Impact of Chemotherapy treatment on SITR Compartmentalization and Modeling of Human Papilloma Virus (HPV)

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Abstract: *In this paper, mathematical model of Human Papilloma Virus (HPV) with chemotherapy as treatment is formulated and analyzed. The cancer cells have been divided into four compartments SITR. The well possedness of the formulated model equations was proved and the equilibrium points of the model have been identified. In addition, the basic reproduction number is derived using next generation matrix method and analyzed the stability of the equilibrium points using Routh Hurwitz criterion. From the analytic and numerical simulation studies it is observed that if the basic reproduction is less than one then the solution converges to the disease free steady state i.e., disease will wipe out and thus the treatment is said to be successful. On the other hand, if the basic reproduction number is greater than one then the solution converges to endemic equilibrium point and thus the infectious cells continue to replicate i.e., disease will persist and thus the treatment is said to be unsuccessful. Sensitivity analysis of the model is analyzed. Finally, the model formulated in the present study effectively addresses the treatment of Human Papilloma Virus.*
Keywords: *Cervical Cancer, Chemotherapy, Basic Reproduction Number, Stability Analysis, Routh Hurwitz criterion*

I. Introduction

Cancer is a general name that refers to a group of such diseases in which normal cells divide uncontrollably i.e., grow more rapidly than normal cells and may eventually spread to other parts of the body by a process called metastasis [1]. According to the National Cancer Registry [2] cancer kills more people than HIV/AIDS, malaria and tuberculosis combined. Statistics show that 18.1 million new cases, 9.6 million cancer related deaths, and 43.8 million people living with cancer in 2018. The number of new cases is expected to rise from 18 million to 22 million by 2030 and the number of global cancer deaths is projected to increase by 45% in the period from 2007 to 2030 [3]. The most common types of cancer include: Cervical cancer, Breast cancer, Prostate cancer, Brain cancer, Lung cancer and Skin cancer among others.

According to Cervical Cancer Action [4] Report Card 2011, cervical cancer is the most common cancer in women in most developing countries and most common cause of cancer deaths. Human Papilloma Virus (HPV) is the family name of a collection of viruses that include more than 100 different types; more than 30 of these viruses are sexually transmitted. Most of the HPV infections are asymptomatic and can fed away without treatment over the course of only some years. For illustration, about 70% of HPV infections fed away within a year and 90% within two years. However, in some people disease can persist for many years and can cause warts (low risk genotype of HPV), while other types lead to different kinds of cancers (high risk genotype of HPV) including cervical cancer. Although HPV itself cannot be treated, the cellular changes that come from any HPV infection can be treated. For examples, genital warts, cervical, anal, and genital cancers can be treated if the infection is diagnosed during the early stage of development. Pre-cancerous cell changes caused by HPV can be detected by Pap tests and treat individuals who are found already infected. Persistent infection with high-risk types of HPV is the most important risk factor for cervical cancer; the development of cervical cancer is always preceded by infection with one of these viruses [5].

Cervical cancer is a disease of the female reproductive organs, with the burden of it borne disproportionately by women in their perimenopausal (the time when the ovaries stop releasing eggs) years: peak cancer incidence occurs at age 50-54 [6]. Cancer is caused by chemical substances, alcoholic beverages, excessive solar radiation, genetic differences, and so on [7]. Various methods are used to cure or inhibit the growth of cancer. Now-a-days various types of treatments are available such as surgery, radiation therapy, chemotherapy, target therapy, immunotherapy, hormonal therapy, and the latest is a gene therapy. However,

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each treatment has side effects attributed to it, for example, vomiting, pressing the blood production, fatigue, hair loss and mouth sores.

Mathematical modeling of infectious diseases began in 1760s with Daniel Bernoulli's modeling of smallpox. Since then, mathematical models have been developed to simulate the spread of a wide range of infectious diseases, such as HIV, tuberculosis, malaria and influenza to name but a few examples. These mathematical models have been developed to address a range of questions that cannot be answered through the use of traditional epidemiological methods.

Many mathematical models have been developed to analyze the dynamics of transmission of HPV infection and its associated health problems, and as well study the impact of some control strategies against the virus [8]. It is an essential and effective way to totally understand the real-world problems by establishing mathematical models and analyzing their dynamical behaviors.

Old and recent studies such as [9-11] are used vaccination and screening for preventing cancer and some other recent studies [8, 12] are used radiation therapy, chemotherapy and so on as treatment. However, Kermack and McKendrick [**1**] develop SIR cancer model and some other recent studies by Akram et al [8] develop the mathematical model that describe interaction between uninfected tumor cells and infected tumor cell. These studies use viral therapy as treatment. But much has not been assumed the treated individual by Chemotherapy as variable for a control or therapy on tumor cells and developed a model treatment for general cancer. So in this study the model in [8] is modified by adding the assumption of treated individuals by chemotherapy and recovery class specifically for Human Papilloma Virus (HPV).

This paper is organized as follows: In section 2, construction of the mathematical model of the problem is presented. Also, model assumptions, description, well possedness and reproduction number are included. In section 3, the equilibrium of the model is determined and the stability analysis is conducted. In section 4, numerical simulations of the study are performed. The outcome and discussion are given in section 5. Finally, in Section 6, conclusions are drawn and the results are discussed for the given model.

II. Model Formulation

In the present model describing Human Papilloma Virus (HPV) with treatment the total cells are divided into four classes: (i) Susceptible class denoted by S consists of cells which are capable of becoming infected (ii) Infected class denoted by I consists of cells which are infected with virus and are also infectious (iii) Treatment class denoted by T consists of cells being treated by chemotherapy and (iv) Recovered class denoted by R consists of recovered cells.
Here, a mathematical model of the Human Papilloma Virus is constructed based on the following assumptions:
(i)   The total population size is assumed to be constant.
(ii)   Both the number of births and death are equal.
(iii)   Human Papilloma Virus HPV model classifies the cell population into four compartments at any time SITR.
(iv)   Susceptible cells are recruited into the compartment $S(t)$ at a constant rate π.
(v)   Susceptible cells are infected when they come into effective contact with infectious cells and the disease transmitted at the rate β.
(vi)   The infected cells join treatment class at a rate α and are treated by chemotherapy.
(vii)   The treated cells join the recovery class at a rate ω after treatment and reduce the transmission of HPV in the community.
(viii) Recovered cells revert to the susceptible class after losing their immunity at a rate φ.
(ix)   All types of cells suffer natural mortality at a rate μ.
(x)   Infected cells die of infection at a rate γ.
(xi)   All parameters in the model are positive.

Table 1 Notations and description of model variables

Variable	Description
S(t)	Population size of susceptible cells
I(t)	Population size of infected and infectious cells
T(t)	Population size of cells under treatment
R(t)	Population size of recovered cells

Table 2 Notations and description of model parameters

Parameter	Description
π	Recruited rate of susceptible cells. With this rate new cells will born and they will enter into susceptible class
β	Transmission rate of infection. With this rate cells transfer from compartment S to I

α	With this rate cells transfer from compartment I to T
ω	Treatment rate. With this rate cells transfer from compartment T to R
φ	Recovery rate. With this rate cells transfer from compartment R to S
γ	Death rate due to infection. With this rate cells of I compartment die of the disease.
μ	Natural death rate. With this rate cells of all the compartments die naturally.

Upon including the basic assumptions together with the description of both model variables and parameters the schematic diagram of the modified model can be given as in Figure 1.
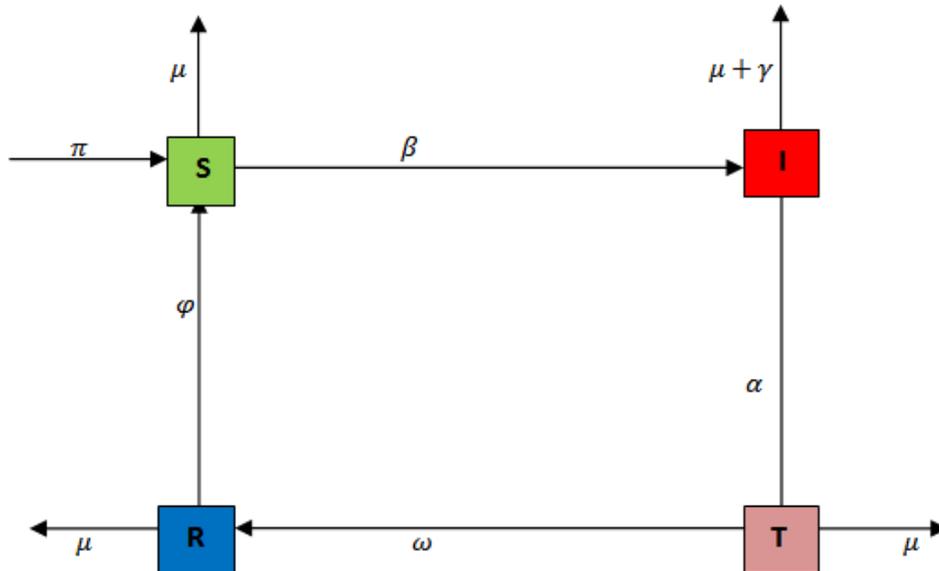
Figure 1 Schematic diagram of compartmental structure of the model

Based on the model assumptions, the notations of variables and parameters and the schematic diagram, the model equations are formulated and given as follows:

$$dS/dt = \pi - \mu S - (\beta IS/N) + \varphi R \qquad (1)$$
$$dI/dt = (\beta IS/N) - (\alpha + \mu + \gamma)I \qquad (2)$$
$$dT/dt = \alpha I - (\omega + \mu)R \qquad (3)$$
$$dR/dt = \omega T - (\varphi + \mu)R \qquad (4)$$

The non-negative initial conditions of the system of model equations $(1) - (4)$ are denoted by $S(0) > 0$, $I(0) \geq 0$, $T(0) \geq 0$, $R(0) \geq 0$. This system consists of four first order non-linear ordinary differential equations.

III. Mathematical analysis of the model

In this section mathematical analysis of the improved and modified model is conducted. The analysis consists of the following features: (i) Existence, positivity and boundedness of solutions (ii) Steady states (iii) Disease free equilibrium points (iv) Endemic equilibrium points (v) Basic reproduction number (vi) Stability analysis of the disease free equilibrium points (vii) Local stability of disease free equilibrium point (viii) Global stability of disease free equilibrium point (ix) Stability analysis of endemic equilibrium point and (x) Local stability of endemic equilibrium point. These mathematical aspects are presented and discussed in the following sub-sections respectively.

3.1 Existence, Positivity and Boundedness of solution
In order to show that the model is biologically valid, it is required to prove that the solutions of the system of differential equations (1) – (4) are both positive and bounded for all time. It is done starting with proving Lemma 1.

Lemma 1 (Positivity) Solutions of the model equations (1) – (4) together with the initial conditions $S(0) > 0, I(0) \geq 0, T(0) \geq 0, R(0) \geq 0$ are always positive (OR) the model variables $S(t)$, $I(t)$, $T(t)$, and $R(t)$ are positive for all t and will remain in $\mathbb{R}_+^4$.

Proof Positivity of the model variables is shown separately for each of the model variables $S(t)$, $I(t)$, $T(t)$, and $R(t)$.

Positivity of $S(t)$: The model equation (1) given by $dS/dt = \pi - \mu S - (\beta IS/N) + \varphi R$ can be expressed without loss of generality, after eliminating the positive terms $(\pi + \varphi R)$ which are appearing on the right hand side, as an inequality as $dS/dt \geq -[\mu + (\beta I/N)]S$. Using variables separable method and on applying integration, the solution of the foregoing differentially inequality can be obtained as $S(t) \geq e^{-\mu t - (\beta/N) \int I dt}$. Recall that an exponential function is always non–negative irrespective of the sign of the exponent, i.e., the exponential function $e^{-\mu t - (\beta/N) \int I dt}$ is a non-negative quantity. Hence, it can be concluded that $S(t) \geq 0$.

Positivity of $I(t)$: The model equation (2) given by $dI/dt = (\beta IS/N) - (\alpha + \mu + \gamma)I$ can be expressed without loss of generality, after eliminating the positive term $(\beta IS/N)$ which are appearing on the right hand side, as an inequality as $dI/dt \geq -(\alpha + \mu + \gamma)I$. Using variables separable method and on applying integration, the solution of the foregoing differentially inequality can be obtained as $I(t) \geq e^{-(\alpha+\mu+\gamma)t}$. Recall that an exponential function is always non–negative irrespective of the sign of the exponent, i.e., the exponential function $e^{-(\alpha+\mu+\gamma)t}$ is a non-negative quantity. Hence, it can be concluded that $I(t) \geq 0$.

Positivity of $T(t)$: The model equation (3) given by $dT/dt = \alpha I - (\omega + \mu)T$ can be expressed without loss of generality, after eliminating the positive term (αI) which are appearing on the right hand side, as an inequality as $dT/dt \geq -(\omega + \mu)T$. Using variables separable method and on applying integration, the solution of the foregoing differentially inequality can be obtained as $T(t) \geq e^{-(\omega+\mu)t}$. Recall that an exponential function is always non–negative irrespective of the sign of the exponent, i.e., the exponential function $e^{-(\omega+\mu)t}$ is a non-negative quantity. Hence, it can be concluded that $T(t) \geq 0$.

Positivity of $R(t)$: The model equation (4) given by $dR/dt = \omega T - (\varphi + \mu)R$ can be expressed without loss of generality, after eliminating the positive term (ωT) which are appearing on the right hand side, as an inequality as $dR/dt \geq -(\varphi + \mu)R$. Using variables separable method and on applying integration, the solution of the foregoing differentially inequality can be obtained as $R(t) \geq e^{-(\varphi+\mu)t}$. Recall that an exponential function is always non–negative irrespective of the sign of the exponent, i.e., the exponential function $e^{-(\varphi+\mu)t}$ is a non-negative quantity. Hence, it can be concluded that $R(t) \geq 0$.

Thus, the model variables $S(t), I(t), T(t),$ and $R(t)$ representing population sizes of various types of cells are positive quantities and will remain in $\mathbb{R}_+^4$ for all t.

Lemma 2 (Boundedness) The positive solutions of the system of model equations (1) – (4) are bounded. That is, the model variables $S(t)$, $I(t)$, $T(t)$, and $R(t)$ are bounded for all t.

Proof: Recall that each population size is bounded if and only if the total population size is bounded. Hence, in the present case it is sufficient to prove that the total population size $N = S(t) + I(t) + T(t) + R(t)$ is bounded for all t. It can be begun by showing that all feasible solutions are uniformly bounded in a proper subset $\Omega \in \mathbb{R}_+^4$ where the feasible region Ω is given by $\Omega = \{(S, \ I, \ T, \ R) \in \mathbb{R}_+^4; N \leq (\pi/\mu)\}$.

Now, summation of all the four equations (1) – (4) of the model gives $dN(t)/dt = \pi - \mu N(t) - \gamma I$. It can be expressed without loss of generality, after eliminating the negative term $(-\gamma I)$ which is appearing on the right hand side, as an inequality as $dN(t)/dt \leq [\pi - \mu N(t)]$. Equivalently this inequality can be expressed as a linear ordinary differential inequality as $dN(t)/dt + \mu N(t) \leq \pi$ giving general solution upon solving as $N(t) \leq (\pi/\mu) + ce^{-\mu t}$. But, the term $N(0)$ denotes the initial values of the respective variable i.e., $N(t) = N(0)$ at $t = 0$. Thus, the particular solution can be expressed as $N(t) \leq (\pi/\mu) + [N(0) - (\pi/\mu)]e^{-\mu t}$. Further, it can be observed that $N(t) \to (\pi/\mu)$ as $t \to \infty$. That is, the total population size $N(t)$ takes off from the value N(0) at the initial time $t = 0$ and ends up with the bounded value (π/μ) as the time t grows to infinity. Thus it can be concluded that $N(t)$ is bounded as $0 \leq N(t) \leq (\pi/\mu)$.

Therefore, (π/μ) is an upper bound of $N(t)$. Hence, feasible solution of the system of model equations (1) – (4) remains in the region Ω which is positively invariant set. Thus, the system is biologically meaningful and mathematically well posed in the domain Ω. Further, it is sufficient to consider the dynamics of the populations represented by the model system (1) – (4) in that domain.

Therefore, it can be summarized the result of Lemma 2 as "the model variables $S(t)$, $I(t)$, $T(t)$, and $R(t)$ are bounded for all t."

Lemma 3 (Existence) Solutions of the model equations (1) – (4) together with the initial conditions $S(0) > 0, I(0) \geq 0, T(0) \geq 0, R(0) \geq 0$ exist in $\mathbb{R}_+^4$ i.e., the model variables $S(t)$, $I(t)$, $T(t)$, and $R(t)$ exist for all t and will remain in $\mathbb{R}_+^4$.

Proof Let the right hand sides of the system of equations (1) – (4) can be expressed as follows:

$$f_1 = \pi - \mu S - (\beta IS/N) + \varphi R$$
$$f_2 = (\beta IS/N) - (\alpha + \mu + \gamma)I$$
$$f_3 = \alpha I - (\omega + \mu)T$$
$$f_4 = \omega T - (\varphi + \mu)R$$

According to Derrick and Groosman theorem, let Ω denote the region $\Omega = \{(S,\ I,\ T,\ R) \in \mathbb{R}_+^4 ; \mathrm{N} \le \pi\mu$. Then equations (1) – (4) have a unique solution if $\partial fi\partial xj,\ i,j=1,2,3,4$ are continuous and bounded in Ω. Here, $x_1 = S,\ x_2 = I,\ x_3 = T,\ x_4 = R$

The continuity and the boundedness are verified as here under:

For f_1:
$|(\partial f_1)/(\partial S)| = |-[\mu + (\beta I/N)]| < \infty$
$|(\partial f_1)/(\partial I)| = |-(\beta S/N)| < \infty$
$|(\partial f_1)/(\partial T)| = 0 < \infty$
$|(\partial f_1)/(\partial R)| = |\varphi| < \infty.$

For f_2:
$|(\partial f_2)/(\partial S)| = |\beta I/N| < \infty$
$|(\partial f_2)/(\partial I)| = |(\beta S/N) - (\alpha + \mu + \gamma)| < \infty$
$|(\partial f_2)/(\partial T)| = 0 < \infty$
$|(\partial f_2)/(\partial R)| = 0 < \infty$

For f_3:
$|(\partial f_3)/(\partial S)| = 0 < \infty$
$|(\partial f_3)/(\partial I)| = |\alpha| < \infty$
$|(\partial f_3)/(\partial T)| = |-(\omega + \mu)| < \infty$
$|(\partial f_3)/(\partial R)| = 0 < \infty$

For f_4:
$|(\partial f_4)/(\partial S)| = 0 < \infty$
$|(\partial f_4)/(\partial I)| = 0 < \infty$
$|(\partial f_4)/(\partial T)| = |\omega| < \infty$
$|(\partial f_4)/(\partial R)| = |-(\varphi + \mu)| < \infty$

Thus, all the partial derivatives $(\partial f_i)/(\partial x_j),\ i,j = 1,2,3,4$ exist, continuous and bounded in Ω. Hence, by Derrick and Groosman theorem, a solution for the model (1) – (4) exists and is unique.

3.2 Steady State
In order to understand the dynamics of the model, it is necessary to determine equilibrium points of the solution region. An equilibrium solution is a steady state solution of the model equations (1) – (4) in the sense that if the system begins at such a state, it will remain there for all times. In other words, the population sizes remain unchanged and thus the rate of change for each population vanishes. Equilibrium points of the model are found, categorized, stability analysis is conducted and the results have been presented in the following sub-sections:

3.2.1 Disease free equilibrium points
Disease free equilibrium points are steady state solutions where there is no disease in the population. In the absence of the disease this implies that $I(t) = T(t) = R(t) = 0$ and the right hand side of the model is equal to zero. We have;
$$\pi - \mu S = 0$$
$$S^0 = (\pi/\mu).$$
Thus, the disease-free equilibrium point of the model equation in (1) – (4) above is given by
$$E_0 = \{S^0, I^0, T^0, R^0\} = \{(\pi/\mu), 0, 0, 0\}$$
3.2.2 Endemic Equilibrium
The endemic equilibrium point $E_1 = \{S^1,\ I^1,\ T^1, R^1\}$ is a steady state solution where the disease persists in the population. The endemic equilibrium point is obtained by setting rates of changes of variables with respect to time in model equations (1) – (4) to zero. That is, setting $dS/dt = dI/dt = dT/dt = dR/dt = 0$ the model equations take the form as
$$\pi - \mu S - (\beta IS/N) + \varphi R = 0 \qquad (5)$$
$$(\beta IS/N) - aI = 0 \qquad (6)$$
$$\alpha I - bT = 0 \qquad (7)$$
$$\omega T - cR = 0 \qquad (8)$$
$$\text{Where } a = \alpha + \mu + \gamma,\ b = \omega + \mu,\ c = \varphi + \mu$$
Now, (6) can be rearranged as $[(\beta S/N) - a]I = 0$ leading to the solutions $(\beta S/N) - a = 0$ or $I = 0$ or both. However, I does not vanish since the disease is assumed to persist. Thus, it leads to the only meaningful solution $(\beta S/N) - a = 0$ or equivalently $S = aN/\beta$.
$$S^1 = aN/\beta \qquad (9)$$
Similarly, solving (7) and (8) gives expression for T and R as

$$T = \alpha I/b \qquad (10)$$
$$R = \omega\alpha I/bc \qquad (11)$$

Further, substituting equations (9) and (11) into (5) gives $\pi - \mu(aN/\beta) - \beta I(aN/\beta N) + \varphi(\omega\alpha I/bc) = 0$ But, since $N = (\pi/\mu)$, after some algebraic simplifications an expression for I can be obtained as

$$I^1 = [\pi bc/(\varphi\omega\alpha - abc)][(a/\beta) - 1] \qquad (12)$$

Finally, substitution of I in (10) and (11) respectively gives the expressions for T and R in terms of parameters as

$$T^1 = [\alpha\pi c/(\varphi\omega\alpha - abc)]\,[(a/\beta) - 1] \qquad (13)$$
$$R^1 = [\omega\alpha\pi/(\varphi\omega\alpha - abc)]\,[(a/\beta) - 1] \qquad (14)$$

Therefore, the endemic equilibrium point is given by $E_1 = \{S^1,\ I^1,\ T^1, R^1\}$ where

$$S^1 = (aN/\beta)$$
$$I^1 = [\pi bc/(\varphi\omega\alpha - abc)][(a/\beta) - 1]$$
$$T^1 = [\alpha\pi c/(\varphi\omega\alpha - abc)]\,[(a/\beta) - 1]$$
$$R^1 = [\omega\alpha\pi/(\varphi\omega\alpha - abc)]\,[(a/\beta) - 1]$$

3.3 Basic Reproduction Number

The basic reproduction number denoted by R_0 and is defined as the expected number of people getting secondary infection among the whole susceptible population [13]. This number determines the potential for the spread of disease within a population. When $R_0 < 1$ each infected individual produces on average less than one new infected individual so that the disease is expected to die out. On the other hand if $R_0 > 1$ then each individual produces more than one new infected individual so that the disease is expected to continue spreading in the population. This means that the threshold quantity for eradicating the disease is to reduce the value of R_0 to less than one.

The basic reproductive number R_0 can be determined using the next generation matrix. In this method, R_0 is defined as the largest eigenvalue of the next generation matrix. The formulation of this matrix involves classification of all compartments of the model in to two classes: infected and non-infected. That is, the basic reproduction number cannot be determined from the structure of the mathematical model alone but depends on the definition of infected and uninfected compartments.

Assume that there are n compartments in the model of which the first m compartments are with infected individuals [3]. From the system (1) – (4) the first three equations are considered and decomposed into two groups; F contains newly infected cases and V contains the remaining terms. Let $X = [I\ T\ S]^t$ be a column vector and the differential equations of the first three compartments are rewritten as $F(X) - V(X)$.

Now, let $F(X) = [F_1\ F_2\ F_3]^t$. Here (i) $F_1 = (\beta SI\ /\ N)$ denote newly infected cases which arrive into the infected compartment; (ii) $F_2 = 0$ denotes newly infected cases arrived into the treated compartment; and (iii) $F_3 = 0$ denotes newly infected case from susceptible compartment.

Further, let $V(X) = [V_1\ V_2\ V_3]^t$. Here $V_1 = aI$; $V_2 = -\alpha I + bT$ and $V_3 = -\pi + (\beta SI\ /\ N) + \mu S$. The parameters a and b denote $a = (\alpha + \gamma + \mu)$ and $b = (\omega + \mu)$ respectively.

The next step is the computation of the square matrices F and V of order $m \times m$, where m is the number of infected classes, defined by $F = [\partial F_i(E_0)/\partial x_j]$ and $V = [\partial V_i(E_0)/\partial x_j]$ with $1 \le i,\ j \le m$, such that F is non-negative, V is a non-singular matrix and E_0 is the disease free equilibrium point DFE.

Since F is non-negative and V non-singular then V^{-1} is non-negative and thus FV^{-1} is also non-negative. Also, the matrix FV^{-1} is called the next generation matrix for the model. Finally, the basic reproduction number R_0 is given by $R_0 = \rho(FV^{-1})$. Here, $\rho(A)$ denotes the spectral radius of matrix A and the spectral radius is the biggest non-negative eigenvalue of the next generation matrix.

The Jacobian matrices for $F(X)$ and $V(X)$ at $(I,\ T,\ S)$ can be constructed as

$$J_F(X) = \begin{bmatrix} (\beta S/N) & 0 & (\beta I/N) \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \quad \text{and} \quad J_V(X) = \begin{bmatrix} a & 0 & 0 \\ -\alpha & b & 0 \\ (\beta S/N) & 0 & (\mu + \beta I) \end{bmatrix}.$$

The Jacobian of F and V at the disease free equilibrium point E_0 takes the form respectively as

$$J_F(E_0) = \begin{bmatrix} \beta & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \quad \text{and} \quad J_V(E_0) = \begin{bmatrix} a & 0 & 0 \\ -\alpha & b & 0 \\ \beta & 0 & \mu \end{bmatrix}.$$

It can be verified that the matrix $J_V(E_0)$ is non-singular as its determinant $det[J_F(E_0)] = ab\mu$ is non-zero and after some algebraic computations its inverse matrix is constructed as

$$[J_V(E_0)]^{-1} = \begin{bmatrix} (1/a) & 0 & 0 \\ (\alpha/ab) & (1/b) & 0 \\ (\beta/\mu a) & 0 & (1/\mu) \end{bmatrix}.$$

The product of the matrices $J_F(E_0)$ and $[J_V(E_0)]^{-1}$ can be computed as

$$[J_F(E_0)][J_V(E_0)]^{-1} = \begin{bmatrix} \beta & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} (1/a) & 0 & 0 \\ (\alpha/ab) & (1/b) & 0 \\ (\beta/\mu a) & 0 & (1/\mu) \end{bmatrix} := \begin{bmatrix} (\beta/a) & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

Now it is possible to calculate the eigenvalue to determine the basic reproduction number R_0 by taking the spectral radius of the matrix $[J_F(E_0)][J_V(E_0)]^{-1}$. Thus, the eigenvalues are computed by evaluating $det[[J_F(E_0)][J_V(E_0)]^{-1} - \lambda I] = 0$ or equivalently solving

$$\begin{vmatrix} (\beta/a) - \lambda & 0 & 0 \\ 0 & -\lambda & 0 \\ 0 & 0 & -\lambda \end{vmatrix} = 0$$

It reduces to the cubic equation for λ as $\lambda^2[(\beta/a) - \lambda] = 0$ giving the three eigenvalues as $\lambda_1 = (\beta/a)$, $\lambda_2 = 0$, $\lambda_3 = 0$. However, the largest eigenvalue here is $\lambda_1 = (\beta/a)$ and is the spectral radius as the threshold value or the basic reproductive number.

Thus, it can be concluded that the reproduction number of the model is $R_0 = (\beta/a)$.

3.4 Stability analysis of the disease free equilibrium
In absence of the infectious disease, the model populations have a unique disease free steady state E_0. To find the local stability of E_0, the Jacobian of the model equations evaluated at DEF E_0 is used. Also, to determine the global stability at E_0 comparison theorem given in [14] is used. It is already shown that the DFE of model $(1) - (4)$ is given by $E_0 = \{\pi/\mu, \; 0, \; 0, \; 0\}$. Now, the stability analysis of DEF is conducted and the results are presented in the form of theorems and proofs as follows:

3.4.1 Local Stability of Disease Free Equilibrium point

Theorem 1: The DFE E_0 of the system $(1) - (4)$ is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Proof Consider the right hand side expressions of the equations $(1) - (4)$ as functions so as to find the Jacobian matrix as follows:

$$dS/dt = \pi - \mu S - (\beta I S/N) + \varphi R \equiv f(S, \; I, \; T, \; R)$$
$$dI/dt = (\beta I S/N) - (\alpha + \mu + \gamma)I \equiv g(S, \; I, \; T, \; R)$$
$$dT/dt = \alpha I - (\omega + \mu)T \equiv h(S, \; I, \; T, \; R)$$
$$dR/dt = \omega T - (\varphi + \mu)R \equiv r(S, \; I, \; T, \; R)$$

Now, the Jacobian matrix of $(f, g, \; h, r)$ with respect to $(S, \; I, \; T, \; R)$ is given by

$$J = \begin{bmatrix} -\mu - (\beta I/N) & (\beta S/N) & 0 & \varphi \\ (\beta I/N) & (\beta S/N) - a & 0 & 0 \\ 0 & \alpha & -b & 0 \\ 0 & 0 & \omega & c \end{bmatrix} \quad (15)$$

Therefore, the Jacobian matrix J of model at the disease free equilibrium E_0 reduces to

$$J(E_0) = \begin{bmatrix} -\mu & -\beta & 0 & \varphi \\ 0 & (\beta - a) & 0 & 0 \\ 0 & \alpha & -b & 0 \\ 0 & 0 & \omega & c \end{bmatrix}$$

Now, the eigenvalues of $J(E_0)$ are required to be found. The characteristic equation $det[J(E_0) - \lambda I] = 0$ is expanded and simplified as follows:

$$\begin{vmatrix} -\mu - \lambda & -\beta & 0 & \varphi \\ 0 & (\beta - a) - \lambda & 0 & 0 \\ 0 & \alpha & -b - \lambda & 0 \\ 0 & 0 & \omega & c - \lambda \end{vmatrix} = 0$$

$$-(\mu + \lambda) \begin{vmatrix} (\beta - a) - \lambda & 0 & 0 \\ \alpha & -b - \lambda & 0 \\ 0 & \omega & c - \lambda \end{vmatrix} = 0$$

$$(\mu + \lambda)(c + \lambda)[(\beta - a - \lambda)(-b - \lambda)] = 0$$
$$(\mu + \lambda)(c + \lambda)[\lambda^2 + (a + b - \beta)\lambda + ab(1 - R_0)] = 0$$
$$(\mu + \lambda) = 0, \qquad (c + \lambda) = 0, \qquad \lambda^2 + (a + b - \beta)\lambda + ab(1 - R_0) = 0$$

Thus, the four eigenvalues of the matrix are determined as

$$\lambda_1 = -\mu$$
$$\lambda_2 = -c$$
$$\lambda_3 = \frac{-(a + b - \beta) + \sqrt{(a + b - \beta)^2 - 4ab(1 - R_0)}}{2}$$

$$\lambda_4 = \frac{-(a+b-\beta) - \sqrt{(a+b-\beta)^2 - 4ab(1-R_0)}}{2}$$

It can be observed that the first two eigenvalues λ_1 and λ_2 are absolutely negative quantities. However, the remaining two λ_3 and λ_4 are also negatives so long as the following restrictions on the parameters are valid: $(a+b) > \beta$ and $(a+b-\beta)^2 > 4ab(1-R_0)$ when $R_0 < 1$.

Therefore, it is concluded that the DFE E_0 of the system of differential equations $(1)-(4)$ is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

3.4.2 Global Stability of Disease Free Equilibrium Point

Theorem 2: The disease free equilibrium point E_0 of the model is globally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Proof Using the comparison theorem as given in [14], the rate of change of the variables representing the disease classes of the model can be rewritten as

$$\begin{bmatrix} I^0 \\ T^0 \\ R^0 \end{bmatrix} = (F-V) \begin{bmatrix} I \\ T \\ R \end{bmatrix} - M\theta \begin{bmatrix} I \\ T \\ R \end{bmatrix} \tag{16}$$

Here in (16), the matrices F and V at the disease free equilibrium E_0 are defined as

$$F = J_F(E_0) = \begin{bmatrix} \beta & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \quad \text{and} \quad V = J_V(E_0) = \begin{bmatrix} a & 0 & 0 \\ -\propto & b & 0 \\ \beta & 0 & \mu \end{bmatrix}.$$

Also, and θ is non-negative matrix. However, $M = [1 - (S^0/N^0)] = 0$ since $S^0 = (\pi/\mu)$ and $N^0 = (\pi/\mu)$. Therefore, the equation (16) reduces to the simplified form as

$$\begin{bmatrix} I^0 \\ T^0 \\ R^0 \end{bmatrix} \le (F-V) \begin{bmatrix} I \\ T \\ R \end{bmatrix}$$

Now, $(F-V)$ can be computed as

$$F - V = \begin{bmatrix} \beta & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} - \begin{bmatrix} a & 0 & 0 \\ -\propto & b & 0 \\ \beta & 0 & \mu \end{bmatrix} = \begin{bmatrix} \beta - a & 0 & 0 \\ \alpha & -b & 0 \\ -\beta & 0 & -\mu \end{bmatrix} \tag{17}$$

The eigenvalues of the matrix (17) are found by evaluating the characteristic equation $\det[(F-V) - \lambda I] = 0$ as follows:

$$\begin{vmatrix} \beta - a - \lambda & 0 & 0 \\ \alpha & -b - \lambda & 0 \\ -\beta & 0 & -\mu - \lambda \end{vmatrix} = 0$$

$$(\beta - a - \lambda)(-b - \lambda)(-\mu - \lambda) = 0$$

$$(\beta - a - \lambda) = 0, \quad (-b - \lambda) = 0, \quad (-\mu - \lambda) = 0$$

$$\lambda_1 = -(a - \beta), \quad \lambda_2 = -b, \quad \lambda_3 = -\mu$$

The notations a, b and c have been defined earlier. Here it can be observed that all the three eigenvalue of (17) have negative real parts and hence the matrix is stable for $R_0 < 1$.

Therefore by the comparison theorem, it follows that $\{I, \quad T, \quad R\} \to \{0, \quad 0, \quad 0\}$ and the remaining equations of model $(1) - (4)$ give the solution $E_0 = \{\pi/\mu, \quad 0, \quad 0, \quad 0\}$. Thus, $\{S, \quad I, \quad T \quad R\} \to E_0$ as $t \to \infty$. Hence, the disease free equilibrium point E_0 is globally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

3.5 Stability Analysis of Endemic Equilibrium Point

By definition it is true that at the endemic equilibrium point $E_1 = \{S^1, \quad I^1, \quad T^1, \quad R^1\}$ the disease persists or exists. To analyze the local stability of E_1, Jacobian of the model evaluated at that equilibrium point is used. Further, recall that the endemic equilibrium point of the given model $(1) - (4)$ is already computed as

$$E_1 = \{aN/\beta, [\pi bc/(\varphi\omega\alpha - abc)][(1/R_0) - 1], [\alpha\pi c/(\varphi\omega\alpha - abc)][(1/R_0) - 1],$$
$$[\omega\alpha\pi/(\varphi\omega\alpha - abc)][(1/R_0) - 1]\}$$

Here in E_1, the expression for the reproduction number is used as $R_0 = (\beta/a)$.

3.5.1 Local Stability of Endemic Equilibrium Point

The local stability of endemic equilibrium point is stated and proved in Theorem 3.

Theorem 3: The endemic equilibrium point $E_1 = \{S^1, \quad I^1, \quad T^1, \quad R^1\}$ is locally asymptotically stable if and only if $R_0 > 1$.

Proof The stability analysis of E_1 is conducted by following the similar procedure adopted as in the case that of E_0. Thus, the procedure starts with the construction of Jacobian matrix at E_1. Now, the Jacobian matrix of the model given in (15) at endemic equilibrium point E_1 takes the form as

$$J(E_1) = \begin{bmatrix} -\mu - (\beta/N)([\pi bc/(\varphi\omega\alpha - abc)][(1/R_0) - 1]) & -(\beta/N)(aN/\beta) & 0 & \varphi \\ (\beta/N)([\pi bc/(\varphi\omega\alpha - abc)][(1/R_0) - 1]) & (\beta/N)(aN/\beta) - a & 0 & 0 \\ 0 & \alpha & -b & 0 \\ 0 & 0 & \omega & c \end{bmatrix}$$

$$J(E_1) = \begin{bmatrix} -\mu - [\beta\mu bc/(\varphi\omega\alpha - abc)][(1/R_0) - 1]) & -a & 0 & \varphi \\ [\beta\mu bc/(\varphi\omega\alpha - abc)][(1/R_0) - 1] & 0 & 0 & 0 \\ 0 & \alpha & -b & 0 \\ 0 & 0 & \omega & c \end{bmatrix}$$

The characteristic equation $det[J(E_1) - \lambda I] = 0$ of the matrix $J(E_1)$ is expanded and simplified as follows:

$$\begin{vmatrix} -\mu - [\beta\mu bc/(\varphi\omega\alpha - abc)][(1/R_0) - 1]) - \lambda & -a & 0 & \varphi \\ [\beta\mu bc/(\varphi\omega\alpha - abc)][(1/R_0) - 1] & -\lambda & 0 & 0 \\ 0 & \alpha & -b - \lambda & 0 \\ 0 & 0 & \omega & c - \lambda \end{vmatrix} = 0$$

$$-\omega \begin{vmatrix} -\mu - [\beta\mu bc/(\varphi\omega\alpha - abc)][(1/R_0) - 1] - \lambda & -a & \varphi \\ [\beta\mu bc/(\varphi\omega\alpha - abc)][(1/R_0) - 1] & -\lambda & 0 \\ 0 & \alpha & 0 \end{vmatrix} + (c$$

$$- \lambda) \begin{vmatrix} -\mu - [\beta\mu bc/(\varphi\omega\alpha - abc)][(1/R_0) - 1] - \lambda & -a & 0 \\ [\beta\mu bc/(\varphi\omega\alpha - abc)][(1/R_0) - 1] & -\lambda & 0 \\ 0 & \alpha & -b - \lambda \end{vmatrix} = 0$$

$$-\omega\varphi \begin{vmatrix} [\beta\mu bc/(\varphi\omega\alpha - abc)][(1/R_0) - 1] & -\lambda \\ 0 & \alpha \end{vmatrix}$$

$$+ (c - \lambda)(-b - \lambda) \begin{vmatrix} -\mu - [\beta\mu bc/(\varphi\omega\alpha - abc)][(1/R_0) - 1] - \lambda & -a \\ [\beta\mu bc/(\varphi\omega\alpha - abc)][(1/R_0) - 1] & -\lambda \end{vmatrix} = 0$$

$$-\omega\varphi\alpha k[(1/R_0) - 1] + (c - \lambda)(-b - \lambda)[(-\lambda)[-\mu - k[(1/R_0) - 1] - \lambda] + ak[(1/R_0) - 1]] = 0$$

Here $k = [\beta\mu bc/(\varphi\omega\alpha - abc)]$. Also observe that $k < 0$ whenever $\varphi\omega\alpha < abc$

`After some simplification, the fourth order characteristic equation can be expressed as

$$\lambda^4 + [\mu + b - c - (1 + a)k[(1/R_0) - 1]]\lambda^3 - [cb + (b - c)(\mu + (1 + a)k[(1/R_0) - 1])]\lambda^2$$
$$+ cb[\mu + (1 + a)k[(1/R_0) - 1]]\lambda + \omega\varphi\alpha k[(1/R_0) - 1] = 0$$

Equivalently, the characteristic equation can be expressed in the general form as

$$\lambda^4 + e_1\lambda^3 + e_2\lambda^2 + e_3\lambda + e_4 = 0$$

Where

$$e_1 = \mu + b - c - (1 + a)k[(1/R_0) - 1]$$
$$e_2 = -[cb + (b - c)[\mu + (1 + a)k[(1/R_0) - 1]]]$$
$$e_3 = cb[\mu + k(1 + a)[(1/R_0) - 1]]$$
$$e_4 = \omega\varphi\alpha k[(1/R_0) - 1]$$

Now, the signs of the solutions i.e., the signs of the eigenvalues of the characteristic equation are determined using Routh-Hurwitz criterion given in [15]. According to the Routh-Hurwitz criteria, E_1 is locally asymptotically stable if the four conditions (1) $e_1 > 0$, (2) $e_3 > 0$, (3) $e_4 > 0$ and (4)$(e_1 e_2 e_3) > [(e_3^2) + (e_1^2 e_4)]$ are satisfied. The satisfaction of these conditions is verified here under.
(1) $e_1 > 0$ holds true whenever $b > c$, $R_0 > 1$ and $k < 0$
(2) $e_3 > 0$ holds true whenever $k < 0$
(3) $e_4 > 0$ holds true whenever $k < 0$
(4) $e_1 e_2 e_3 > e_3^2 + e_1^2 e_4$ holds true whenever $k < 0$
Hence, following Routh-Hurwitz criteria it can be concluded that the endemic equilibrium point E_1 is locally asymptotically stable if and only if $R_0 > 1$.

IV. Numerical Simulation
In this section, the numerical simulation study of model equations (1) – (4) is carried out using the software DE Discover 2.6.4. To conduct the study, a set of meaningful values are assigned to the model

parameters. These values are either taken from literature or assumed. These sets of parametric values are given in Tables 3 and 4.

Table 3 Parameter values used in Figure 2

Parameter	Value	Reference
π	0.0500	assumed
μ	0.0020	[5]
β	0.0100	[3]
φ	0.0410	assumed
α	0.0780	assumed
γ	0.0001	assumed
ω	0.0001	assumed

Using the parameter values given in Table 2 and the initial conditions $S(0) = 60, I(0) = 80, R(0) = 60$ and $T(0) = 50$ in the model equations (1) – (4) a simulation study is conducted and the results are given in Figure 2. In this case the steady state is disease free equilibrium point and $R_0 = 0.1248 < 1$ i.e. disease will wipe out and thus the treatment is said to be successful.
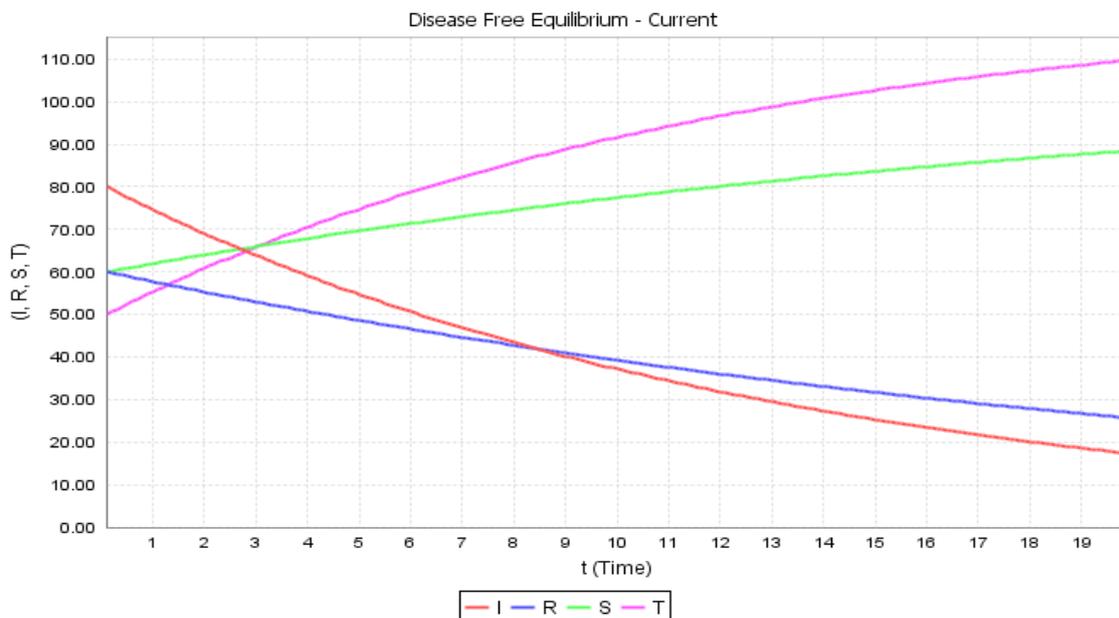
Figure 2: Numerical simulation of disease free equilibrium point

In Figure 2, it can be observed that as the treatment (T) increases the infection (I) decreases. Also, since the recovered cells loose immunity and they go to susceptible class, the susceptible (S) is increasing while the recovered (R) is decreasing.

Table 4: Parameter Values

Parameter	Value	Reference
π	0.0310	assumed
μ	0.0020	[5]
β	0.5780	assumed
φ	0.0750	assumed
α	0.0380	assumed
γ	0.0220	assumed
ω	0.2530	assumed

By considering the parameter values in Table 3 and the initial conditions $S(0) = 120, I(0) = 70, R(0) = 60$ and $T(0) = 100$ we obtain the results in Figure 3. In this case the steady state is endemic equilibrium point and $R_0 = 9.3226 > 1$. Thus, the infectious cells continue to replicate and it means that the therapy is not successful.
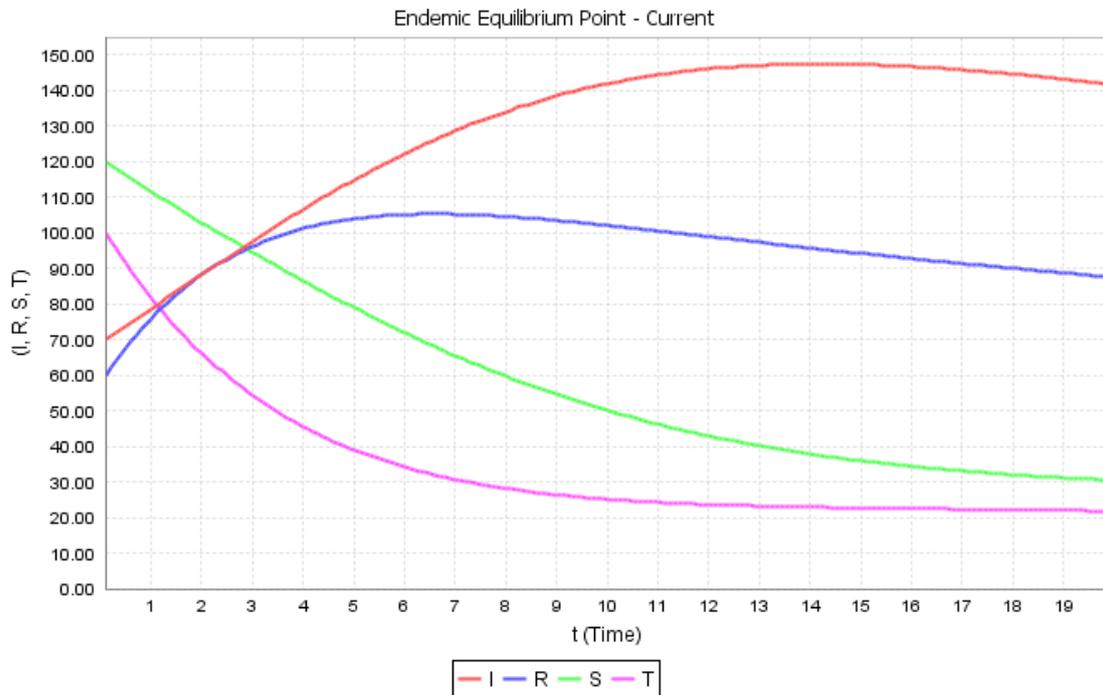
Figure 3: Numerical simulation of endemic equilibrium point

In Figure 3, it can be observed that as the treatment (T) decreases the infection (I) increases. Also, as a result both the susceptible (S) and the recovered (R) are decreasing. The scenario here is just opposite to that which is illustrated in Figure 2.

Both similarities and diffences of the existing and modified model are compared in following two tables respectively:

Table 4 Diffences of existing and modified model.

	Differences	
SN	**Existing model [8]**	**Modified model**
1	Tumor cell already exists	Tumor cell exists after susceptible
2	Used only tumor cell as target cell and classify as uninfected and infected tumor cell	Assumed different cell as target cell and classify as Susceptible cell, infected cell, treated cell and recovery
3	Assumed only natural mortality	Assumed both death due to sick and natural mortality
4	Treatments assumed for all cancer	Treatments assumed only for HPV
5	The treatments are through infection of virus OR Oncolytic virus	The treatments are through Chemotherapy
6	There is no treatment representation as parameter or variable	Treatment taken as Variable (class)
7	Has no recovery class	Has recovery class
8	Analysis done by comparing the two classes	Analysis done using reproduction number

Table 5 Similarities of existing and modified model.

Similarities
Both existing and modified model have:
✓ transmission rate
✓ natural mortality
✓ Infected cell
✓ Treatment successful and in some case not successful
✓ Equilibrium point
✓ Numerical simulation

V. Sensitivity Analysis
Sensitivity analysis is used to determine how "sensitive" a model is to changes in the value of the parameters of the model and to changes in the structure of the model. It is used to discover parameters that have a high impact on R_0 and should be targeted by intervention strategies. More precisely, sensitivity indices's allows to measure the relative change in a variable when parameter changes. If the result is negative, then the relationship between the parameters and R_0 is inversely proportional. In this case, we will take the modulus of the sensitivity index so that we can deduce the size of the effect of changing that parameter. On the other hand, a positive sensitivity index means an increase in the value of a parameter.

The explicit expression of R_0 is given by $R_0 = (\beta/a)$. Since R_0 depends only on four parameters, we derive an analytical expression for its sensitivity to each parameter using the normalized forward sensitivity index as by Chitnis [16] as follows:

$$\Upsilon_\beta^{R_0} = [\partial R_0/\beta] \times [\beta/R_0] = 1$$
$$\Upsilon_\alpha^{R_0} = [\partial R_0/\alpha] \times [\alpha/R_0] = -\alpha/a$$
$$\Upsilon_\mu^{R_0} = [\partial R_0/\mu] \times [\mu/R_0] = -\mu/a$$
$$\Upsilon_\gamma^{R_0} = [\partial R_0/\gamma] \times [\gamma/R_0] = -\gamma/a$$

Table 6 Sensitivity of R_0 evaluated for the parameter values given in Table 4.

Parameter	Sensitivity index
β	+1
α	-0.6129
μ	-0.0322
γ	-0.3548

From Table 6, we obtain $\Upsilon_\beta^{R_0} = 1$, this means that an increase in β will cause an increase of exactly the same proportion in R_0 . Similarly, a decrease in β will cause a decrease in R_0, as they are directly proportional. We also note that α or μ or $\gamma < 0$ hence these parameters are inversely proportional to R_0.

We can arrange these parameters in the order of their magnitude from largest to the smallest as follows: α, γ and the least sensitive parameter is μ. It can also be noted that there is a need to minimize contact between the susceptible and the infected so as to limit the spread of HPV; it is customary to quarantine the infected individual with the main purpose of minimizing contact rate hence reducing the outbreak of HPV.

VI. Result and Discussion

In this study, a mathematical model describing the dynamics of Human Papilloma Virus (HPV) with treatment by chemotherapy is formulated and analyzed. The model is developed based on biologically reasonable assumptions made about Human Papilloma Virus (HPV) and its treatment. The mathematical analysis has shown that if the reproduction number $R_0 < 1$ then the disease free equilibrium point is locally and globally asymptotically stable implying that the disease wipes out and the treatment is successful. Also, if $R_0 > 1$ then the disease free equilibrium point is unstable implying that the treatment is not successful. These theoretical results have been supported by the simulation study as it is shown in Figure 2. Furthermore, the endemic equilibrium point is stable if $R_0 > 1$ resulting that the infectious cells continue to replicate. This fact has also been supported by Figure 3.

VII. Conclusion

In this paper, a mathematical model of Human Papilloma Virus (HPV) using chemotherapy as treatment has been formulated. Moreover, existence, positivity and boundedness of the formulated model is verified to illustrate that the model is biologically meaningful and mathematically well posed. In particular, the stability analyses of the model were investigated using the basic reproduction number and Routh Hurwitz criterion. And also, the solution of the model equation is numerically supplemented and sensitivity analysis of the model is analyzed. Furthermore, results of the research work presented in this paper reveal that the model formulated here effectively addresses the treatment of cervical cancer.

Acknowledgements

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