac{\beta_1A+\beta_2C}{N}\right)S-\lambda_E\left(\frac{\beta_1A+\beta_2C}{N}\right)S$$

$$\frac{\partial H}{\partial u_2} = A_2 u_2 - \rho_1 A\lambda_A - \rho_2 C\lambda_C + \rho_1 A\lambda_R + \rho_2 C\lambda_R \tag{54}$$

We therefore solve for u_1 and u_2 by equating $\frac{\partial H}{\partial u_1} = 0$ and $\frac{\partial H}{\partial u_2} = 0$ as described by Lenhart and Workman (2002).

By equating system (42) to zero we obtain

$$u_1 = (\lambda_E - \lambda_S)\left(\frac{\beta_1 A + \beta_2 C}{NA_1}\right)S$$

$$u_2 = \frac{\rho_1 A\lambda_A + \rho_2 C\lambda_C - \rho_1 A\lambda_R - \rho_2 C\lambda_R}{A_2} \tag{55}$$

From the system (55) then $\bar{u}_1 = u_1$ and $\bar{u}_2 = u_2$. Hence the optimality conditions is written as

$$u_1^* = \max\left\{0, \min\left(1, (\lambda_E - \lambda_E)\left(\frac{\beta_1 A + \beta_2 C}{NA_1}\right)S\right)\right\}$$

$$u_2^* = \max\left\{0, \min\left(1, \left(\frac{\rho_1 A\lambda_A + \rho_2 C\lambda_C - \rho_1 A\lambda_R - \rho_2 C\lambda_R}{A_2}\right)\right)\right\} \tag{56}$$

By standard control arguments involving the bounds on the controls, we conclude similarly as [5] that

$$u_1^* = \begin{cases} 0 & \text{if} \quad \bar{u}_1 \le 0 \\ \bar{u}_1 & \text{if} \quad 0 < \bar{u}_1 < 1 \\ 1 & \text{if} \quad \bar{u}_1 \ge 1 \end{cases} \text{ and } u_2^* = \begin{cases} 0 & \text{if} \quad \bar{u}_2 \le 0 \\ \bar{u}_2 & \text{if} \quad 0 < \bar{u}_2 < 1 \\ 1 & \text{if} \quad \bar{u}_2 \ge 1 \end{cases} \tag{57}$$

According to the prior boundedness of the state system , the adjoint system and the resulting Lipschitz structure of the ODEs, we obtain the uniqueness of the optimal control for small T. The uniqueness of the optimal control follows from the uniqueness of the optimality system, which consist of equations (51) and (52) and transversality condition with characterization (56).

There is a restriction on the length of time interval in order to guarantee the uniqueness of the optimality system. This smallness restriction of the length on the time due to the opposite time orientations of (51) and (52); the state problem has initial values and the adjoint problem has final values. This restriction is common in control problems ([20], [21], [22]).

VII. NUMERICAL RESULTS AND DISCUSSIONS

In this section, we study numerically an optimal transmission parameter control for the HCV model. In order to study the effects of control u_1 (education, health care and immunization) and u_2 (treatment) on transmission dynamics of HCV infection, the numerical simulations of the model (3) are carried out using the following set of estimated parameter values: β_1 =0.8, β_2 =0.352, θ =0.00952, k_1 =0.5, k_2 =0.344, ρ_1 =*0.5*, ρ_2 =0.2, a =0.0034, d =0.5, μ =0.0031, Q =5, N = 2. Assume the weights at final time are being kept fixed as, $B_1 = 20$, $B_2 = 15$, $A_1 = 10$, $A_2 = 7$, to illustrate the effect of various optimal strategies on the transmission dynamics of HCV.

Figures 4 show the simulation of the model with education, health care, immunization u_1 only. With this strategy, only the control u_1 on education, health care and immunization is used to optimize the objective function J, while the control u_2 on treatment is set to zero.

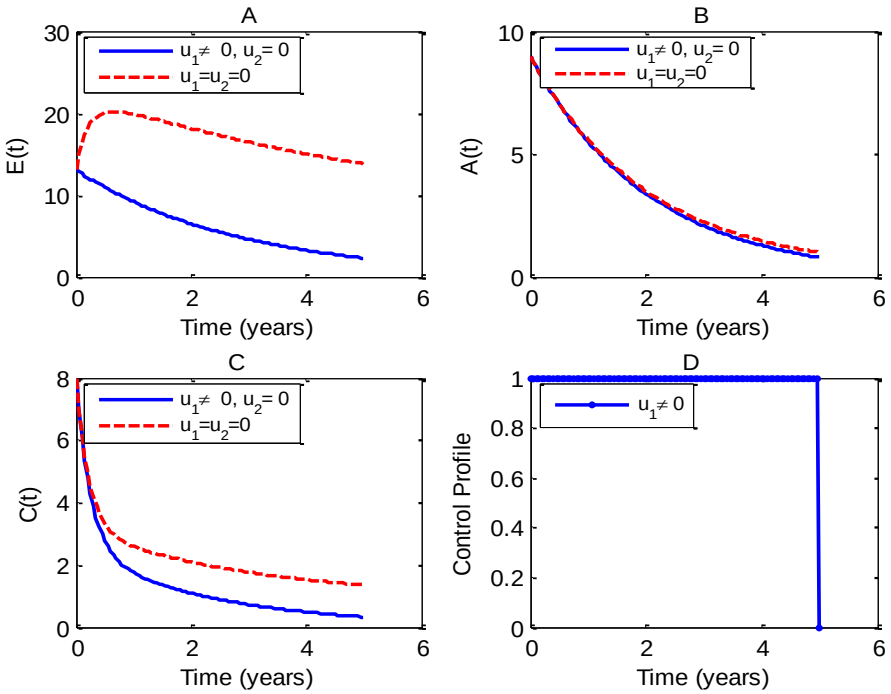

Fig. 4. Simulations of the model showing the effects of education, health care, immunization (u_1) on the spread of HCV.

The results in figures 4(A-C) show a significance difference in the numbers of exposed and infectious humans with optimal strategy compared to the number without controls. Due to the control strategies, the number of exposed population decreases while the population of exposed increases when there is no control. In Fig.4(B) and (C), the infectious population decrease in the presence of control strategies while an incresed number is observed for the uncontrolled case. From the control profile shown in fig. 4(D), the results suggests control on education, health care, immunization u_1 to be at the upper bound for 4.95 years before dropping gradually to the lower bound.

Figures 5 show the simulation of the model with treatment (u_2). The treatment u_2 is used to optimize the objective functional J while we set, education, health care, immunization u_1 to zero.

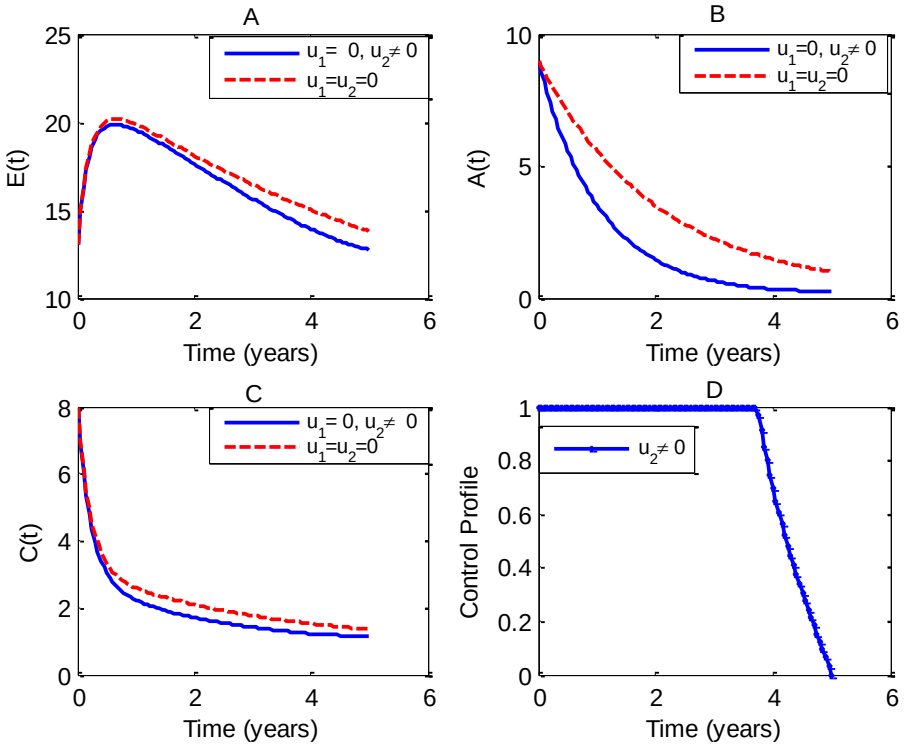

Fig. 5. Simulations of the model showing the effects of treatment (u_2) on the spread of HCV.

In figures 4, the results show a significant difference in the number of exposed humans E, acute infected humans A and chronic infected humans C with optimal strategy compared to E, A and C without control. Specifically, it is observed that in figure 4(A) the control strategies lead to a decrease in the number of exposed humans E as against increases in the uncontrolled case. Similarly in fig. 5(B) and (C), the uncontrolled case resulted in increased number of acute infected humans A and chronic infected humans while the control strategy lead to a decrease in the number of infected humans. The control profile is shown in fig. 5(D), that the optimal treatment u_2 is at the upper bound, till the time $T = 3.7$years before dropping to the lower bound.

Figures 6 show the simulation of the model where both controls u_1 and u_2 are optimized. We use all the three controls, education, health care, immunization (u_1) and treatment u_3 to optimize the objective functional J.

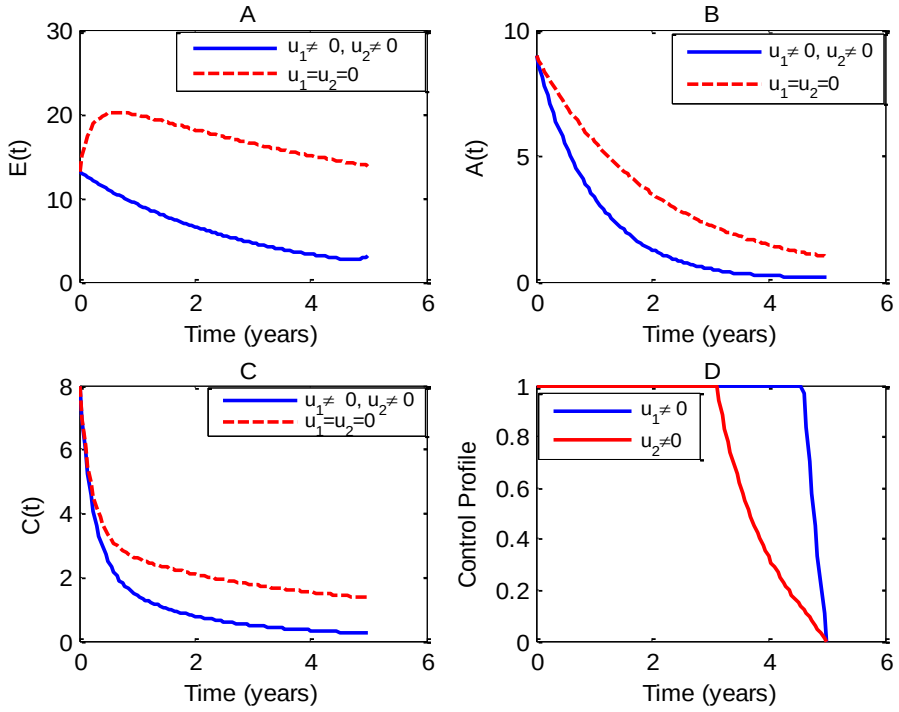

Fig. 6. Simulations of the model showing the effects of all controls on spread of HCV

It is observed in figures 6(A-C) that the control strategies results in a decrease in the numbers of exposed E, acute infected A and chronic infected C while there is increases in the numbers of E, A and C in the uncontrolled cases. The control profile in fig. 6(D) suggests that education, health care, immunization u_1 to be at the upper bound for 4.6 years before dropping gradually to the lower bound while the control on treatment u_2 to be at the upper bound for 3.15 years before dropping gradually to the lower bound at the final time. Therefore, an effective education, health care, immunization and treatment will be beneficial to the community for the control of HCV disease.

VIII. COST EFFECTIVENESS ANALYSIS

To determine the most cost effective strategy to use to control HCV disease (education, health care and immunization only, treatment only, and education, health care, immunization with treatment), we use cost effectiveness analysis. For this we need to compare the differences between the costs and health outcomes of these interventions. This is done by calculating the Incremental Cost-Effectiveness Ratio (ICER) which is generally described as the additional cost per additional health outcome. When comparing two competing intervention strategies incrementally, one intervention should be compared with the next-less-effective alternative [5] .The ICER numerator includes the differences in intervention costs, averted disease costs, costs of prevented cases and averted productivity losses if applicable. While, the ICER denominator is the differences in health outcomes (e.g. total number of infection averted, number of susceptibility cases prevented).

We rank the strategies in increasing order of effectiveness, namely education, health care and immunization only (strategy A), treatment only (strategy B) and the combination of education, health care and immunization with treatment (strategy C). The difference between the total infectious individuals without control and the total infectious individuals with control was used to determine the "total number of infection averted" used in the table of cost-effectiveness analysis. Based on the

model simulation results, we rank the strategies in order of increasing effectiveness. In table 1 we compare strategy A and B in order of increasing effectiveness.

Table 1: Compare Strategy A and B

Strategies	Total infection averted	Total costs ($)	ICER
No strategy	0	0	-
Strategy A	1.0483	24.8264	23.6825336
Strategy B	3.3116	17.3652	-3.29660231

The ICER, is calculated as follows:

$$\text{ICER(A)} = \frac{24.8264}{1.0483} = 23.6825336$$

$$\text{ICER(B)} = \frac{17.3652 - 24.8264}{3.3116 - 1.0483} = -3.29660231$$

The comparison between strategies A and B shows a cost saving of $\$3.29660231$ for strategy B over strategy A. The ICER for strategy B indicates the strategy A is "strongly dominated". That is, strategy A is more costly and less effective than strategy B. Therefore strategy A, the strongly dominated is excluded from the set of alternatives so that it does not consume limited resources. We exclude A and compare strategies B and C. From the numerical results we have.

In Table 2 we compare strategy A and C in order of increasing effectiveness.

Table 5.2: Compare Strategy B and C

Strategies	Total infection averted	Total costs ($)	ICER
Strategy B	3.3116	17.3652	5.24374925
Strategy C	4.2786	39.2783	22.66091

$$\text{ICER(B)} = \frac{17.3652}{3.3116} = 5.24374925$$

$$\text{ICER(C)} = \frac{39.2783 - 17.3652}{4.2786 - 3.3116} = 22.66091$$

The comparison between ICER (B) and ICER (C) shows a cost saving of $\$5.24374925$ for strategy B over strategy C. Similarly, the ICER for strategy B indicates the strategy C is "strongly dominated". That is, strategy C is more costly and less effective than strategy B. Therefore, strategy C, the strongly dominated is excluded.

With this result, we therefore conclude that strategy B (treatment) is the most cost-effective of all the strategies for HCV disease control considered.

IX. CONCLUSION

In paper, a deterministic model was derived and analysed for the transmission of HCV disease in the presence of education, health care and immunization and treatment of infectives and performed an optimal control analysis of the model. The necessary conditions for the optimal control of the disease were derived and analysed. The cost-effectiveness of the controls was investigated to determine the most effective strategy for eliminating HCV with minimum costs. Using ICER, it was established that the total cost of the objective function for the two interventions together; education, health care and immunization and treatment of infective individuals (strategy C) is $39.2783; which is very costly. Also, the total cost of the objective function for the treatment of infective individuals (strategy A) is $24.4769. This strategy is very effective in eliminating the disease. The costs for using education, health care and immunization (strategy B) is costs $17.3652, which is lower compared to the cost of implementing strategy A. This strategy is very effective for efficient control

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of the disease. It is concluded that, according to the model, the most cost-effective strategy for HCV control is the treatment of infective individuals.

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