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Optimal Control Strategy on Human Papilloma Virus (HPV) model with Backward Bifurcation Analysis

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Abstract: *In this study it is proposes and analyzed a compartmental nonlinear deterministic mathematical model for the human Papilloma virus epidemic together with the inclusion of optimal control strategies in a community with varying population. The model is studied qualitatively using stability theory of differential equations. The basic reproductive number that governs the disease transmission is obtained from the largest eigenvalue of the next-generation matrix. Both local and global asymptotic stability conditions for disease-free and endemic equilibria are determined. It is observed that the model exhibits a backward bifurcation and the sensitivity analysis is performed. The optimal control problem is designed by applying Pontryagin maximum principle with three control strategies viz. prevention strategy, treatment strategy and screening strategy. Numerical results of the optimal control model reveal that a combination of prevention, screening and treatment is the most effective strategy to eradicate the disease from the community.*

Keywords: *Reproductive Number, Stability Analysis, Bifurcation, Optimal Control, Numerical Simulation*

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I. Introduction

Human Papilloma Virus (HPV) is highly transmissible and is now regarded as the most common sexually transmitted infection (STI). It is estimated that over half of all sexually active males and females will be infected with HPV at some time. HPV is generally transmitted via skin-to-skin contact during sexual intercourse and less commonly through other forms of non-penetrative genital contact. Sexual behavior is directly related to the probability of acquiring a HPV infection. Prevalence of cervical HPV infection is highest amongst women under the age of 25 and lowest amongst women who have never had sex. Increased risk of exposure to HPV is proportionally linked to infection and therefore abstaining from sexual activity ensures the lowest risk. A monogamous sexual relationship with a partner who has had no or few previous partners decreases the risk of contracting an infection, as does the correct use of physical barriers such as condoms [1].

However, most of the HPV infections are asymptomatic and can feed away without treatment over the course of a few years. For instance, about 70% of HPV infections fed away with in a year and 90 % within two years. However, in some people infection can persist for many years and can cause warts or low risk genotype of HPV, while other types lead to different kinds of cancers or high risk genotype of HPV, including cervical cancer [2-3]. 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 [3].

According to the National Cancer Registry, cancer kills more people than HIV/AIDS, malaria and tuberculosis combined [4]. Statistics show that there are 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% by 2030 [5].

Mathematical modeling plays an important role in increasing our understanding of the dynamics of infectious diseases and also to investigate the optimal use of intervention strategies to control the spread of infectious diseases. Old and recent studies such as [1, 6, 7] amongst others have shown that mathematical modeling is a widely used tool for resolving questions on public health. Several SIR models [8-10] have been developed to assess the potential impact of vaccination against Human Papilloma Virus. Also, [11, 12] formulated an SIS model for Human Papilloma Virus transmission with vaccination as a control strategy and [13] developed a dynamic model for the heterosexual transmission of Human Papilloma Virus types 16 and 18, which are covered by available vaccines.

However, none of them considered optimal control strategy and also no study have been undertaken by applying optimal control. In view of the above, we developed a deterministic mathematical model to investigate the dynamics of Human Papilloma Virus with optimal control strategies.

II. Model Description and Formulation

Mathematical modeling process requires translation of a biological scenario into a mathematical problem. It begins with a clear description of the processes based on the scientists understanding of the system. The translation into mathematical equations should be made with a specific goal or biological question in mind. Then the verbal description of the system is encoded in mathematical equations. Mathematical models usually consist of parameters and variables that are connected by relationships. Variables are abstractions of the system properties that can be quantified or measured and parameters describe the rate of variables [14].

The model divides the total population into six sub-classes according to their disease status as Susceptible $S(t)$, Vaccinated $V(t)$, Asymptomatic $A(t)$, Infected $I(t)$, Recovered $R(t)$, and Cervical cancer $C(t)$. Here, a mathematical model of the Human Papilloma Virus model is constructed based on the following assumptions:

(i) The model assumes that a fraction of the population has been vaccinated before the disease outbreak at the rate p and $(1-p)$ fraction of population susceptible.

(ii) The susceptible class is increased from vaccinated class in which those individuals who are vaccinated but did not respond to vaccination with waning rate of φ and from recovered class in which those individuals who lose their temporary immunity by ω rate.

(iii) Individuals from susceptible class move to vaccinated class with vaccination rate of α .

(iv) The susceptible class is infected by asymptomatic or symptomatically infected individuals with a force of infection $\lambda = \beta[I + \gamma A]/N$ where, $\beta = \kappa\tau$, κ is contact rate, τ is the probability that a contact is effective to cause infection and γ is the transmission coefficient for the asymptomatic individuals. If $\gamma > 1$ then, the asymptomatic infect susceptible more likely than infective. If $\gamma = 1$, then both asymptomatic and infective have equal chance to infect the susceptible, but if $\gamma < 1$ then, the infective have good chance to infect susceptible than asymptomatic.

(v) The HPV vaccine is assumed to not confer permanent immunity and vaccinated individuals also have a change of being infectious or asymptomatic with small proportion and the force of infection for the vaccinated class is $\lambda_v = \varepsilon\lambda$, where $0 \leq \varepsilon \leq 1$ and ε is the proportion of the serotype not covered by the vaccine.

(vi) Newly infected individuals by the force of infection become either asymptomatic with a probability of ρ to join the asymptomatic class or more to the infected class with probability of $(1-\rho)$.

(vii) The asymptomatic class can develop disease symptom or can screen themselves and join the infected class with a rate of θ or recover by gaining natural immunity at ϕ rate.

(viii) Individuals in the infected class move to recovered compartment at a rate of η by treatment, with treatment efficacy of q proportion of individuals join the recovered class or join the asymptomatic class with $(1-q)$ proportion by adapting the treatment or may progress to develop cervical cancer is a result of failure of the treatment used at a rate δ thus moving to cervical cancer compartment.

(ix) Individual infected with cervical cancer may die as a result of the cancer infection at a rate ξ.

(x) In all compartments μ is the natural mortality rate of individuals and also all the parameters are positive.

(xi) All parameters in the model are positive.

2.1 Description of Variables and Parameters

The variables and parameters used in this model are introduced in Tables 1 and 2. Their notations and descriptions are also included.

Table 1 Description of Variables used in the model equations (1) – (6)

Variable	Description
$\mathbf{N(t)}$	The total population at time t
$\mathbf{S(t)}$	The number of Susceptible individuals at time t
$\mathbf{V(t)}$	The number of Vaccination individuals at time t
$\mathbf{A(t)}$	The number of Asymptomatic individuals at time t
$\mathbf{I(t)}$	The number of Infected individuals at time t
$\mathbf{R(t)}$	The number of Recovered individuals at time t

Table 2 Description of parameters used in the model equations (1) – (6)

Parameter	Description
$\boldsymbol{\Pi}$	Recruited rate of susceptible individuals.
$\boldsymbol{\beta}$	Transmission rate.
$\boldsymbol{\kappa}$	Contact rate.
$\boldsymbol{\gamma}$	Transmission coefficient.
$\boldsymbol{\tau}$	The probability that a contact is effective.
$\boldsymbol{\lambda}$	Force of infection for susceptible class.
$\boldsymbol{\lambda_v = \varepsilon\lambda}$	Force of infection for vaccination class.
$\boldsymbol{\alpha}$	Vaccination rate of susceptible individuals.

φ	Waning rate i.e., individuals who are vaccinated but did not respond to vaccination.
ω	Recovery rate. With this rate cells transfer from compartment R to S.
ϕ	Recovery rate of asymptomatic due to natural immunity.
ε	The proportion of the serotype not covered by the vaccine.
η	Rate of treatment.
δ	Rate of failure of treatment.
θ	Infection rate of asymptomatic.
ξ	Death rate due to infection.
μ	Natural death rate.

Based on the model assumptions the population flow diagram can be visualized as shown in Figure 1.

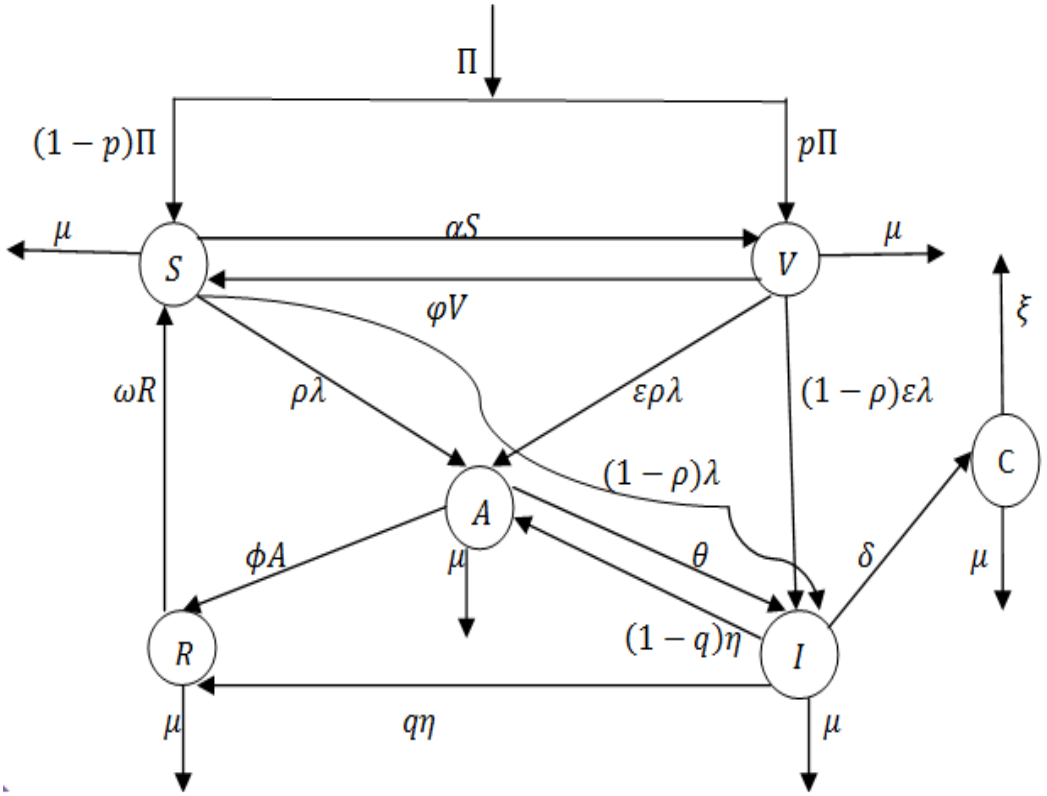

Figure 1 Schematic Diagram of the Model

The population flow diagram as shown in Figure 1 can be translated into a system of six differential equations as follows:

$$dS/dt = (1-p)\Pi + \varphi V - (\alpha + \rho\lambda + \mu)S + \omega R, \quad (1)$$
$$dV/dt = p\Pi + \alpha S - (\varphi + \varepsilon\lambda + \mu)V, \quad (2)$$
$$dA/dt = \rho\lambda S + \rho\varepsilon\lambda V + (1-q)\eta I - (\theta + \phi + \mu)A\,, \quad (3)$$
$$dI/dt = (1-\rho)\lambda S + (1-\rho)\varepsilon\lambda V + \theta A - (\delta + \eta + \mu)I \quad (4)$$
$$dR/dt = \phi A + q\eta I - (\omega + \mu)R \quad (5)$$
$$dC/dt = \delta I - (\xi + \mu)C \quad (6)$$

The non-negative initial conditions of the system of model equations (1) – (6) are denoted by $S(0) = S_0,\ V(0) = V_0,\ A(0) = A_0,\ I(0) = I_0,\ R(0) = R_0,\ C(0) = C_0$. This system consists of six first order non-linear ordinary differential equations.

III. Model Analysis

a. Invariant Region

We obtained the invariant region, in which the model solution is bounded. To do this, first we considered the total human population (N), Here $N = S + V + A + I + R + C$. Then, differentiating N both sides with respect to t leads to;

$$dN/dt = (dS/dt) + (dV/dt) + (dA/dt) + (dI/dt) + (dR/dt) + (dC/dt) \quad (7)$$

By combining $(1-6)$ and (7), we can get

$$dN/dt = \Pi - \mu N - \delta C \quad (8)$$

In the absence of mortality due to cervical cancer disease (8) becomes

$$dN/dt = \Pi - \mu N \quad (9)$$

Equivalently this inequality can be expressed as a linear ordinary differential inequality as $[\mathrm{dN(t)/dt}] + \mu \mathrm{N(t)} \leq \Pi$ giving general solution upon solving as $\mathrm{N(t)} \leq (\Pi/\mu) + ce^{-\mu t}$. But, the term $N(0)$ denotes the initial values of the respective variable i.e., $\mathrm{N(t)} = \mathrm{N(0)}$ at $\mathrm{t} = 0$. Thus, the particular solution can be expressed as $\mathrm{N(t)} \leq (\Pi/\mu) + [\mathrm{N(0)} - (\Pi/\mu)]e^{-\mu t}$. Further, it can be observed that $N(t) \rightarrow (\Pi/\mu)$ as $t \rightarrow \infty$. That is, the total population size $N(t)$ takes off from the value $\mathrm{N(0)}$ at the initial time $\mathrm{t} = 0$ 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 $0 \leq N(t) \leq (\Pi/\mu)$. Thus, the feasible solution set of the system equation of the model enters and remains in the region:

$$\Omega = \{(S, \quad V, \quad A, \quad I, \quad R, \quad C) \in \Re_+^6 : N \leq \Pi/\mu\}$$

Therefore, the basic model is well posed epidemiologically and mathematically. Hence, it is sufficient to study the dynamics of the basic model in the region Ω.

b. Existence of the solution

Lemma 1 (Existence) Solutions of the model equations (1) – (6) together with the initial conditions $S(0) > 0,\ V(0) > 0,\ A(0) > 0,\ I(0) > 0,\ R(0) > 0,\ C(0) > 0$ exist in $\mathbb{R}_+^6$ i.e., the model variables $S(t),\ V(t),\ A(t),\ I(t), R(t)$ and $C(t)$ exist for all t and will remain in $\mathbb{R}_+^6$.

Proof The right hand sides of the system of equations (1) – (6) can be expressed as follows:

$$f_1(S, \quad V, \quad A, \quad I, \quad R, \quad C) = (1-p)\Pi + \varphi \mathrm{V} - (\alpha + \rho\lambda + \mu)S + \omega R$$

$$f_2(S, \quad V, \quad A, \quad I, \quad R, \quad C) = p\Pi + \alpha S - (\varphi + \varepsilon\lambda + \mu)V$$

$$f_3(S, \quad V, \quad A, \quad I, \quad R, \quad C) = \rho\lambda S + \rho\varepsilon\lambda V + (1-q)\eta I - (\theta + \phi + \mu)A \quad (10)$$

$$f_4(S, \quad V, \quad A, \quad I, \quad R, \quad C) = (1-\rho)\lambda S + (1-\rho)\varepsilon\lambda V + \theta A - (\delta + \eta + \mu)I$$

$$f_5(S, \quad V, \quad A, \quad I, \quad R, \quad C) = \phi A + q\eta I - (\omega + \mu)R$$

$$f_6(S, \quad V, \quad A, \quad I, \quad R, \quad C) = \delta I - (\xi + \mu)C$$

According to Derrick and Groosman theorem, let Ω denote the region $\Omega = \{(S, \quad V, \quad A, \quad I, \quad R, \quad C) \in \mathbb{R}+6; \mathrm{N} \leq \Pi\mu$. Then equations (1) – (6) have a unique solution if $\partial f i \partial x j,\ i,j=1, 2, 3, 4, 5, 6$ are continuous and bounded in Ω. Here, $x_1 = S,\ x_2 = V,\ x_3 = A,\ x_4 = I,\ x_5 = R$ and $x_6 = C$. The continuity and the boundedness are verified as here under:

Table 3 Continuity and boundedness of the model solution

$\lvert(\partial f_1)/(\partial S)\rvert = \lvert-[\beta(I+\gamma A)/N + \alpha + \mu]\rvert < \infty$ $\lvert(\partial f_1)/(\partial V)\rvert = \lvert\varphi\rvert < \infty$ $\lvert(\partial f_1)/(\partial A)\rvert = \lvert-(\beta\gamma S/N)\rvert < \infty$ $\lvert(\partial f_1)/(\partial I)\rvert = \lvert-(\beta S/N)\rvert < \infty$ $\lvert(\partial f_1)/(\partial R)\rvert = \lvert\omega\rvert < \infty$ $\lvert(\partial f_1)/(\partial C)\rvert = 0 < \infty.$	$\lvert(\partial f_2)/(\partial S)\rvert = \lvert\alpha\rvert < \infty$ $\lvert(\partial f_2)/(\partial V)\rvert = \lvert-(\varphi + \varepsilon\lambda + \mu)\rvert < \infty$ $\lvert(\partial f_2)/(\partial A)\rvert = \lvert-(\beta\gamma\varepsilon S/N)\rvert < \infty$ $\lvert(\partial f_2)/(\partial I)\rvert = \lvert-(\beta\varepsilon S/N)\rvert < \infty$ $\lvert(\partial f_2)/(\partial R)\rvert = 0 < \infty$ $\lvert(\partial f_2)/(\partial C)\rvert = 0 < \infty.$
$\lvert(\partial f_3)/(\partial S)\rvert = \lvert\rho\lambda\rvert < \infty$ $\lvert(\partial f_3)/(\partial V)\rvert = \lvert\rho\lambda\varepsilon\rvert < \infty$ $\lvert(\partial f_3)/(\partial A)\rvert = \lvert-(\theta + \phi + \mu)\rvert < \infty$ $\lvert(\partial f_3)/(\partial I)\rvert = \lvert(1-q)\eta\rvert < \infty$ $\lvert(\partial f_3)/(\partial R)\rvert = 0 < \infty$ $\lvert(\partial f_3)/(\partial C)\rvert = 0 < \infty.$	$\lvert(\partial f_4)/(\partial S)\rvert = \lvert(1-\rho)\lambda\rvert < \infty$ $\lvert(\partial f_4)/(\partial V)\rvert = \lvert(1-\rho)\varepsilon\lambda\rvert < \infty$ $\lvert(\partial f_4)/(\partial A)\rvert = \lvert(1-\rho)(\beta\gamma S/N) + (1-\rho)(\beta\gamma\varepsilon SV/N)\rvert < \infty$ $\lvert(\partial f_4)/(\partial I)\rvert = \lvert-(\beta\varepsilon S/N)\rvert < \infty$ $\lvert(\partial f_4)/(\partial R)\rvert = 0 < \infty$ $\lvert(\partial f_4)/(\partial C)\rvert = 0 < \infty.$
$\lvert(\partial f_5)/(\partial S)\rvert = 0 < \infty$ $\lvert(\partial f_5)/(\partial V)\rvert = 0 < \infty$ $\lvert(\partial f_5)/(\partial A)\rvert = \lvert\phi\rvert < \infty$ $\lvert(\partial f_5)/(\partial I)\rvert = \lvert q\eta\rvert < \infty$ $\lvert(\partial f_5)/(\partial R)\rvert = \lvert-(\omega + \mu)\rvert < \infty$ $\lvert(\partial f_5)/(\partial C)\rvert = 0 < \infty.$	$\lvert(\partial f_6)/(\partial S)\rvert = 0 < \infty$ $\lvert(\partial f_6)/(\partial V)\rvert = 0 < \infty$ $\lvert(\partial f_6)/(\partial A)\rvert = 0 < \infty$ $\lvert(\partial f_6)/(\partial I)\rvert = \lvert\delta\rvert < \infty$ $\lvert(\partial f_6)/(\partial R)\rvert = 0 < \infty$ $\lvert(\partial f_6)/(\partial C)\rvert = \lvert-(\xi + \mu)\rvert < \infty.$

Thus, all the partial derivatives $(\partial f_i)/(\partial x_j),\ i,j = 1,2,3,4,5,6$ exist, continuous and bounded in Ω. Hence, by Derrick and Groosman theorem, a solution for the model (1) – (6) exists and is unique.

c. Positivity of the solution

We assumed that the initial condition of the model is nonnegative, and now we also will show that the solution of the model is also positive.

Theorem 1 Let $\Omega = \{(S,\ V,\ A,\ I,\ R,\ C) \in \mathbb{R}^6_+; \mathrm{S}_0 > 0,\ \mathrm{V}_0 > 0,\ \mathrm{A}_0 > 0,\ \mathrm{I}_0 > 0,\ \mathrm{R}_0 > 0,\ \mathrm{C}_0 > 0\}$; then the solutions of $\{S,\ V,\ A,\ I,\ R,\ C\}$ are positive for all $t \geq 0$.

Proof Positivity is verified separately for each of the model variables $S(t)$, $V(t)$, $A(t)$, $I(t)$, $R(t)$, and $C(t)$.

Positivity of $S(t)$*:* The model equation (1) given by $dS/dt = (1-P)\Pi + \varphi \mathrm{V} - [\beta(I+\gamma A)/N + \alpha + \mu]S + \omega R$ can be expressed without loss of generality, after eliminating the positive terms $[(1-P)\Pi + \varphi \mathrm{V} + \omega R]$ which are appearing on the right hand side, as an inequality as $dS/dt \geq -[\beta(I+\gamma A)/N + \alpha + \mu]S$. Using variables separable method and on applying integration, the solution of the foregoing differentially inequality can be obtained as $S(t) \geq S_0[exp - (\alpha + \lambda + \mu)t]$ Recall that an exponential function is always non–negative irrespective of the sign of the exponent, i.e., the exponential function $[exp - (\alpha + \lambda + \mu)t]$ is a non-negative quantity. Hence, it can be concluded that $S(t) \geq 0$.

Positivity of $V(t)$*:* The model equation (2) given by $dV/dt = p\Pi + \alpha S - (\varphi + \varepsilon\lambda + \mu)V$ can be expressed without loss of generality, after eliminating the positive term $[p\Pi + \alpha S]$ which are appearing on the right hand side, as an inequality as $dV/dt \geq -(\varphi + \varepsilon\lambda + \mu)V$. Using variables separable method and on applying integration, the solution of the foregoing differentially inequality can be obtained as $V(t) \geq V_0[exp - (\varphi + \varepsilon\lambda + \mu)t$. Recall that an exponential function is always non–negative irrespective of the sign of the exponent, i.e., the exponential function $[exp - (\varphi + \varepsilon\lambda + \mu)t]$ is a non-negative quantity. Hence, it can be concluded that $V(t) \geq 0$.

Positivity of $A(t)$*:* The model equation (3) given by $dA/dt = \rho\lambda S + \rho\varepsilon\lambda V + (1-q)\eta I - (\theta + \phi + \mu)A$ can be expressed without loss of generality, after eliminating the positive term $[\rho\lambda S + \rho\varepsilon\lambda V + (1-q)\eta I]$ which are appearing on the right hand side, as an inequality as $dA/dt \geq -(\theta + \phi + \mu)A$. Using variables separable method and on applying integration, the solution of the foregoing differentially inequality can be obtained as $A(t) \geq A_0[exp - (\theta + \phi + \mu)t]$. Recall that an exponential function is always non–negative irrespective of the sign of the exponent, i.e., the exponential function $[exp - (\theta + \phi + \mu)t]$ is a non-negative quantity. Hence, it can be concluded that $A(t) \geq 0$.

Positivity of $I(t)$*:* The model equation (4) given by $dI/dt = (1-\rho)\lambda S + (1-\rho)\varepsilon\lambda V + \theta A - (\delta + \eta + \mu)I$ can be expressed without loss of generality, after eliminating the positive term $[(1-\rho)\lambda S + (1-\rho)\varepsilon\lambda V + \theta A$which are appearing on the right hand side, as an inequality as $dI/dt \geq -\delta + \eta + \mu I$. Using variables separable method and on applying integration, the solution of the foregoing differentially inequality can be obtained as $I(t) \geq I_0[exp - (\delta + \eta + \mu)t]$. Recall that an exponential function is always non–negative irrespective of the sign of the exponent, i.e., the exponential function $[exp - (\delta + \eta + \mu)t]$ is a non-negative quantity. Hence, it can be concluded that $I(t) \geq 0$.

Positivity of $R(t)$*:* The model equation (5) given by $dR/dt = \phi A + q\eta I - (\omega + \mu)R$ can be expressed without loss of generality, after eliminating the positive term $[\phi A + q\eta I]$which are appearing on the right hand side, as an inequality as $dR/dt \geq -(\omega + \mu)R$. Using variables separable method and on applying integration, the solution of the foregoing differentially inequality can be obtained as $R(t) \geq R_0[exp - (\omega + \mu)t]$. Recall that an exponential function is always non–negative irrespective of the sign of the exponent, i.e., the exponential function $[exp - (\omega + \mu)t]$ is a non-negative quantity. Hence, it can be concluded that $R(t) \geq 0$.

Positivity of $C(t)$*:* The model equation (5) given by $dC/dt = \delta I - (\xi + \mu)C$ can be expressed without loss of generality, after eliminating the positive term (δI)which are appearing on the right hand side, as an inequality as $dC/dt \geq -(\xi + \mu)C$. Using variables separable method and on applying integration, the solution of the foregoing differentially inequality can be obtained as $C(t) \geq C_0[exp - (\xi + \mu)t]$. Recall that an exponential function is always non–negative irrespective of the sign of the exponent, i.e., the exponential function $[exp - (\xi+\mu)t$ is a non-negative quantity. Hence, it can be concluded that $Ct \geq 0$.

Thus, the model variables $S(t)$, $V(t)$, $A(t)$, $I(t), R(t)$ and $C(t)$ representing population sizes of various types of cells are positive quantities and will remain in $\mathbb{R}^6_+$ for all t.

3.4 The Disease Free Equilibrium (DFE)

To find the disease free equilibrium, we equated the right hand sides of model equations $(1-6)$ to zero, evaluating it at $A = I = C = 0$ and solving for the non-infected and non-asymptomatic variables. Thus, the disease-free equilibrium point of the model equation in (1) – (6) above is given by

$$E_0 = \{S^0, V^0,\quad A^0,\quad I^0,\quad R^0,\quad C^0\} = \{[\pi/\mu]\mathrm{h}_1,\ [\pi/\mu]\mathrm{h}_2, 0, 0, 0, 0\}$$

Where $h_1 = [\varphi - \mu + \mu p]/[\alpha + \varphi + \mu]$ and $h_2 = [\alpha + \mu p]/[\alpha + \varphi + \mu]$.

3.5 The Basic Reproduction Number $(\Re_0)$

In this section we obtained the threshold parameter that governs the spread of a disease which is called the basic reproduction number is obtained. To obtain the basic reproduction number, we used the next-generation matrix method so that it is the spectral radius of the next-generation matrix [14].

The model equations are rewritten starting with newly infective classes:

$$dA/dt = \rho\lambda S + \rho\varepsilon\lambda V + (1-q)\eta I - (\theta + \phi + \mu)A\ ,$$
$$dI/dt = (1-\rho)\lambda S + (1-\rho)\varepsilon\lambda V + \theta A - (\delta + \eta + \mu)I,$$
$$dC/dt = \delta I - (\xi + \mu)C$$

Then by the principle of next-generation matrix, we obtained

$$F_i = \begin{bmatrix} [\rho\beta(I+\gamma A)S]/N + [\rho\varepsilon\beta(I+\gamma A)V]/N \\ [(1-\rho)\beta(I+\gamma A)S]/N + [(1-\rho)\varepsilon\beta(I+\gamma A)V]/N \\ 0 \end{bmatrix} \text{ and } \quad V_i = \begin{bmatrix} (\theta+\phi+\mu)A - (1-q)\eta I \\ (\delta+\eta+\mu)I - \theta A \\ (\xi+\mu)C - \delta I \end{bmatrix}$$

(11)

The Jacobian matrices of F_i and V_i evaluated at DFE are given by F and V, respectively, such that

$$F = \begin{bmatrix} \rho\beta\gamma k_1 & \rho\beta k_1 & 0 \\ (1-\rho)\beta\gamma k_1 & (1-\rho)\beta k_1 & 0 \\ 0 & 0 & 0 \end{bmatrix} \text{ and } \quad V = \begin{bmatrix} c & -(1-q)\eta & 0 \\ -\theta & d & 0 \\ 0 & -\delta & f \end{bmatrix} \qquad (12)$$

Here $k_1 = h_1 + \varepsilon h_2$ and $k_2 = cd - \theta\eta(1-q)$.

It can be verified that the matrix V is non-singular as its determinant $det[V] = f\eta[cd - \theta(1-q)]$ is non-zero and after some algebraic computations its inverse matrix is constructed as

$$V^{-1} = \begin{bmatrix} (d/k_2) & ([1-q]\eta/k_2) & 0 \\ (\theta/k_2) & (c/k_2) & 0 \\ (-\theta\delta/fk_2) & (c\delta/fk_2) & (1/f) \end{bmatrix}.$$

The product of the matrices F and V^{-1} can be computed as:

$$FV^{-1} = \begin{bmatrix} \rho\beta\gamma k_1 & \rho\beta k_1 & 0 \\ (1-\rho)\beta\gamma k_1 & (1-\rho)\beta k_1 & 0 \\ 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} (d/k_2) & ([1-q]\eta/k_2) & 0 \\ (\theta/k_2) & (c/k_2) & 0 \\ (-\theta\delta/fk_2) & (c\delta/fk_2) & (1/f) \end{bmatrix}$$

$$= \begin{bmatrix} [(\rho\beta k_1 k_3/k_2) + (\rho\beta k_1/k_2)] & \left[\left((1-q)\,\eta\rho\beta\gamma k_1/k_2\right) + (c\rho\beta k_1/k_2)\right] & 0 \\ [(d\rho\beta\gamma k_1/k_2) + (\theta\rho\beta k_1/k_2)] & \left[\left((1-\rho)(1-q)\,\eta\beta\gamma k_1/k_2\right) + \left((1-\rho)\,c\beta k_1/k_2\right)\right] & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

$$= \begin{bmatrix} [[k_1 k_3\rho\beta]/k_2] & [[k_1 k_4\rho\beta]/k_2] & 0 \\ [(1-\rho)(k_1 k_3/k_2)] & [(1-\rho)(\beta k_1 k_4/k_2)] & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

Now it is possible to calculate the eigenvalue to determine the basic reproduction number $\mathfrak{R}_0$ by taking the spectral radius of the matrix FV^{-1}. Thus, the eigenvalues are computed by evaluating $det[\,FV^{-1} - \psi I] = 0$ or equivalently solving

$$\begin{vmatrix} [[k_1 k_3\rho\beta]/k_2] & [[k_1 k_4\rho\beta]/k_2] & 0 \\ [(1-\rho)(k_1 k_3/k_2)] & [(1-\rho)(\beta k_1 k_4/k_2)] & 0 \\ 0 & 0 & 0 \end{vmatrix} = 0$$

It reduces to the cubic equation for ψ as

$$-\psi\left[[[k_1 k_3\rho\beta]/k_2][(1-\rho)(\beta k_1 k_4/k_2)] - \psi[[k_1 k_3\rho\beta]/k_2] - \psi[(1-\rho)(\beta k_1 k_4/k_2)] + \psi^2\right] = 0\ .$$

Giving the three eigenvalues as

$$\psi_1 = \left[[[k_1 k_3\rho\beta]/k_2] + [(1-\rho)(\beta k_1 k_4/k_2)]\right]$$
$$\psi_2 = 0$$
$$\psi_3 = 0$$

Here, $h_1 = [\varphi - \mu + \mu p]/[\alpha + \varphi + \mu]$,
$h_2 = [\alpha + \mu p]/[\alpha + \varphi + \mu]$,
$k_1 = h_1 + \varepsilon h_2$,
$k_2 = cd - \theta\eta(1-q)$,
$k_3 = d\gamma + \theta$,

$k_4 = (1-q)\eta\gamma + c,$
$a = (\alpha + \lambda + \mu),$
$b = (\varphi + \varepsilon\lambda + \mu),$
$c = (\theta + \phi + \mu),$
$d = (\delta + \eta + \mu),$
$e = (\omega + \mu),$
$f = (\xi + \mu).$

However, the dominant eigenvalue here is $\psi_1 = [\kappa\tau k_1/k_2][k_3\rho + (1-\rho)k_4]$ 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 $\Re_0 = [\kappa\tau k_1/k_2][k_3\rho + (1-\rho)k_4]$.

3.6 Local Stability of Disease Free Equilibrium

Theorem 2 The disease free equilibrium point E_0 of the system (1) – (6) is locally asymptotically stable if $\Re_0 < 1$ and unstable if $\Re_0 > 1$.

Proof To proof this theorem first we obtain the Jacobian matrix of system (10) at the disease free equilibrium E_0 as follows:

$$J(E_0) = \begin{bmatrix} -a & \varphi & \beta\gamma h_1 & \beta h_1 & \omega & 0 \\ \alpha & -b & \beta\varepsilon\gamma h_2 & \beta\varepsilon h_2 & 0 & 0 \\ 0 & 0 & \rho\beta\gamma k_1 - c & \rho\beta k_1 - (1-q)\eta & 0 & 0 \\ 0 & 0 & (1-\rho)\beta\gamma k_1 + \theta & (1-\rho)\beta k_1 - d & 0 & 0 \\ 0 & 0 & \phi & q\eta & -e & 0 \\ 0 & 0 & 0 & \delta & 0 & -f \end{bmatrix}$$

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

$$\begin{vmatrix} -a-\psi & \varphi & \beta\gamma h_1 & \beta h_1 & \omega & 0 \\ \alpha & -b-\psi & \beta\varepsilon\gamma h_2 & \beta\varepsilon h_2 & 0 & 0 \\ 0 & 0 & [\rho\beta\gamma k_1 - c] - \psi & \rho\beta k_1 - (1-q)\eta & 0 & 0 \\ 0 & 0 & (1-\rho)\beta\gamma k_1 + \theta & [(1-\rho)\beta k_1 - d] - \psi & 0 & 0 \\ 0 & 0 & \phi & q\eta & -e-\psi & 0 \\ 0 & 0 & 0 & \delta & 0 & -f-\psi \end{vmatrix} = 0$$

$$[-f-\psi][-e-\psi]\big[(\rho\beta\gamma k_1 - c - \psi)\big((1-\rho)\beta k_1 - d - \psi\big) - \big((1-\rho)\beta\gamma k_1 + \theta\big)(\rho\beta k_1 - (1-q)\eta)\big][(-a-\psi)(-b-\psi) - \alpha\varphi] = 0$$

$[-f-\psi] = 0,$ $[-e-\psi] = 0,$ $\big[(\rho\beta\gamma k_1 - c - \psi)\big((1-\rho)\beta k_1 - d - \psi\big) - \big((1-\rho)\beta\gamma k_1 + \theta\rho\beta k1 - (1-q)\eta = 0,\ -a-\psi-b-\psi-\alpha\varphi = 0$

Thus, the five eigenvalues of the matrix are determined as

$$\psi_1 = -f$$
$$\psi_2 = -e$$
$$\psi_3 = \left[-(a+b) + \sqrt{(a+b)^2 - 4(ab - \alpha\varphi)}\right]/2$$
$$\psi_4 = \left[-(a+b) - \sqrt{(a+b)^2 - 4(ab - \alpha\varphi)}\right]/2$$
$$\psi_5 = \frac{(\rho\beta\gamma k_1 - c + (1-\rho)\beta k_1 - d) + \sqrt{(\rho\beta\gamma k_1 - c + (1-\rho)\beta k_1 - d)^2 - 4k_3)}}{2}$$
$$\psi_6 = \frac{(\rho\beta\gamma k_1 - c + (1-\rho)\beta k_1 - d) - \sqrt{(\rho\beta\gamma k_1 - c + (1-\rho)\beta k_1 - d)^2 - 4k_3)}}{2}$$

It can be observed that the first three eigenvalues ψ_1 and ψ_2 are absolutely negative quantities. However, the remaining two ψ_3, ψ_4, ψ_5 and ψ_6 are also negatives so long as the following restrictions on the parameters are valid: $ab > \alpha\varphi$, $2(ab - \alpha\varphi) < (a+b)^2$, $4k_3 > 2(\rho\beta\gamma k_1 + (1-\rho)\beta k_1)^2$ and $k_3 < 0$ respectively, when $\Re_0 < 1$.

Therefore, it is concluded that the DFE E_0 of the system of differential equations (1) – (6) is locally asymptotically stable if $\Re_0 < 1$ and unstable if $\Re_0 > 1$.

3.7 Global Stability of the DFE E_0

Theorem 3 The disease free equilibrium point E_0 of the model is globally asymptotically stable if $\Re_0 < 1$ and unstable if $\Re_0 > 1$.

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

$$\begin{bmatrix} A' \\ I' \\ C' \end{bmatrix} = (F - V)\begin{bmatrix} A \\ I \\ C \end{bmatrix} - M\theta \begin{bmatrix} A \\ I \\ C \end{bmatrix} \qquad (12)$$

However, $M = [1 - (S^0/N^0)] = 0$ since $S^0 = (\pi/\mu)$, $N^0 = (\pi/\mu)$ and θ is non-negative matrix. Therefore, the equation (12) reduces to the simplified form as

$$\begin{bmatrix} I_u{}' \\ I_s{}' \\ C^0 \end{bmatrix} \leq (F - V)\begin{bmatrix} I_u \\ I_s \\ C \end{bmatrix}$$

Here in (12), the matrices F and V at the disease free equilibrium E_0 are defined as

$$F = \begin{bmatrix} \rho\beta\gamma k_1 & \rho\beta k_1 & 0 \\ (1-\rho)\beta\gamma k_1 & (1-\rho)\beta k_1 & 0 \\ 0 & 0 & 0 \end{bmatrix} \quad \text{and} \quad V = \begin{bmatrix} c & -(1-q)\eta & 0 \\ -\theta & d & 0 \\ 0 & -\delta & f \end{bmatrix}$$

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

$$F - V = \begin{bmatrix} \rho\beta\gamma k_1 & \rho\beta k_1 & 0 \\ (1-\rho)\beta\gamma k_1 & (1-\rho)\beta k_1 & 0 \\ 0 & 0 & 0 \end{bmatrix} - \begin{bmatrix} c & -(1-q)\eta & 0 \\ -\theta & d & 0 \\ 0 & -\delta & f \end{bmatrix}$$

$$= \begin{bmatrix} \rho\beta\gamma k_1 - c & \rho\beta k_1 + (1-q)\eta & 0 \\ (1-\rho)\beta\gamma k_1 + \theta & (1-\rho)\beta k_1 - d & 0 \\ 0 & \delta & -f \end{bmatrix} \qquad (13)$$

Next, elementary row-operations are used to row-reduce the matrix in (13) to a lower triangular as in (14).

$$F - V = \begin{bmatrix} \big[[\rho\beta k_1 + (1-q)\eta][(1-\rho)\beta\gamma k_1 + \theta] + [\rho\beta\gamma k_1 - c][(1-\rho)\beta k_1 - d]\big]/[(1-\rho)\beta k_1 - d] & 0 & 0 \\ [(1-\rho)\beta\gamma k_1 + \theta] & [(1-\rho)\beta k_1 - d] & 0 \\ 0 & \delta & -f \end{bmatrix} \qquad (14)$$

The eigenvalues of matrix (14) are found by evaluating the characteristic equation $\det[(F - V) - \psi I] = 0$ as follows:

$$\psi_1 = f,$$

$$\psi_2 = [(1-\rho)\beta k_1 - d],$$

$$\psi_3 = \big[[\rho\beta k_1 + (1-q)\eta][(1-\rho)\beta\gamma k_1 + \theta] + [\rho\beta\gamma k_1 - c][(1-\rho)\beta k_1 - d]\big]/[(1-\rho)\beta k_1 - d].$$

Here it can be observed that the first eigenvalue ψ_1 is absolutely negative quantity. However, the remaining eigenvalue ψ_2 is also negative when $(1-\rho)\beta k_1 < d$ and ψ_3 is negative when $-[\rho\beta k_1 + (1-q)\eta][(1-\rho\beta\gamma k1+\theta<\rho\beta\gamma k1-c1-\rho\beta k1-d$. Hence, the disease free equilibrium point $E0$ is globally asymptotically stable if $\Re_0 < 1$ and unstable if $\Re_0 > 1$.

3.8 The Endemic Equilibrium

Endemic equilibrium point E_1 is a steady state solution where the disease persists in the community. For the existence and uniqueness of endemic equilibrium $E_1 = \{S^*, V^*, A^*, I^*, R^*, C^*\}$, its coordinates should satisfy the conditions $E_1 = \{S^*, V^*, A^*, I^*, R^*, C^*\} \neq 0$, where $S_0 > 0$, $V_0 > 0$, $A_0 > 0$, $I_0 > 0$, $R_0 > 0$, and$C_0 > 0$. The endemic equilibrium point is obtained by setting left hand sides of equations of the system (1) – (6) to zero. We then solved for state variables in terms of the force of infection, λ^* and obtain the following;

$$S^* = [bV^* - p\Pi]/\alpha$$

$$V^* = [p\Pi(1-\rho)\lambda^* + \alpha C^* k_5 - \alpha\theta e d R^*]/[(1-\rho)\lambda^*]$$

$$A^* = [e\delta R^* - q\eta f C^*]/[\delta]$$

$$I^* = fC^*/\delta$$

$$R^* = [\mathrm{k}_8\mathrm{C}^*]/[k_6]$$

$$V^* = \left[\Pi\mathrm{k}_6(1-\rho)[\mathrm{p}\lambda^*(\mathrm{ab}-\alpha) - \mathrm{pa} - \alpha(1-\mathrm{p})]\right]/[k_7k_8 - k_5k_6(ab-\alpha)]$$

Here $k_5 = fd + \theta q\eta f,\ k_6 = \delta e[\delta\rho\theta + (1-\rho)c],\ k_7 = \theta ed(ab-\alpha) + \omega\lambda^*(1-\rho)$ and $k_8 = [\delta\rho k_5 + f\eta(1-\rho)][(1-\rho) + qc]$.

On substituting the expression for I^* and A^* into the force of infection, that is, $\lambda^* = [\beta(I^* + \gamma A^*)]/N$, characteristic polynomial of force of infection is obtained as

$$p(\lambda^*) = D_1\lambda^* - D_2$$

Here $D_1 = \mu\beta pk_9(1-\rho)(ab-\alpha)$ and $D_2 = -\mu\beta k_9(1-\rho)[pa + \alpha(1-p)]$, where, $k_9 = fk_6 - k_6\gamma q\eta f + \gamma e\delta k_8$.

Clearly, $D_1 > 0$ and $D_2 \leq 0$, whenever $\mathfrak{R}_0 < 1$, and $\lambda^* = D_2/D_1 \geq 0$. From this, we see that, for $\mathfrak{R}_0 < 1$, there is a unique endemic equilibrium for this model. Therefore, this condition shows that it is possible for backward bifurcation in the model if $\mathfrak{R}_0 < 1$.

Lemma 2 A unique endemic equilibrium point E_1 exists and is positive if $\mathfrak{R}_0 > 1$.

3.9 The global stability of the endemic equilibrium

Theorem 4 If $\mathfrak{R}_0 > 1$, the endemic equilibrium E_1 of the model $(1-6)$ is globally asymptotically stable.

Proof To prove the global asymptotic stability of the endemic equilibrium we use the method of Lyapunov functions. Define

$$\begin{aligned}L(S^*,\ V^*,\ A^*,\ I^*,\ R^*,\ C^*) &= [S - S^* - S^*ln(S^*/S)] + [V - V^* - V^*ln(V^*/V)] + [A - A^* - A^*ln(A^*/A)]\\ &+ [I - I^* - I^*ln(I^*/I)] + [R - R^* - R^*ln(R)] + [C - C^* - C^*ln(C^*/C)]\end{aligned}$$

By direct calculating the derivative of L along the solution $(1-6)$ we have

$$\begin{aligned}dL/dt &= [(S-S^*)/S]\,dS/dt + [(V-V^*)/V]\,dV/dt + [(A-A^*)/A]\,dA/dt + [(I-I^*)/I]\,dI/dt +\\ &\quad [(R-R^*)/R]\,dR/dt + [(C-C^*)/C]\,dC/dt,\\ &= [(S-S^*)/S][(1-p)\Pi + \varphi\mathrm{V} - (\alpha+\rho\lambda+\mu)S + \omega R] + [(V-V^*)/V][p\Pi + \alpha S - (\varphi+\varepsilon\lambda+\mu)V]\\ &\quad + [(A-A^*)/A][\rho\lambda S + \rho\varepsilon\lambda V + (1-q)\eta I - (\theta+\phi+\mu)A\,]\\ &\quad + [(I-I^*)/I][(1-\rho)\lambda S + (1-\rho)\varepsilon\lambda V + \theta A - (\delta+\eta+\mu)I]\\ &\quad + [(R-R^*)/R][\phi A + q\eta I - (\omega+\mu)R] + [(C-C^*)/C][\delta I - (\xi+\mu)C]\\ &= [1-S^*/S][(1-p)\Pi + \varphi\mathrm{V} - (\alpha+\rho\lambda+\mu)S + \omega R] + [1-V^*/V][p\Pi + \alpha S - (\varphi+\varepsilon\lambda+\mu)V]\\ &\quad + [1-A^*/A][\rho\lambda S + \rho\varepsilon\lambda V + (1-q)\eta I - (\theta+\phi+\mu)A\,]\\ &\quad + [1-I^*/I][(1-\rho)\lambda S + (1-\rho)\varepsilon\lambda V + \theta A - (\delta+\eta+\mu)I]\\ &\quad + [1-R^*/R][\phi A + q\eta I - (\omega+\mu)R] + [1-C^*/C][\delta I - (\xi+\mu)C]\\ dL/dt &= \Pi + [(1-\rho)\varepsilon\lambda VI^*]/I + \alpha S^* + \rho\lambda S^* + \varphi V^* + \varepsilon\lambda V^* + \theta A^* + \phi A^* + \delta I^* + \eta I^* + \omega R^* + \xi C^*\\ &\quad + [S^* + V^* + A^* + I^* + R^* + C^*]\mu + \lambda S\\ &\quad - [((1-p)\Pi S^*/S) + (\varphi\mathrm{V}S^*/S) + (\omega\mathrm{R}S^*/S) + (\mathrm{p}\Pi V^*/V) + (\alpha\mathrm{I}V^*/V) + (\rho\lambda SA^*/A)\\ &\quad + (\rho\varepsilon\lambda\mathrm{V}A^*/A) + ((1-\mathrm{q})\eta\mathrm{I}A^*/A) + ((1-\rho)\lambda SI^*/I) + (\theta\mathrm{A}I^*/I) + (\phi\mathrm{A}R^*/R)\\ &\quad + (\mathrm{q}\eta\mathrm{I}R^*/R) + (\delta\mathrm{I}C^*/C) + N\mu + \rho\lambda S + \xi C]\end{aligned}$$

Thus collecting positive and negative terms together we obtain

$$\begin{aligned}dL/dt &= \Pi + [(1-\rho)\varepsilon\lambda VI^*]/I + \alpha S^* + \rho\lambda S^* + \varphi V^* + \varepsilon\lambda V^* + \theta A^* + \phi A^* + \delta I^* + \eta I^* + \omega R^* + \xi C^* + N^*\mu\\ &\quad + \lambda S\\ &\quad - [((1-p)\Pi S^*/S) + (\varphi\mathrm{V}S^*/S) + (\omega\mathrm{R}S^*/S) + (\mathrm{p}\Pi V^*/V) + (\alpha\mathrm{I}V^*/V) + (\rho\lambda SA^*/A)\\ &\quad + (\rho\varepsilon\lambda\mathrm{V}A^*/A) + ((1-\mathrm{q})\eta\mathrm{I}A^*/A) + ((1-\rho)\lambda SI^*/I) + (\theta\mathrm{A}I^*/I) + (\phi\mathrm{A}R^*/R)\\ &\quad + (\mathrm{q}\eta\mathrm{I}R^*/R) + (\delta\mathrm{I}C^*/C) + N\mu + \rho\lambda S + \xi C],\end{aligned}$$

$$dL/dt = Q - K.$$

Here, $Q = \Pi + [(1-\rho)\varepsilon\lambda VI^*]/I + \alpha S^* + \rho\lambda S^* + \varphi V^* + \varepsilon\lambda V^* + \theta A^* + \phi A^* + \delta I^* + \eta I^* + \omega R^* + \xi C^* + N^*\mu + \lambda S,$

$$\begin{aligned}K &= [((1-p)\Pi S^*/S) + (\varphi\mathrm{V}S^*/S) + (\omega\mathrm{R}S^*/S) + (\mathrm{p}\Pi V^*/V) + (\alpha\mathrm{I}V^*/V) + (\rho\lambda SA^*/A) + (\rho\varepsilon\lambda\mathrm{V}A^*/A)\\ &\quad + ((1-\mathrm{q})\eta\mathrm{I}A^*/A) + ((1-\rho)\lambda SI^*/I) + (\theta\mathrm{A}I^*/I) + (\phi\mathrm{A}R^*/R) + (\mathrm{q}\eta\mathrm{I}R^*/R) + (\delta\mathrm{I}C^*/C)\\ &\quad + N\mu + \rho\lambda S + \xi C]\end{aligned}$$

$N = S + V + A + I + R + C$ and $N^* = S^* + V^* + A^* + I^* + R^* + C^*$

Thus if $Q < K$, then $dL/dt \leq 0$. Noting that $dL/dt = 0$ if and only if $S = S^*,\ V = V^*,\ A = A^*,\ I = I^*,\ R = R^*,\ C = C^*$. Therefore, the largest compact invariant set in $\{(S^*,\ V^*,\ A^*,\ I^*,\ R^*,\ C^*) \in \Omega:\ dL/dt = 0\}$ is the singleton E_1 is the endemic equilibrium of the system $(1-6)$. By LaSalle's invariant principle (LaSalle's, 1976), it implies that E_1 is globally asymptotically stable in Ω if $Q < K$.

IV. Backward Bifurcation Analysis

The possible presence of backwards bifurcations in simple disease models has important qualitative implications. Backward bifurcation allows multiple stable states with fixed parameters. Further, small changes in parameters can produce large changes in equilibrium behavior. Imagine a population in which the disease is absent and $\Re_0$ is changing slowly. In backward bifurcation, once $\Re_0 > 1$, the disease can invade to a relatively high endemic level. Further, decreasing $\Re_0$ to its former level will not necessarily make the disease disappear.

Moreover, if a disease lowers its reproductive rate by invading, it would be expected that when $\Re_0 < 1$ and it cannot invade a population, it could never persist at all. Further when $\Re_0$ is slightly above 1, the disease would be expected to reach a low endemic level, because of this negative feedback. In particular, when $\Re_0 = 1$, each infection exactly replaces itself in the linear approximation. Hence, we would expect the disease to be able to invade at $\Re_0 = 1$ in backward bifurcation.

Intuitively speaking, we are going to develop a criterion for whether the disease can invade when $\Re_0 = 1$ by assuming that the disease invades a small amount along the dominant eigenvector, calculating the vector field at a point along the dominant eigenvector near the disease free equilibrium, and multiplying by the dominant left eigenvector to find out if the component of the vector field in the direction of the dominant eigenvector is positive or negative.

We investigate the nature of the bifurcation by using the method introduced in [15], which is based on the use of the central manifold theory. In short, the method is summarized by theorem 4.1 in [15]. In such a theorem, there are two important quantities the coefficients, a and b, of the normal form representing the dynamics of the system on the central manifold. These coefficients decide the bifurcation. In particular, if $a < 0$ and $b > 0$, then the bifurcation is forward and if $a > 0$ and $b > 0$, then the bifurcation is backward. This is done by renaming the variables as follows;

Let $S = x_1,\ V = x_2,\ A = x_3,\ I = x_4,\ R = x_5,\ C = x_6$ further by introducing the vector notation $x = (x_1,\ x_2,\ x_3,\ x_4,\ x_5,\ x_6,)^T$. Then the model can be written in the form of:

$$dx/dt = F(x)$$

Where $F = (f_1,\ f_2,\ f_3,\ f_4,\ f_5,\ f_6,)^T$

As follows

$$\begin{aligned} dx_1/dt &= (1-p\chi)\Pi + \varphi x_2 + \omega x_5 - (\alpha + \rho\lambda + \mu)x_1, \\ dx_2/dt &= p\chi\Pi + \alpha x_1 - (\varphi + \varepsilon\lambda + \mu)x_2, \\ dx_3/dt &= \rho\lambda x_1 + \rho\varepsilon\lambda x_2 + (1-q)\eta x_4 - (\theta + \phi + \mu)x_3\ , \\ dx_4/dt &= (1-\rho)\lambda x_1 + (1-\rho)\varepsilon\lambda x_2 + \theta x_3 - (\delta + \eta + \mu)x_4, \\ dx_5/dt &= \phi x_3 + q\eta x_4 - (\omega + \mu)x_5, \\ dx_6/dt &= \delta x_4 - (\xi + \mu)x_6 \end{aligned} \quad (16)$$

Where $N = x_1 + x_2 + x_3 + x_4 + x_5 + x_6$

Then the Jacobian system at the disease free;

$$J(E_0) = \begin{bmatrix} -a & \varphi & \beta\gamma h_1 & \beta h_1 & \omega & 0 \\ \alpha & -b & \beta\varepsilon\gamma h_2 & \beta\varepsilon h_2 & 0 & 0 \\ 0 & 0 & \rho\beta\gamma k_1 - c & \rho\beta k_1 - (1-q)\eta & 0 & 0 \\ 0 & 0 & (1-\rho)\beta\gamma k_1 + \theta & (1-\rho)\beta k_1 - d & 0 & 0 \\ 0 & 0 & \phi & q\eta & -e & 0 \\ 0 & 0 & 0 & \delta & 0 & -f \end{bmatrix} \quad (17)$$

Suppose that $\beta = \beta^*$ is a bifurcation, the system (17) is linearized at the disease free equilibrium point when $\beta^* = \beta$ with $\Re_0 = 1$, solving for β^* for $\Re_0 = 1$ from:

$$\Re_0 = \frac{\beta\left[(\varphi - \mu + \mu p)\left[[(\delta + \eta + \mu)\gamma + \theta]\rho + (1-\rho)(1-q)\eta\gamma(\theta + \phi + \mu)\right]\right]}{(\alpha + \varphi + \mu)(\theta + \phi + \mu)(\delta + \eta + \mu) - \theta\eta(1-q)} = 1$$

We obtained

$$\beta^* = \frac{(\alpha + \varphi + \mu)(\theta + \phi + \mu)(\delta + \eta + \mu) - \theta\eta(1-q)}{\beta\left[(\varphi - \mu + \mu p)\left[[(\delta + \eta + \mu)\gamma + \theta]\rho + (1-\rho)(1-q)\eta\gamma(\theta + \phi + \mu)\right]\right]}$$

The system (18) with $\beta = \beta^*$ has a simple zero eigenvalues, hence the central manifold theory will be used to analyze the dynamics of the system near $\beta = \beta^*$. The Jacobian matrix near $\beta = \beta^*$ has a right eigenvector associated with the zero eigenvalue given by $w = (w_1,\ w_2,\ w_3,\ w_4,\ w_5,\ w_6)^T$ from the system;

$$J(E_0)=\begin{bmatrix}-a & \varphi & \beta\gamma h_1 & \beta h_1 & \omega & 0\\ \alpha & -b & \beta\varepsilon\gamma h_2 & \beta\varepsilon h_2 & 0 & 0\\ 0 & 0 & \rho\beta\gamma k_1-c & \rho\beta k_1-(1-q)\eta & 0 & 0\\ 0 & 0 & (1-\rho)\beta\gamma k_1+\theta & (1-\rho)\beta k_1-d & 0 & 0\\ 0 & 0 & \phi & q\eta & -e & 0\\ 0 & 0 & 0 & \delta & 0 & -f\end{bmatrix}\begin{bmatrix}w_1\\ w_2\\ w_3\\ w_4\\ w_5\\ w_6\end{bmatrix}=\begin{bmatrix}0\\ 0\\ 0\\ 0\\ 0\\ 0\end{bmatrix} \quad (18)$$

The system of equation becomes;

$$\begin{gathered}-aw_1+\varphi w_2+\beta\gamma h_1 w_{3+}\beta h_1 w_4+\omega w_5=0\\ \alpha w_1-bw_2+\beta\varepsilon\gamma h_1 w_{3+}\beta\varepsilon h_1 w_4=0\\ (\rho\beta\gamma k_1-c)w_3+(\rho\beta k_1-(1-q)\eta)w_4=0\\ \big((1-\rho)\beta\gamma k_1+\theta\big)w_3+\big((1-\rho)\beta k_1-d\big)w_4=0\\ \phi w_3+q\eta w_4-ew_5=0\\ \delta w_4-fw_6=0\end{gathered} \quad (19)$$

Solving system of equation (19) we obtained;

$$\begin{gathered}w_1=[bw_2+\beta\varepsilon\gamma h_1 w_{3+}\beta\varepsilon h_1 w_4]/[\alpha]\\ w_2=w_2>0\\ w_3=[(1-q)\eta-\rho\beta k_1]w_4/[\rho\beta\gamma k_1-c]\\ w_4=w_4>0\\ w_5=[\phi w_3+q\eta w_4]/[e]\\ w_6=\delta w_4/[f]\end{gathered}$$

The left eigenvectors of $J(E_0)$ associated with the zero eigenvalue at $\beta^*=\beta$ is given by $v=(v_1,\ v_2,\ v_3,\ v_4,\ v_5,\ v_6)^T$ from the system (16)

$$J(E_{01})=\begin{bmatrix}-a & \alpha & 0 & 0 & 0 & 0\\ \varphi & -b & 0 & 0 & 0 & 0\\ \beta\gamma h_1 & \beta\varepsilon\gamma h_2 & \rho\beta\gamma k_1-c & (1-\rho)\beta\gamma k_1+\theta & \phi & 0\\ \beta h_1 & \beta\varepsilon h_2 & \rho\beta k_1-(1-q)\eta & (1-\rho)\beta k_1-d & q\eta & \delta\\ \omega & 0 & 0 & 0 & -e & 0\\ 0 & 0 & 0 & 0 & 0 & -f\end{bmatrix}\begin{bmatrix}v_1\\ v_2\\ v_3\\ v_4\\ v_5\\ v_6\end{bmatrix}=\begin{bmatrix}0\\ 0\\ 0\\ 0\\ 0\\ 0\end{bmatrix} \quad (20)$$

The system of equation (20) becomes;

$$\begin{gathered}-av_1+\alpha v_2=0\\ \varphi v_1-bv_2=0\\ \beta\gamma h_1 v_1+\beta\varepsilon\gamma h_2 v_2+(\rho\beta\gamma k_1-c)v_3+\big((1-\rho)\beta\gamma k_1+\theta\big)v_4+\phi v_5=0\\ \beta h_1 v_1+\beta\varepsilon h_2 v_2+(\rho\beta k_1-(1-q)\eta)v_3+\big((1-\rho)\beta k_1-d\big)v_4+q\eta v_5+\delta v_6=0\\ \omega v_1-ev_5=0,\quad -fv_6=0\end{gathered} \quad (21)$$

Solving system of equation (21) we obtained;

$$\begin{gathered}v_1=v_2\\ v_3=[(1-\rho)\beta\gamma k_1+\theta]v_4/[c-\rho\beta\gamma k_1]\\ v_4=v_4\\ v_5=v_6=0\end{gathered}$$

To compute a and b we use a formula explained in [15]

$$a=\sum_{k,j,i=1}^{n} v_k w_i w_j\big[\partial^2 f/\partial x_i\partial x_j\big](S_0,\quad V_0,\quad 0,\quad 0,\quad 0,\quad 0)$$

$$b=\sum_{k,i=1}^{n} v_k w_i[\partial^2 f/\partial x_i\partial\beta]$$

Where

$$\begin{aligned}f_1&=(1-p\chi)\Pi+\varphi x_2+\omega x_5-(\alpha+\rho\lambda+\mu)x_1,\\ f_2&=p\chi\Pi+\alpha x_1-(\varphi+\varepsilon\lambda+\mu)x_2,\\ f_3&=\rho\lambda x_1+\rho\varepsilon\lambda x_2+(1-q)\eta x_4-(\theta+\phi+\mu)x_3,\\ f_4&=(1-\rho)\lambda x_1+(1-\rho)\varepsilon\lambda x_2+\theta x_3-(\delta+\eta+\mu)x_4,\\ f_5&=\phi x_3+q\eta x_4-(\omega+\mu)x_5,\\ f_6&=\delta x_4-(\xi+\mu)x_6\end{aligned} \quad (22)$$

Taking into account system (22) and considering only the non zero components of the left eigenvectors v_3 and v_4, then we obtained;

$$\begin{gathered}a=(2\beta w_4 v_4)r_1\\ b=\beta w_4 v_4(\gamma r_2+1)[\rho(r_3-1)+1]k_1\end{gathered}$$

Here $r_1 = [\rho(r_3 - 1) + 1][\gamma r_2(w_1 + \varepsilon w_2) + w_1 + \varepsilon w_2]$
$r_2 = [(1-\rho)\beta\gamma k_1 + \theta]/[c - \rho\beta\gamma k_1]$
$r_3 = [(1-q)\eta - \rho\beta k_1]/[\rho\beta\gamma k_1 - c]$

Since the coefficient b is always positive and $a > 0$ depend on whether r_1 is greater or less than 0. Thus we have established the following results.

Theorem If $r_1 > 0, a > 0$ then model system $(1-6)$ has a backward bifurcation at $\Re_0 = 1$, otherwise $a < 0$ and a unique endemic equilibrium is locally asymptotically stable for, $\Re_0 > 1$ but close to 1.

V. Extension of the Model into an Optimal Control

In this section, we apply optimal control strategies on the model equation $(1-6)$. This helped us to identify the best intervention strategy that helps to eradicate the disease in the specified time. The optimal control model is an extension HPV model by including the following three controls defined as:

a. u_1 a prevention effort, which protect susceptible from contacting the disease.
b. u_2 a treatment effort, to minimize infection by treating infectious.
c. u_3 a screening effort, to help asymptomatic to screen themselves.

After incorporating, u_1, u_2 and u_3 in model equation $(1-6)$, we obtain the following optimal control model of equation:

$$\begin{cases} dS/dt = (1-p)\Pi + \varphi V + \omega R - p(1-u_1)[\beta(I+\gamma A)/N]S - (\alpha+\mu)S, \\ dV/dt = p\Pi + \alpha S - (1-u_1)[\beta(I+\gamma A)/N]\varepsilon V - (\varphi+\mu)V, \\ dA/dt = \rho(1-u_1)[\beta(I+\gamma A)/N](S+\varepsilon V) + (1-q)(1-u_2)\eta I - (u_3+\theta)A - (\phi+\mu)A \\ dI/dt = (1-\rho)(1-u_1)[\beta(I+\gamma A)/N](S+\varepsilon V) + (u_3+\theta)A - (u_2+\eta)I - (\delta+\mu)I, \\ dR/dt = \phi A + (u_2+q\eta)I - (\omega+\mu)R, \\ dC/dt = \delta I - (\xi+\mu)C\ . \end{cases} \quad (23)$$

To study the optimal levels of the controls, the control set U is Lebesgue measurable and it is defined as: $U = \{(u_1(t),\ u_2(t),\ u_3(t)); 0 \le u_1 < 1,\ 0 \le u_2 < 1,\ 0 \le u_3 < 1, 0 \le t \le T\}$ .Our aim is to obtain a control u and $S,\ V,\ A,\ I,\ R$ and C that minimize the proposed objective function J and the form of the objective functional is taken in line with literature on epidemic models [17], given by:

$$J = \min_{u_1,u_2,u_3} \int_0^{t_f} \left(b_1 A + b_2 I + \frac{1}{2}\sum_{i=1}^{3} w_i u_i^2 \right) dt$$

Where $b_1,\ b_2$ and w_i are positive. The expression $\frac{1}{2}w_i u_i^2$ represents cost which is associated with the controls u_i.The form is quadratic because we assume that costs are non-linear in its nature. Our aim is to minimize the number of asymptomatic, infective and costs. Thus, we seek to find an optimal triple controls $(u_1^*,\ u_2^*,\ u_3^*)$ such that

$$J(u_1^*,\ u_2^*,\ u_3^*) = min\{J(u_1^*,\ u_2^*,\ u_3^*): u_i \in U\}$$

Here $U = \{(u_1^*,\ u_2^*,\ u_3^*)\}$ each u_i is measurable with $0 \le u_i < 1$ for $0 \le t \le t_f$.

6.1 The Hamiltonian and Optimality System

By using the principle of [17]," Pontryagins Maximum Principle Pontryagin", we got the necessary conditions which is satisfied by optimal pair. Therefore, by this principle we obtained a Hamiltonian (H) defined as:

$$H = (Integrand) + (adjoint)(RHS\ of\ ODE)$$

$$\begin{aligned} \mathrm{H(S,V,A,I,R,C,t)} &= \mathrm{L(A,I},u_1,u_2\ ,u_3,\mathrm{t}) + \lambda_1(\mathrm{dS/dt}) + \lambda_2(\mathrm{dV/dt}) + \lambda_3(\mathrm{dA/dt}) + \lambda_4(\mathrm{dI/dt}) + \lambda_5(\mathrm{dR/dt}) \\ &\quad + \lambda_6(\mathrm{dC/dt}) \end{aligned}$$

Here $\mathrm{L(A,I},u_1,u_2\ ,u_3,\mathrm{t}) = b_1A + b_2I + \frac{1}{2}\sum_{i=1}^{3} w_i u_i^2,\ \lambda_i, i = 1, \dots 6$ are the adjoint variable functions to be determined suitably by applying Pontryagin's maximal principle [17] and also using [18] for existence of the optimal control pairs.

Theorem 5 There exist an optimal control set $u_1, u_2\ , u_3$ and the corresponding solution $\mathrm{S,V,A,I,R}$ and C that minimize $J(u_1^*,\ u_2^*,\ u_3^*)$ over U. Furthermore, there exist adjoint functions $\lambda_1, \dots\ , \lambda_6$ such that

$$\begin{aligned} d\lambda_1/dt &= -\partial H/\partial S \\ &= -[-((1-u_1)\beta(I+\gamma A)/N) - \alpha - \mu]\lambda_1 - \alpha\lambda_2 - [\rho(1-u_1)\beta(I+\gamma A)/N]\lambda_3 \\ &\quad - [(1-\rho)(1-u_1)\beta(I+\gamma A)/N]\lambda_4 \end{aligned}$$

$$d\lambda_2/dt = -\partial H/\partial V$$
$$= -\varphi\lambda_1 - [-((1-u_1)\varepsilon\beta(I+\gamma A)/N) - \varphi - \mu]\lambda_2 - [\rho\varepsilon(1-u_1)\beta(I+\gamma A)/N]\lambda_3$$
$$- [(1-\rho)(1-u_1)\varepsilon\beta(I+\gamma A)/N]\lambda_4$$
$$d\lambda_3/dt = -\partial H/\partial A$$
$$= [(1-u_1)\beta\gamma S/N]\lambda_1 + [(1-u_1)\beta\gamma V/N]\lambda_2$$
$$- [\rho(1-u_1)\beta\gamma(\varepsilon V+S)/N - u_3 - \theta - \mu - \phi]\lambda_3$$
$$- [(1-\rho)(1-u_1)\beta\gamma(S+\varepsilon V)/N + u_3 + \theta]\lambda_4 - \phi\lambda_5 - b_1$$
$$d\lambda_4/dt = -\partial H/\partial I$$
$$= [(1-u_1)\beta S/N]\lambda_1 + [(1-u_1)\beta V/N]\lambda_2$$
$$- [\rho(1-u_1)\beta(\varepsilon V+S)/N + (1-q)(1-u_2)\eta]\lambda_3$$
$$- [(1-\rho)(1-u_1)\beta(S+\varepsilon V)/N - u_2 - \eta - \delta - \mu]\lambda_4 - (u_2+q\eta)\lambda_5 - \delta\lambda_6 - b_2$$
$$d\lambda_5/dt = -\partial H/\partial R = -\omega\lambda_1 - (-\omega-\mu)\lambda_5$$
$$d\lambda_6/dt = -\partial H/\partial C = -(-\omega-\mu)\lambda_6$$

With transversality conditions, $\lambda_i(t_f) = 0, i = 1, \dots, 6$.

Similarly we follow the approach of Pontryagin to get the control as in [17]. We solved the equation, $\partial H/\partial u_i = 0$ at u_i^* for $i = 1, 2, 3$ and we obtain the control set $(u_1^*,\ u_2^*,\ u_3^*)$ characterized by:

$$\mathrm{u}_1^* = \max\{0,\ \min(1, \Phi_1)\}$$
$$\mathrm{u}_2^* = \max\{0,\ \min(1, \Phi_2)\}$$
$$\mathrm{u}_3^* = \max\{0,\ \min(1, \Phi_3)\}$$

Where $\Phi_1 = \beta(\gamma\mathrm{A}+\mathrm{I})[\rho\mathrm{V}\varepsilon\lambda_3 - \rho\mathrm{V}\varepsilon\lambda_4 + \rho\mathrm{S}\lambda_3 - \rho\mathrm{S}\lambda_4 + \mathrm{V}\varepsilon\lambda_4 - \mathrm{V}\varepsilon\lambda_2 - \mathrm{S}\lambda_1 + \mathrm{S}\lambda_4]/\mathrm{N}\omega_1$

$$\Phi_2 = -\mathrm{I}[q\eta\lambda_3 - \eta\lambda_3 - \lambda_4 + \lambda_5]/\omega_2$$
$$\Phi_3 = \mathrm{A}\,[\lambda_3 - \lambda_4]/\omega_3$$

Proof The form of the adjoint equation and transversality conditions are standard results from Pontryagin's maximum principle [17]. We differentiate the Hamiltonian with respect to states S, V, A, I, R and C respectively and then the adjoint system can be written as:

$$d\lambda_1/dt = -dH/dS$$
$$= -[-((1-u_1)\beta(I+\gamma A)/N) - \alpha - \mu]\lambda_1 - \alpha\lambda_2 - [\rho(1-u_1)\beta(I+\gamma A)/N]\lambda_3$$
$$- [(1-\rho)(1-u_1)\beta(I+\gamma A)/N]\lambda_4$$
$$d\lambda_2/dt = -dH/dV$$
$$= -\varphi\lambda_1 - [-((1-u_1)\varepsilon\beta(I+\gamma A)/N) - \varphi - \mu]\lambda_2 - [\rho\varepsilon(1-u_1)\beta(I+\gamma A)/N]\lambda_3$$
$$- [(1-\rho)(1-u_1)\varepsilon\beta(I+\gamma A)/N]\lambda_4$$
$$d\lambda_3/dt = -dH/dA$$
$$= [(1-u_1)\beta\gamma S/N]\lambda_1 + [(1-u_1)\beta\gamma V/N]\lambda_2$$
$$- [\rho(1-u_1)\beta\gamma(\varepsilon V+S)/N - u_3 - \theta - \mu - \phi]\lambda_3$$
$$- [(1-\rho)(1-u_1)\beta\gamma(S+\varepsilon V)/N + u_3 + \theta]\lambda_4 - \phi\lambda_5 - b_1$$
$$d\lambda_4/dt = -dH/dI$$
$$= [(1-u_1)\beta S/N]\lambda_1 + [(1-u_1)\beta V/N]\lambda_2$$
$$- [\rho(1-u_1)\beta(\varepsilon V+S)/N + (1-q)(1-u_2)\eta]\lambda_3$$
$$- [(1-\rho)(1-u_1)\beta(S+\varepsilon V)/N - u_2 - \eta - \delta - \mu]\lambda_4 - (u_2+q\eta)\lambda_5 - \delta\lambda_6 - b_2$$
$$d\lambda_5/dt = -dH/dR = -\omega\lambda_1 - (-\omega-\mu)\lambda_5$$
$$d\lambda_6/dt = -dH/dC = -(-\omega-\mu)\lambda_6$$

Similarly by following the approach of [17], to get the controls, we solved the equation, $\partial H/\partial u_i = 0$ at u_i for $i = 1, 2, 3$ and obtained:

$$\mathrm{u}_1^* = \beta(\gamma\mathrm{A}+\mathrm{I})[\rho\mathrm{V}\varepsilon\lambda_3 - \rho\mathrm{V}\varepsilon\lambda_4 + \rho\mathrm{S}\lambda_3 - \rho\mathrm{S}\lambda_4 + \mathrm{V}\varepsilon\lambda_4 - \mathrm{V}\varepsilon\lambda_2 - \mathrm{S}\lambda_1 + \mathrm{S}\lambda_4]/\mathrm{N}\omega_1$$
$$\mathrm{u}_2^* = -\mathrm{I}[q\eta\lambda_3 - \eta\lambda_3 - \lambda_4 + \lambda_5]/\omega_2$$
$$\mathrm{u}_3^* = \mathrm{A}\,[\lambda_3 - \lambda_4]/\omega_3$$

When we write by using standard control arguments involving the bounds on the controls, we conclude:

$$\mathrm{u}_1^* = \begin{cases} \Phi_1, \text{if } 0 < \Phi_1 < 1 \\ 0, \text{if } \Phi_1 \le 0, \\ 1, \text{if } \Phi_1 \ge 1. \end{cases}$$
$$\mathrm{u}_2^* = \begin{cases} \Phi_2, \text{if } 0 < \Phi_2 < 1 \\ 0, \text{if } \Phi_2 \le 0, \\ 1, \text{if } \Phi_2 \ge 1. \end{cases}$$
$$\mathrm{u}_3^* = \begin{cases} \Phi_3, \text{if } 0 < \Phi_3 < 1 \\ 0, \text{if } \Phi_3 \le 0, \\ 1, \text{if } \Phi_3 \ge 1. \end{cases}$$

In compact notation

$$u_1^* = \max\{0, \min(1, \Phi_1)\}$$
$$u_2^* = \max\{0, \min(1, \Phi_2)\}$$
$$u_3^* = \max\{0, \min(1, \Phi_3)\}$$

Where $\Phi_1 = \beta(\gamma A + I)[\rho V\varepsilon\lambda_3 - \rho V\varepsilon\lambda_4 + \rho S\lambda_3 - \rho S\lambda_4 + V\varepsilon\lambda_4 - V\varepsilon\lambda_2 - S\lambda_1 + S\lambda_4]/N\omega_1$

$$\Phi_2 = -I[q\eta\lambda_3 - \eta\lambda_3 - \lambda_4 + \lambda_5]/\omega_2$$
$$\Phi_3 = A[\lambda_3 - \lambda_4]/\omega_3$$

The optimality system is formed from the optimal control system (the state system) and the adjoint variable system by incorporating the characterized control set and initial and transversal condition.

$$\begin{aligned}
dS/dt &= (1-p)\Pi + \varphi V + \omega R - (1-u_1^*)[\beta(I+\gamma A)/N]S - (\alpha+\mu)S,\\
dV/dt &= p\Pi + \alpha S - (1-u_1^*)[\beta(I+\gamma A)/N]\varepsilon V - (\varphi+\mu)V,\\
dA/dt &= \rho(1-u_1^*)[\beta(I+\gamma A)/N](S+\varepsilon V) + (1-q)(1-u_2^*)\eta I - (u_3^*+\theta)A - (\phi+\mu) \quad (15)\\
dI/dt &= (1-\rho)(1-u_1^*)[\beta(I+\gamma A)/N](S+\varepsilon V) + (u_3^*+\theta)A - (u_2^*+\eta)I - (\delta+\mu)I,\\
dR/dt &= \phi A + (u_2^*+q\eta)I - (\omega+\mu)R,\\
dC/dt &= \delta I - (\xi+\mu)C\,.
\end{aligned}$$

$$\begin{aligned}
d\lambda_1/dt &= -[-((1-u_1)\beta(I+\gamma A)/N) - \alpha - \mu]\lambda_1 - \alpha\lambda_2 - [\rho(1-u_1)\beta(I+\gamma A)/N]\lambda_3\\
&\quad - [(1-\rho)(1-u_1)\beta(I+\gamma A)/N]\lambda_4\\
d\lambda_2/dt &= -\varphi\lambda_1 - [-((1-u_1)\varepsilon\beta(I+\gamma A)/N) - \varphi - \mu]\lambda_2 - [\rho\varepsilon(1-u_1)\beta(I+\gamma A)/N]\lambda_3\\
&\quad - [(1-\rho)(1-u_1)\varepsilon\beta(I+\gamma A)/N]\lambda_4\\
d\lambda_3/dt &= [(1-u_1)\beta\gamma S/N]\lambda_1 + [(1-u_1)\beta\gamma V/N]\lambda_2 - [\rho(1-u_1)\beta\gamma(\varepsilon V+S)/N - u_3 - \theta - \mu - \phi]\lambda_3\\
&\quad - [(1-\rho)(1-u_1)\beta\gamma(S+\varepsilon V)/N + u_3 + \theta]\lambda_4 - \phi\lambda_5 - b_1\\
d\lambda_4/dt &= [(1-u_1)\beta S/N]\lambda_1 + [(1-u_1)\beta V/N]\lambda_2 - [\rho(1-u_1)\beta(\varepsilon V+S)/N + (1-q)(1-u_2)\eta]\lambda_3\\
&\quad - [(1-\rho)(1-u_1)\beta(S+\varepsilon V)/N - u_2 - \eta - \delta - \mu]\lambda_4 - (u_2+q\eta)\lambda_5 - \delta\lambda_6 - b_2\\
d\lambda_5/dt &= -\omega\lambda_1 - (-\omega-\mu)\lambda_5\\
d\lambda_6/dt &= -(-\omega-\mu)\lambda_6
\end{aligned}$$

$$\lambda_i(t_f) = 0, i = 1, \dots, 6, \qquad S(0) = S_0, V(0) = V_0, A(0) = A_0, I(0) = I_0, R(0) = R_0, C(0) = C_0.$$

6.2 Uniqueness of the Optimality System

Due to the priori boundedness of the state, adjoint functions and the resulting Lipschitz structure of the ODEs, we can obtain the uniqueness of solutions of the optimality system for the small time interval. Hence the following theorem

Theorem 6 For $t \in [0, t_f]$, the bounded solutions to the optimality system is unique.

For the proof of the theorem, see [19].

VI. Numerical Simulation

We perform numerical simulation of the optimal control system or the state system by using the software DE Discover 2.6.4. To examine the impact of each control on eradication of HPV, we used the following strategy:

(i) Applying prevention only u_1 as intervention
(ii) Applying treatment only u_2 as intervention
(iii) Applying screening only u_3 as intervention
(iv) Implementing prevention u_1 and treatment u_2 intervention
(v) Implementing prevention u_1 and screening u_3 intervention
(vi) Implementing treatment u_2 and screening u_3 intervention
(vii) Using all the three controls: prevention effort u_1, treatment effort u_2, and also screening u_3

To conduct the study, a set of meaningful values are assigned to the model parameters. These values are either taken from literature or assumed. Using the parameter values given in Table 4 and the initial conditions $S(0) = 150000, V(0) = 116200, R(0) = 96600, A(0) = 122400, I(0) = 93840$ and $C(0) = 32500$ in the model equations (15) a simulation study is conducted and the results are given in Figures $(2-8)$.

Table 4 Parameter values used in Numerical Simulations

Parameter	Value	Reference
Π	175	[14]
μ	0.0100	[14]
φ	0.1830	Assumed
α	0.0080	Assumed
γ	0.3000	[14]
ω	0.1000	Assumed
ε	0.0020	Assumed
δ	0.1000	Assumed
ϕ	0.0025	Assumed

p	0.2970	Assumed
ρ	0.0500	Assumed
q	0.5000	Assumed
η	0.2000	Assumed
θ	0.3910	Assumed
ξ	0.0300	Assumed
κ	0.5000	Assumed
τ	0.8900	Assumed

7.1 Numerical results in the presence of prevention only

We simulated the optimality control system by incorporating prevention intervention only. Figures 2(a) and 2(b) shows that the decrease of asympw4tomatic population in the specified time but the number of infectious individuals did not go to zero over the period of implementation of this intervention strategy. The reason is that due to lack of prevention susceptible individuals still get infected. Therefore, we conclude that applying optimized prevention only as control intervention decreases the burden of the disease but it cannot eradicate HPV in the community.

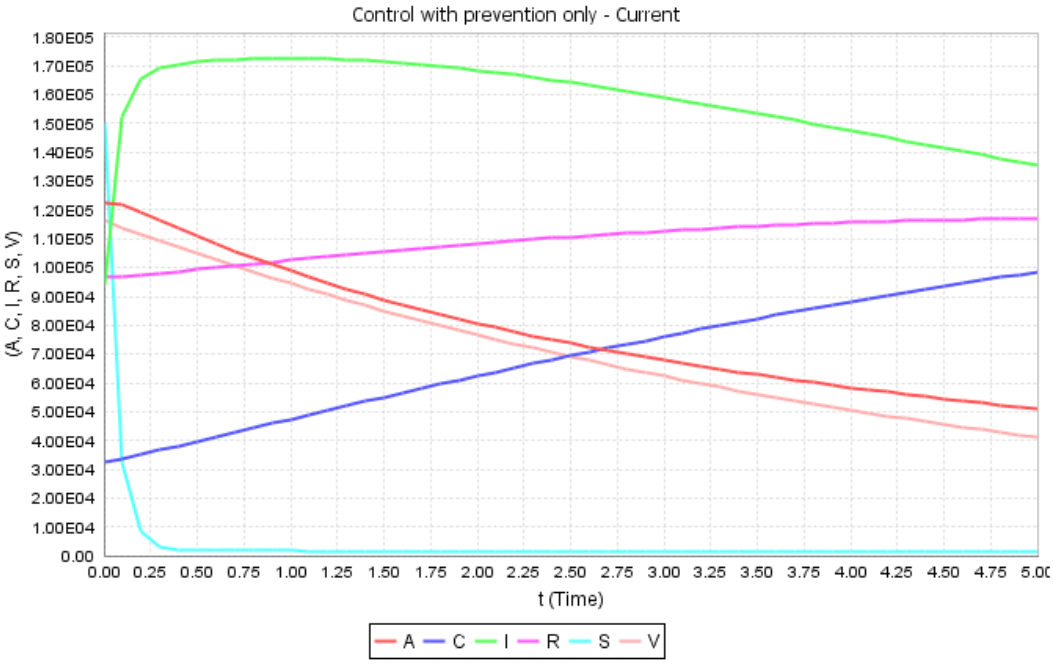

Figure 2(a): Simulations of optimal control with prevention only (Combined plot)

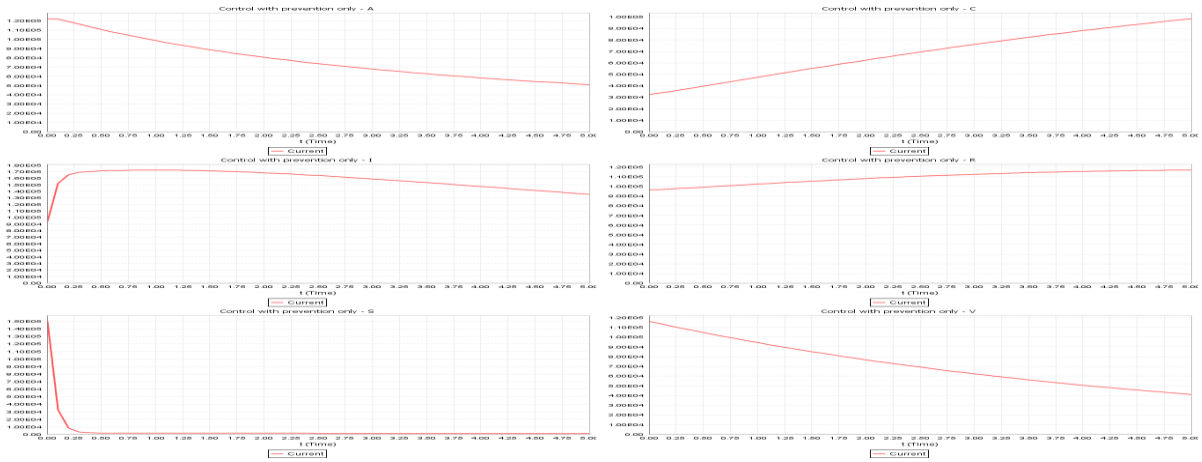

Figure 1(b): Simulations of optimal control with prevention only (individual plot)

7.2 Numerical results in the presence of treatment only

We applied treatment only as intervention that is treating individuals who develop disease symptom. . Figures 3(a) and 3(b) clearly show that the infectious and asymptomatic population has gone to zero at the end of the implementation period. Therefore, we conclude that this strategy is effective in eradicating the HPV from the community in a specified period of time.

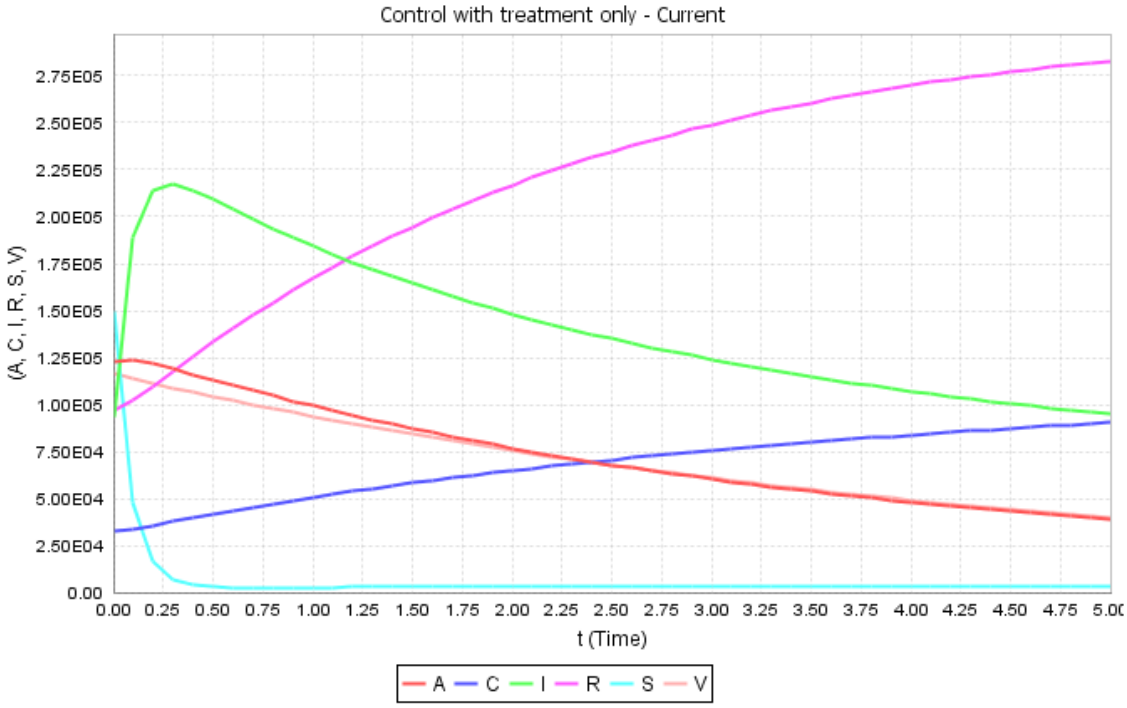

Figure 2(a): Simulations of optimal control with treatment only (combined plot)

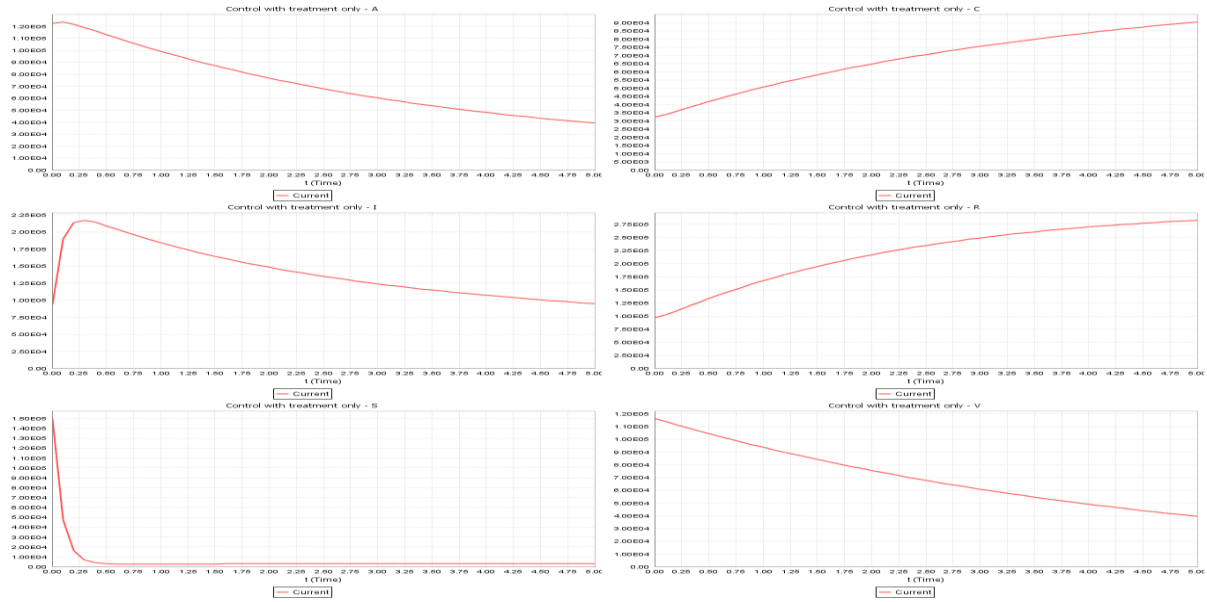

Figure 3(b): Simulations of optimal control with treatment only (individual plot)

7.3 Numerical results in the presence of Screening only

As we know screening helps asymptomatic to identify their status as they are leaving with the virus or not. Therefore, Figures 4(a) and 4(b) show that the infectious and asymptomatic population goes down by screening effort but their number cannot be zero. New infection always appears in the community because the diseases are not prevented and individuals who develop the symptom of the disease are not getting treatment. Therefore, control with screening only reduces the burden in some extent but it is not helpful to eradicate HPV totally from the community.

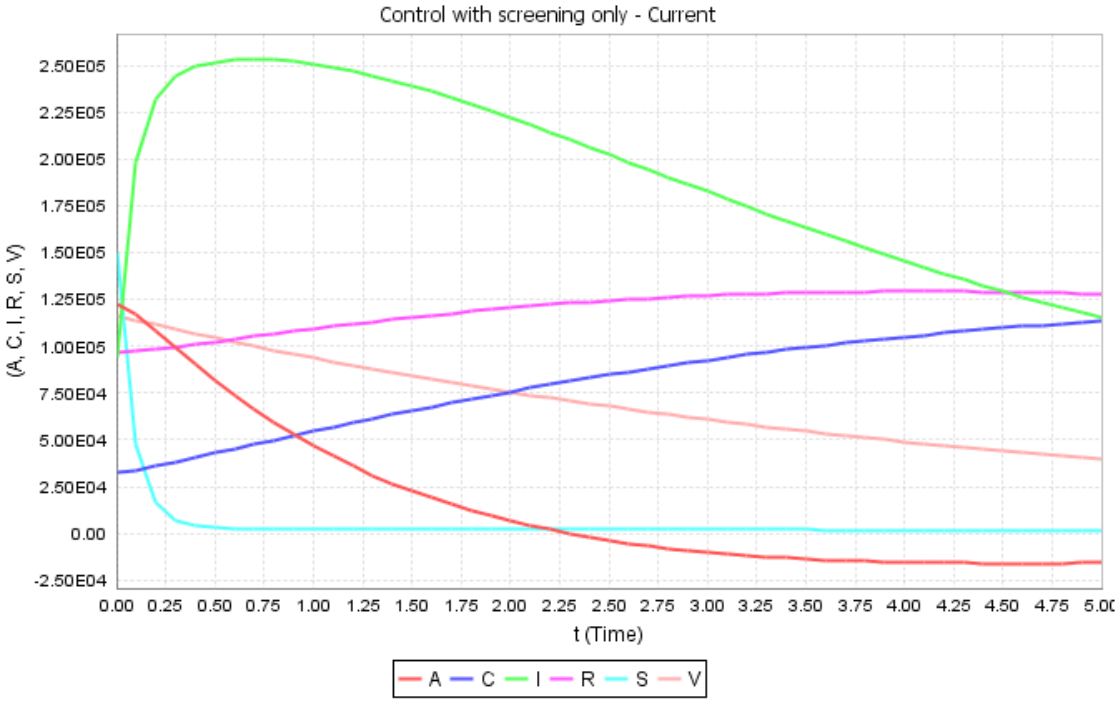

Figure 4(a): Simulations of optimal control with screening only (combined plot)

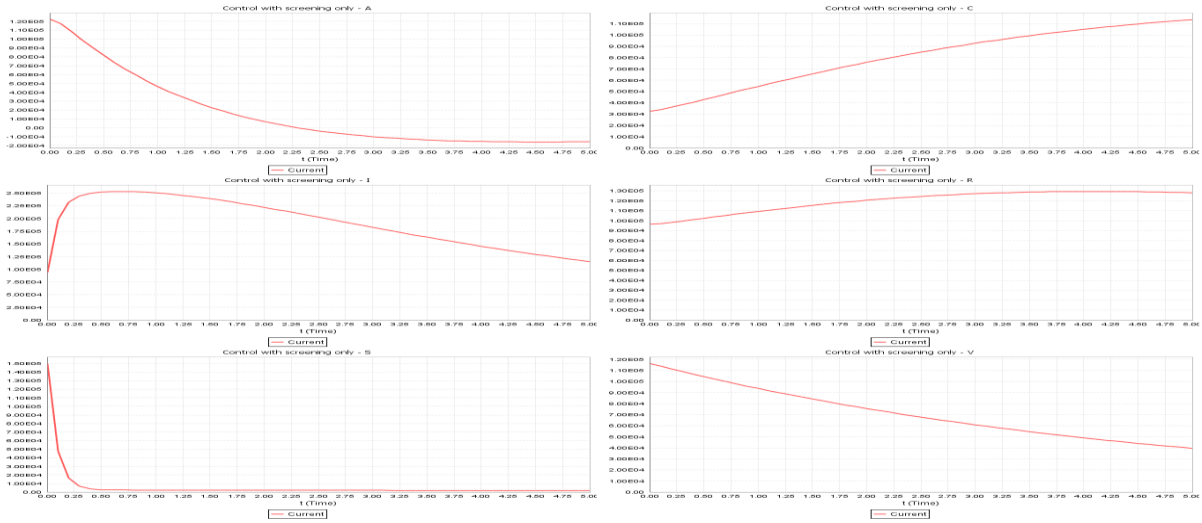

Figure 4(b): Simulations of optimal control with screening only (individual plot)

7.4 Numerical results in the presence of prevention and treatment

We simulate the model using a combination of prevention and treatment as intervention strategy for control of HPV in the community. Figures 5(a) and 5(b) shows that the number of infectious individuals and asymptomatic did not go to zero over the period of implementation of this intervention strategy. The reason is that due to lack of prevention susceptible individuals still get infected and due to lack of treatment individuals develop disease symptom. Therefore, this strategy is not 100% effective in eradicating the HPV in the specified period of time.

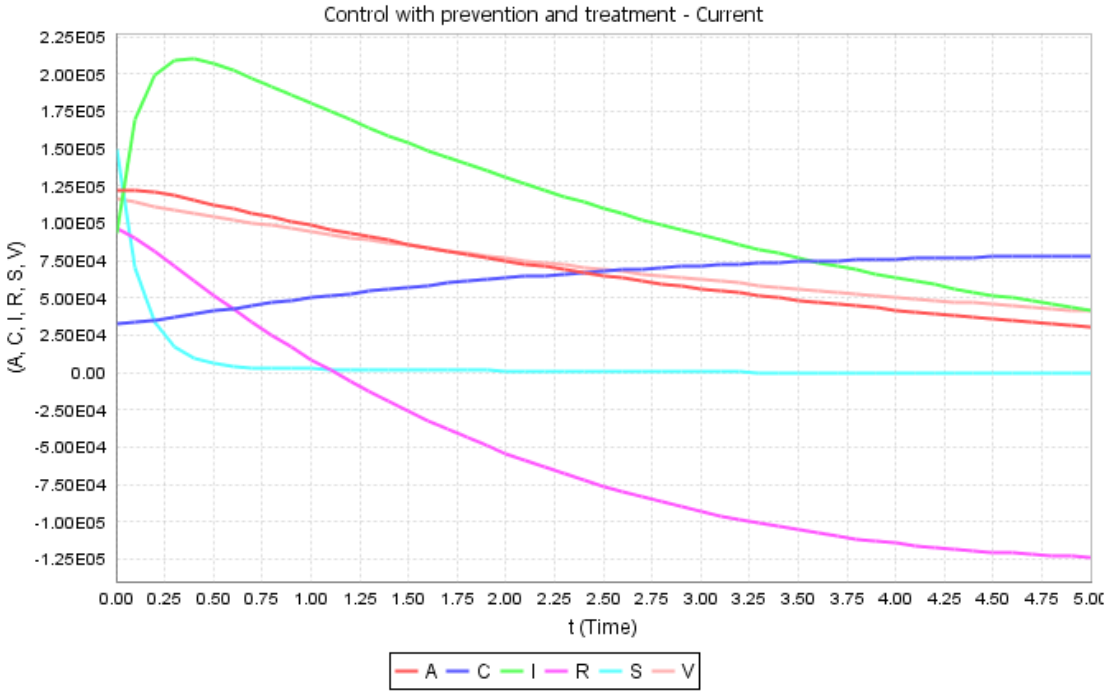

Figure 5(a): Simulations of optimal control with prevention and treatment (combined plot)

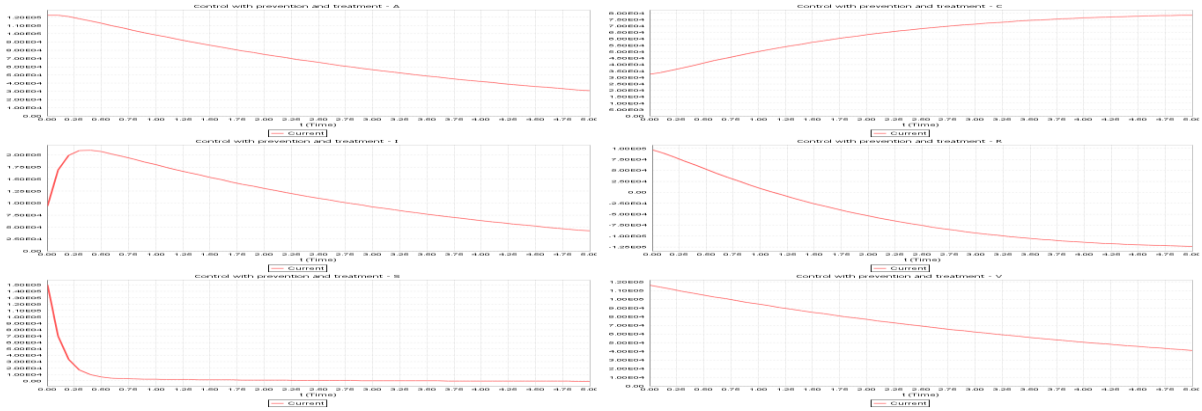

Figure 5(b): Simulations of optimal control with prevention and treatment (individual plot)

7.5 Numerical results in the presence of prevention and screening

In this strategy, we applied prevention and screening as intervention to control HPV. Figures 6(a) and 6(b) shows that the number of infectious individuals and asymptomatic did not go to zero over the period of implementation of this intervention strategy. The reason is that due to lack of prevention susceptible individuals still get infected and due to lack of screening asymptomatic individuals. Therefore, control with prevention and screening reduces the burden in some extent but it is not helpful to eradicate HPV totally from the community.

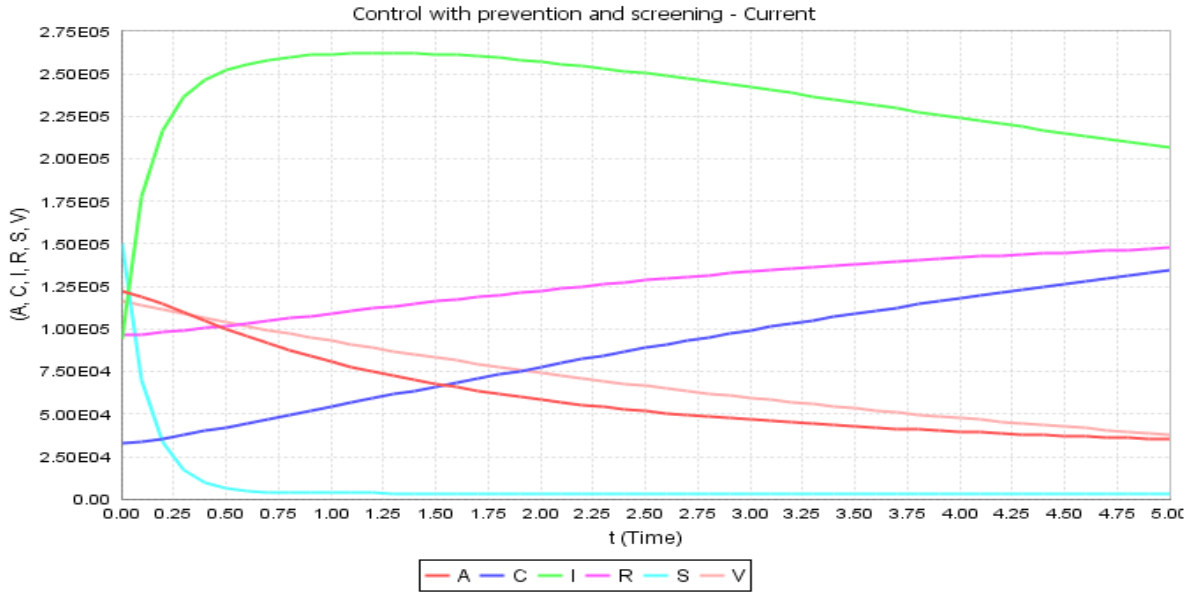

Figure 6(a): Simulation of optimal control with prevention and screening (combined plot)

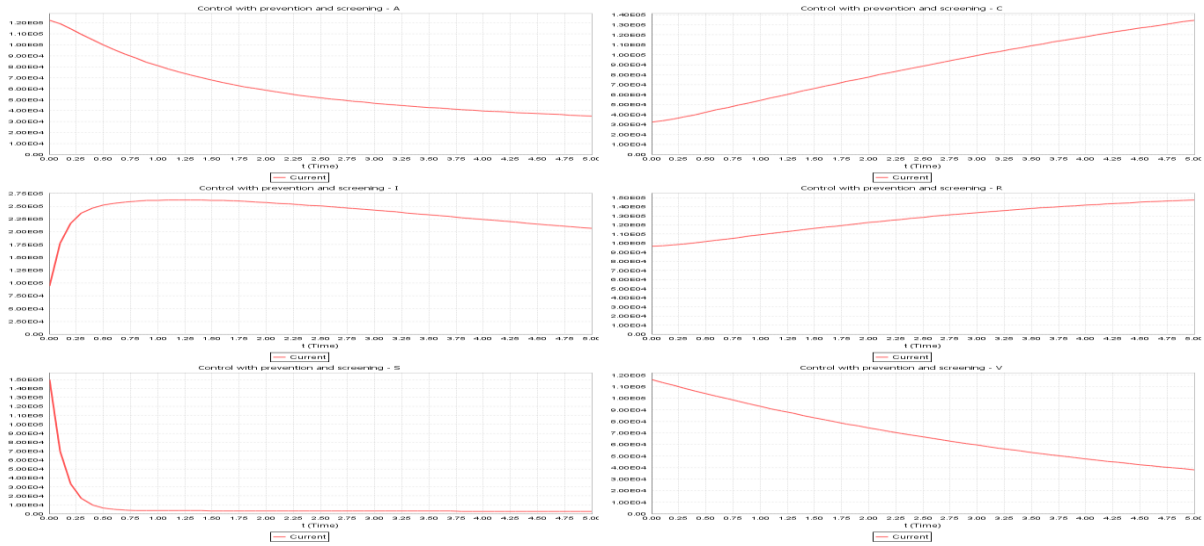

Figure 6(b): Simulations of optimal control with prevention and screening (individual plot)

7.6 Numerical results in the presence of treatment and screening

We simulate the model using a combination of treatment and screening as intervention strategy for control of HPV in the community. Figures 7(a) and 7(b) clearly show that the infectious and asymptomatic population has gone to zero at the end of the implementation period. Therefore, we conclude that this strategy is effective in eradicating HPV from the community in a specified period of time.

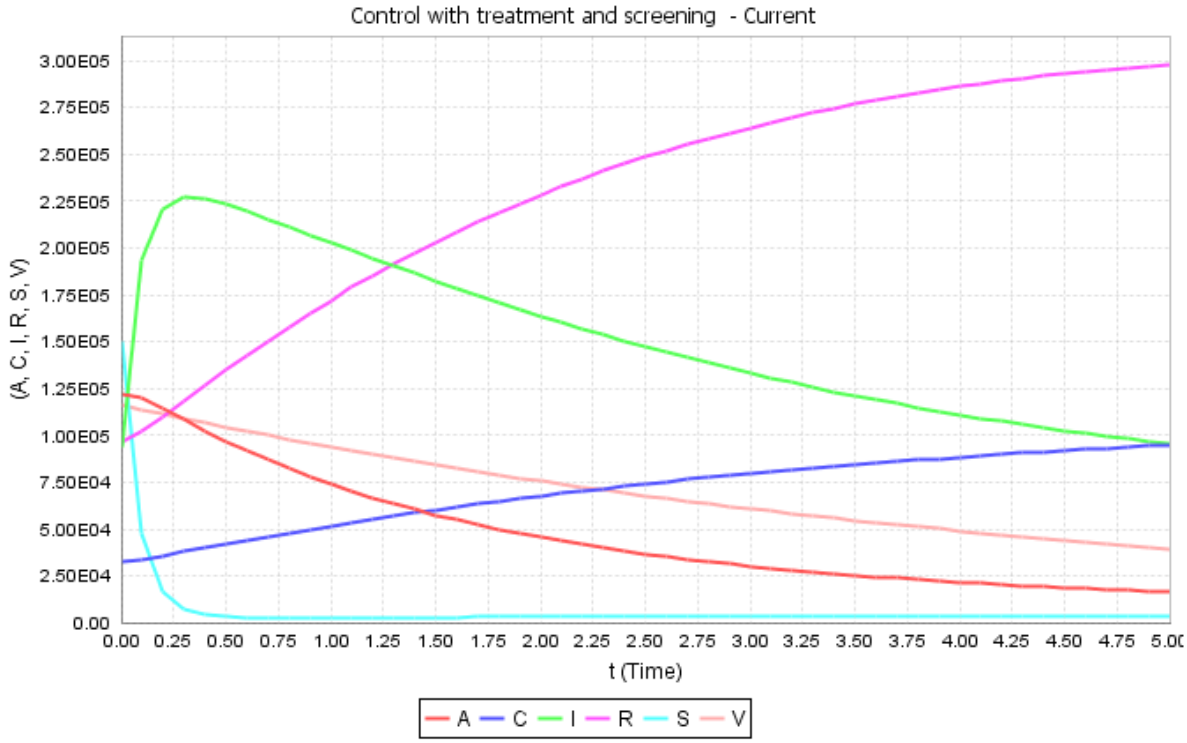

Figure 7(a): Simulations of optimal control with treatment and screening (combined plot)

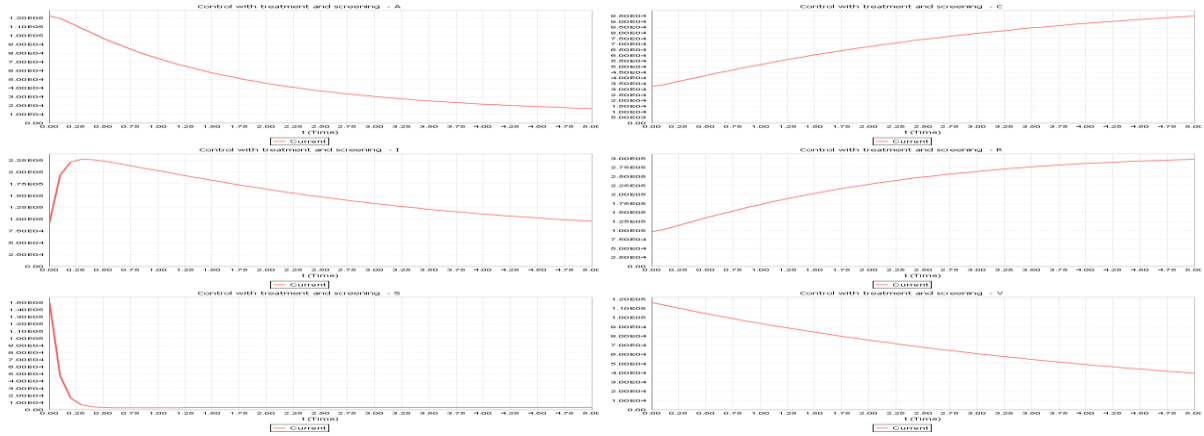

Figure 7(b): Simulations of optimal control with treatment and screening (individual plot)

7.7 Numerical results in the presence of prevention, screening and treatment

In this strategy, we implemented all the three controls (prevention, treatment, and screening) as intervention to eradicate HPV from the community. Figures 8(a) and 8(b) show that the number of infectious individuals and asymptomatic goes to zero at the end of the implementation period. Therefore, applying this strategy is effective in eradicating HPV form the community in a specified period of time.

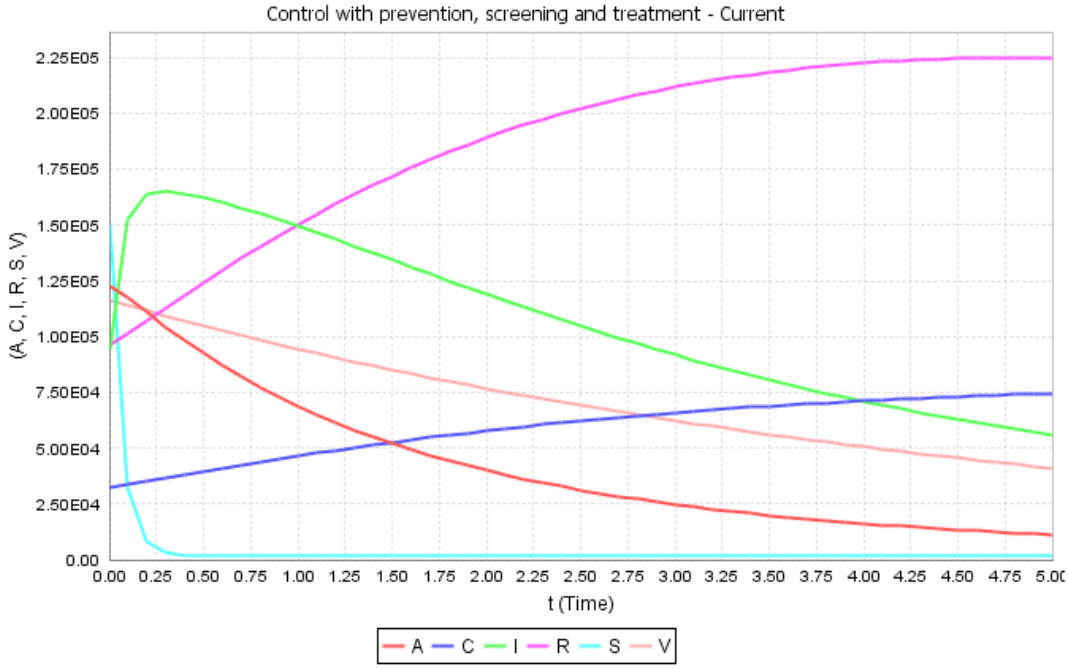

Figure 8(a): Simulations of optimal control with prevention, treatment and screening (combined plot)

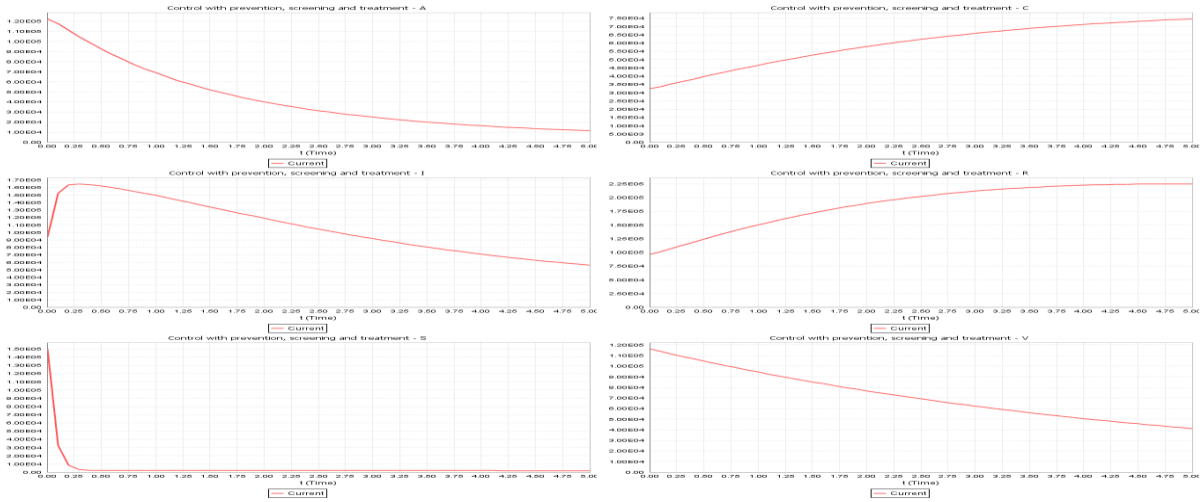

Figure 8(b): Simulations of optimal control with prevention, treatment and screening (individual plot)

VII. Sensitivity Analysis of Model Parameters

We carried out the sensitivity analysis to determine the model robustness to parameter values. The normalized forward sensitivity index of a variable to a parameter is a ration of the relative change in the variable to the relative change in the variable to the relative change in the parameter. If a variable is a differentiable function of the parameter, the sensitivity index may be alternatively defined using partial derivatives [20].

Definition: The normalized forward sensitivity index of a variable, u, which depend differentiability on index of a parameter, p is defined as $\Upsilon_p^u = (\partial u/\partial p)(p/u)$.

From an explicit formula for $\mathfrak{R}_0$, we derive an analytical expression for the sensitivity of $\mathfrak{R}_0$ as $\Upsilon_p^{\mathfrak{R}_0} = (\partial\, \mathfrak{R}_0/\partial p)(p/\, \mathfrak{R}_0)$ to each of the parameter involved in $\mathfrak{R}_0$. For example, the sensitivity index of $\mathfrak{R}_0$ with respect to $(\partial\, \mathfrak{R}_0/\partial\tau)(\tau/\, \mathfrak{R}_0) = 1$ other indices $\Upsilon_\kappa^{\mathfrak{R}_0}$, $\Upsilon_\varphi^{\mathfrak{R}_0}$, $\Upsilon_\mu^{\mathfrak{R}_0}$, $\Upsilon_p^{\mathfrak{R}_0}$, $\Upsilon_\delta^{\mathfrak{R}_0}$, $\Upsilon_\eta^{\mathfrak{R}_0}$, $\Upsilon_\gamma^{\mathfrak{R}_0}$, $\Upsilon_\theta^{\mathfrak{R}_0}$, $\Upsilon_\phi^{\mathfrak{R}_0}$, $\Upsilon_\rho^{\mathfrak{R}_0}$, $\Upsilon_q^{\mathfrak{R}_0}$ where obtained and evaluated at, $p = 0.7, q = 0.5$, $\eta = 0.0238$, $\kappa = 6$, $\tau = 0.89$, $\rho = 0.338$, $\mu = 0.002$, $\varphi = 0.001$, $\theta = 0.00274$, $\gamma = 0.9$, $\phi = 0.0115$, $\delta = 0.33$ to obtain the following results.

Table 5 Sensitivity indices Table.

Parameter Symbol	Sensitivity indices
η	652.54
φ	192.38
γ	115.72
ρ	18.63
p	3.5
κ	1
τ	1
μ	-0.000000415
δ	-4.83
q	-11.249
θ	-510.82
ϕ	-34063.69

Table 5 shows the sensitivity indices of $\Re_0$ to the parameters for the model equation $(1-6)$. The parameters are ordered from most sensitive to least. The most sensitive parameter is the contact rate, and the least sensitive parameter is the progression proportion of the disease. This result implies that, when the parameters $\eta, \varphi, \gamma, \rho, p, \tau,$ and κ are increased keeping other parameters constant, they increase the value of $\Re_0$ thus, they increase the endemicity of the disease as they have positive indices. While the parameters μ, δ, q, θ and ϕ decrease the value of $\Re_0$ when they are increased while keeping the other parameters constant, implying that they decrease the endemicity of the disease as they have negative indices.

VIII. Discussions and Conclusions

In this study, we formulated a deterministic model on the transmission dynamics of HPV. The qualitative analysis of the model shows that the solution of the model is bounded and positive and also the equilibria points of the model are obtained and their local as well as global stability condition is established. The study also obtained the basic reproduction number that governs the disease transmission from the largest eigenvalue of the next-generation matrix. The model exhibits a backward bifurcation and the sensitivity analysis is performed. The optimal control problem is designed by applying Pontryagin maximum principle with three control strategies, namely, prevention strategy, treatment strategy and screening strategy. Numerical results for the human papillomavirus outbreak dynamics and its optimal control revealed that a combination of prevention, screening and treatment is the most effective strategy to eradicate the disease from the community.

Although eradication of HPV infection remain a challenge especially in developing countries, but from results of this study we recommend that, the government should introduce education programmers on the importance of voluntary and routinely screening on HPV infection. Also, there is need to increase the number of hospitals to deal with HPV infection as well as cancers to ensure that, many people have access to the facilities, because HPV infection in long run results into different types of human cancers which pose serious health problem. Moreover, the future work should consider; incorporating asymptomatic and treatment against HPV transmission dynamics in the model.

Reference

[1]. Kathryn Marie Tobin, "Mathematical Models of the spread of the Human Papillomavirus (HPV) and simulation of the impact of an immunization programme in Ireland" August 21st, 2012.

[2]. A. S. Bergot, A. Kassianos, I.A. Frazer, D. Mittal, "New Approaches to immunotherapy for HPV associated cancers", *OPEN ACESS, Cancers (2011)*, 346-3495; doi 10.3390/cancers 3033461.

[3]. D. R. Lowy and J.T. Schiller, "Prophylactic human papillomavirus vaccines", *J C Invest* (2006), 116(5):1167-1173.

[4]. National Cancer Registry of South Africa. Available online: http://www.cansa.org.za/files/2015/10/NCR_Final_2010_tables1.pdf *(accessed on 24 April 2018).*

[5]. WHO list of priority medical devices for cancer management? *Geneva: World Health Organization*; 2017. Licence: CC BY-NC-SA 3.0 IGO.

[6]. S.L. Lee and A.M. Tameru, "A Mathematical model of Human papillomavirus in the United States and its impact on cervical cancer", *Ivyspring International Publisher J cancer (2012)* 3:262-266 doi: 10.7150/jca.4161.

[7]. L A Reynolds and E M Tansey, "History of Cervical Cancer and the role of the Human Papillomavirus, 1960–2000", London, on 13

[8]. Ruanne V Barnabas, Päivi Laukkanen, Pentti Koskela, Osmo Kontula, Matti Lehtinen, and Geoff P Garnett. Epidemiology of HPV 16 and cervical cancer in finland and the potential impact of vaccination: mathematical modelling analyses. *PLoS Med*, 3(5):e138, May 2006.

[9]. Elamin H Elbasha, Erik J Dasbach, and Ralph P Insinga. Model for assessing human papillomavirus vaccination strategies. *Emerg Infect Dis*, 13(1):28–41, Jan 2007.

[10]. James P Hughes, Geoff P Garnett, and Laura Koutsky. The theoretical population-level impact of a prophylactic human papilloma virus vaccine. *Epidemiology*, 13(6):631–639, Nov 2002.

[11]. L. Ribassin-Majed and R. Lounes, A SIS Model for Human papillomavirus transmission, 2010, hal-00555733, Version 1-14 Jan (2011)

[12]. Al V Taira, Christopher P Neukermans, and Gillian D Sanders. Evaluating human papillomavirus vaccination programs. *Emerg Infect Dis*, 10(11):1915–1923, Nov 2004.

[13]. L. Ribassin-Majed, R. Lounes, S. Clemencos, Efficacy of vaccination against HPV infections to prevent cervical cancer in France: Present assessment and Pathways to improve vaccination policies (2012), PLoS ONE 7(3):e32251.doi:10.-1371/journal, Pone 0032251
[14]. Eshetu Dadi Gurmu, Purnachandra Rao Koya. Sensitivity Analysis and Modeling the Impact of Screening on the Transmission Dynamics of Human Papilloma Virus (HPV). *American Journal of Applied Mathematics.* Vol. 7, No. 3, 2019, pp. 70-79.doi: 10.11648/j.ajam.20190703.11
[15]. C. Castillo-Chavez, B. Song, Dynamical models of tuberculosis and their applications, Math. Biosci. Eng. 1 (2) (2004) 361–404
[16]. S. Baba and O.D. Makinde, *Optimal control of HIV/AIDS in the workplace in the presence of careless individuals*, Comput. Math. Methods Med. 2014, pp. 1–19.
[17]. L.S. Pontryagin, V.G. Boltyanskii, R.V. Gamkrelize, and E.F. Mishchenko, *The Mathematical Theory of Optimal Processes*, John Wiley & Sons, New York, 1986.
[18]. W. H. Fleming and R. W. Rishel, *Deterministic and Stochastic Optimal Control*, vol. 1, Springer, New York, NY, USA, 1975.
[19]. K. R. Fister, S. Lenhart, and J. S. McNally, "Optimizing chemotherapy in an HIV model," *Electronic Journal of Differential Equations*, vol. 1998, 12 pages, 1998.
[20]. Eshetu Dadi Gurmu and Purnachandra Rao Koya, Impact of Chemotherapy treatment of SITR Compartmentalization and Modeling of Human Papilloma Virus (HPV), IOSR Journal of Mathematics (IOSR – JM), Vol. 15, Issue 3, Ser. I, May – June 2019, Pp 17 – 29. DOI: 10.9790/5728-1503011729 http://iosrjournals.org/iosr-jm/papers/Vol15-issue3/Series-1/C1503011729.pdf

Eshetu Dadi Gurmu. " Optimal Control Strategy on Human Papilloma Virus (HPV) model with Backward Bifurcation Analysis." IOSR Journal of Mathematics (IOSR-JM) 15.6 (2019): 65-87.