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# **Mathematical Modelling of Cervical Cancer with HPV infection PROJECT – REPORT**

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## **Abstract**

Cervical cancer is one of the most prevalent cancers among women worldwide, with over 600,000 new cases and more than 340,000 deaths reported annually. More than 95% of cervical cancer cases are attributed to persistent infections with high-risk human papillomavirus (HPV). The disease burden is significantly higher in low- and middle-income countries, where access to screening and vaccination remains limited. In this paper, we develop and analyze a compartmental mathematical model to understand the transmission dynamics of HPV and its progression to cervical cancer. The population is categorized into four compartments: susceptible ( $S$ ), infected ( $I$ ), cancer ( $C$ ), and recovered ( $R$ ) individuals. The model incorporates key epidemiological parameters, including the transmission rate, progression rate to cancer, recovery rate, and natural mortality. By applying the next-generation matrix method, we determine the basic reproduction number ( $R_0$ ), which serves as a threshold parameter indicating whether the disease persists or is eradicated. Numerical simulations using realistic population data demonstrate that when  $R_0 < 1$ , the disease-free equilibrium is globally asymptotically stable, leading to infection elimination. Conversely, when  $R_0 > 1$ , the model stabilizes at an endemic equilibrium, where infection and cancer persist at steady levels.

# 1 Introduction

Cervical cancer, primarily caused by persistent infection with high-risk human papillomavirus (HPV) strains, remains a major global health challenge. According to the World Health Organization (WHO), cervical cancer is the fourth most common cancer among women, with an estimated 600,000 new cases and 340,000 deaths reported globally in 2023 [1]. Despite advances in early detection and preventive measures, disparities in healthcare accessibility continue to contribute to high morbidity and mortality rates [2]. The disease is particularly prevalent in low- and middle-income countries where HPV vaccination and screening programs remain insufficient [3].

Mathematical modeling has emerged as a crucial tool in understanding disease progression, optimizing resource allocation, and guiding public health policies. Compartmental epidemiological models classify populations based on disease status and provide valuable insights into the transmission dynamics of infectious diseases [4]. Traditional models, such as the susceptible-infected-recovered (SIR) framework, have been extensively used for diseases like tuberculosis and COVID-19 [5]. However, cervical cancer progression involves multiple biological and behavioral factors, requiring more complex modeling approaches.

Several studies have expanded upon the standard SIR framework by incorporating additional compartments representing HPV infection stages, cervical intraepithelial neoplasia (CIN), and cancer progression [6]. These models have been applied to different population settings, particularly high-risk regions such as Sub-Saharan Africa and South-east Asia, where HPV prevalence is significantly high [7]. Furthermore, research indicates that early screening and vaccination programs significantly impact disease outcomes [8].

Despite the insights gained from compartmental models, their predictive capabilities are often limited by assumptions about disease progression and population dynamics. To address these challenges, data-driven approaches, including machine learning and deep learning models, have been increasingly utilized in cervical cancer research [9]. These models leverage large-scale epidemiological datasets to identify hidden patterns and predict disease trends more accurately. Studies have shown the effectiveness of deep learning in predicting HPV infection persistence and optimizing screening strategies in resource-limited settings [10]. However, while data-driven methods offer flexibility, they are prone to overfitting and often lack mechanistic disease progression insights.

To bridge the gap between mechanistic and data-driven approaches, recent research has integrated epidemiological models with deep learning techniques. Hybrid frameworks that combine compartmental disease models with neural networks enhance predictive accuracy while maintaining epidemiological interpretability [11]. In the context of cervical cancer, such models incorporate factors like vaccination coverage, screening rates, and demographic influences to improve early detection and intervention strategies. Additionally, network-based models have been employed to capture spatial heterogeneity and population interactions, enabling more precise predictions of HPV transmission dynamics [12].

Given the global burden of cervical cancer and the need for efficient intervention strategies, mathematical modeling remains an essential tool in guiding public health policies. Future research should focus on improving predictive accuracy by incorporating real-world data and refining hybrid models to enhance decision-making in HPV prevention and control.

## 2 Mathematical model formulation of cervical cancer

The dynamics of the population is governed by the following system of equations:

$$\begin{aligned}\frac{dS}{dt} &= \Lambda - \frac{\beta SI}{1 + \alpha' I} - \mu S + \alpha R \\ \frac{dI}{dt} &= \frac{\beta SI}{1 + \alpha' I} - \gamma I - \delta I - \mu I \\ \frac{dC}{dt} &= \delta I - \xi C - \mu C \\ \frac{dR}{dt} &= \gamma I - \alpha R - \mu R\end{aligned}\tag{2.1}$$

with initial conditions

$$S(0) > 0, I(0) \geq 0, C(0) \geq 0, R(0) \geq 0\tag{2.2}$$

where

Variable	Description
$S(t)$	Susceptible population
$I(t)$	Infected population (with HPV infection)
$C(t)$	Cancer population (with cervical cancer)
$R(t)$	Recovered population (after HPV infection)

Table 1: Description of variables

Parameter	Description
$\Lambda$	Rate of new individuals entering the susceptible population
$\beta$	Transmission rate of HPV infection
$\alpha$	Rate of immunity loss in recovered individuals
$\alpha'$	Saturation factor
$\gamma$	Recovery rate from HPV infection
$\delta$	Rate of progression from infection to cancer
$\xi$	Recovery rate from cervical cancer
$\mu$	Natural mortality rate

Table 2: Description of biologically meaningful parameters

### 3 Positivity and Uniform boundedness

**Theorem 3.1.** *The solutions  $(S(t), I(t), C(t), R(t))$  of the system (2.1) remain nonnegative for all  $t > 0$  with the initial conditions  $S(0) > 0$  and  $I(0), C(0), R(0) \geq 0$ .*

*Proof.* From first equation of system (2.1), we start with the given differential equation neglecting  $\alpha R$ :

$$\begin{aligned}\frac{dS}{dt} &\geq \Lambda - \frac{\beta IS}{1 + \alpha' I} - \mu S \\ \Rightarrow \frac{dS}{dt} &\geq \Lambda - \beta SI - \mu S \left[ \text{since } -\frac{\beta SI}{1 + \alpha' I} \geq -\beta SI \right] \\ &\therefore \frac{dS}{dt} + (\beta I + \mu)S \geq \Lambda\end{aligned}$$

$$\begin{aligned}\Rightarrow S(t) &\geq S(0) \exp \left( - \int_0^t \beta I(v) dv - \mu t \right) + \exp \left( - \int_0^t \beta I(v) dv - \mu t \right) \times \\ &\quad \int_0^t \Lambda \exp \left( \int_0^z \beta I(v) dv + \mu z \right) dz > 0 \text{ [ since } S(0) > 0 \text{ ]}\end{aligned}$$

Now, from second equation of system (2.1), we start with the given differential equation neglecting  $\frac{\beta SI}{1 + \alpha' I}$ :

$$\begin{aligned}\frac{dI}{dt} + (\mu + \gamma + \delta)I &\geq 0 \\ \Rightarrow \frac{dI}{I} + (\mu + \gamma + \delta)dt &\geq 0.\end{aligned}$$

Integrating both sides, we have:

$$\begin{aligned}\int_{I(0)}^{I(t)} \frac{dI}{I} &\geq - \int_{u=0}^t (\mu + \gamma + \delta) du \\ \Rightarrow I(t) &\geq I(0) \exp(-(\mu + \gamma + \delta)t)\end{aligned}$$

$\therefore I(t) \geq 0$ , since  $I(0) \geq 0$ .

From third equation of system (2.1), we start with the given differential equation neglecting  $\delta I$ :

$$\begin{aligned}\frac{dC}{dt} &\geq -(\zeta + \mu)C. \\ \Rightarrow C(t) &\geq C(0) \exp(-(\zeta + \mu)t)\end{aligned}$$

$\therefore C(t) \geq 0$ , since  $C(0) \geq 0$ .

From fourth equation of system (2.1), we start with the given differential equation neglecting  $\gamma I$ :

$$\frac{dR}{dt} + (\alpha + \mu)R \geq 0.$$

$$\Rightarrow R(t) \geq R(0) \exp(-(\alpha + \mu)t).$$

$\therefore R(t) \geq 0$ , since  $R(0) \geq 0$ .

Hence, the proof.  $\square$

**Theorem 3.2.** *Let  $(S(t), I(t), C(t), R(t))$  be any solution of the model (2.1) with (2.2) in  $\mathbb{R}_+^4$ , then the feasible region*

$$\Omega = \left\{ (S(t), I(t), C(t), R(t)) \in \mathbb{R}_+^4 : 0 < N(t) < \frac{\Lambda}{\mu} + \epsilon, \epsilon > 0 \right\}$$

*Proof.* The total population is defined as:

$$N(t) = S(t) + I(t) + C(t) + R(t).$$

Differentiating both sides w.r.t.  $t$ , we have:

$$\begin{aligned} \frac{dN}{dt} &= \frac{dS}{dt} + \frac{dI}{dt} + \frac{dC}{dt} + \frac{dR}{dt} \\ &= \Lambda - \mu S - \mu I - \mu R - \mu C - \zeta C \\ &= \Lambda - \mu N - \zeta C \\ &\leq \Lambda - \mu N. \end{aligned}$$

$$\begin{aligned} \therefore \frac{dN}{dt} + \mu N &\leq \Lambda \\ \Rightarrow N(t)e^{\mu t} &\leq \frac{\Lambda}{\mu}e^{\mu t} + \text{constant} \\ \Rightarrow N(t) &\leq N(0)e^{-\mu t} + \frac{\Lambda}{\mu}(1 - e^{-\mu t}). \end{aligned}$$

$\therefore 0 < N(t) < \frac{\Lambda}{\mu} + \epsilon$  for  $t \rightarrow \infty$  and  $\epsilon > 0$ .

A globally attractive system means that regardless of the initial population sizes, the system always converges to a steady state over time. Thus, in the long run, the distribution of susceptible, infected, cancer, and recovered individuals stabilizes, and the population does not grow or shrink indefinitely.  $\square$

## 4 Equilibrium Points

To analyze the equilibrium states of the model, we solve for the disease-free equilibrium (DFE) and endemic equilibrium (EE) points, based on the mathematical model described in the paper.

### Disease-free equilibrium (DFE)

occurs when there are no infections in the population, i.e.,  $I = 0$  and  $C = 0$ . Setting the system of equations to zero:

$$S^* = \frac{\Lambda}{\mu}, \quad I^* = 0, \quad C^* = 0, \quad R^* = 0.$$

This represents the state where no infection exists, and the susceptible population remains at a stable level determined by the birth and death rates.

## Endemic equilibrium (EE)

occurs when the infection persists in the population, meaning  $I^* \neq 0$  and  $C^* \neq 0$ . The endemic equilibrium points are given by:

$$S^* = \frac{(\delta + \gamma + \mu)(1 + \alpha'I)}{\beta}, \quad I^* = \frac{(\Lambda\beta - \mu(\delta + \gamma + \mu))(\alpha + \mu)}{\beta[(\alpha + \mu)(\delta + \gamma + \mu) - \alpha\delta] + \alpha'\mu(\alpha + \mu)(\gamma + \delta + \mu)},$$

$$C^* = \frac{\delta I^*}{\xi + \mu}, \quad R^* = \frac{\gamma I^*}{\alpha + \mu}.$$

These equations describe the steady-state levels of each compartment when the disease remains endemic in the population.

## 5 Basic reproduction number and its computation

The basic reproduction number (denoted by  $R_0$ ) is the estimated number of secondary cases created by a typical infected person during its entire cycle of infectiousness in a fully susceptible population. We calculate the basic reproduction number of the model using the method of the next-generation matrix developed by Van den Driessche and Watmough.

### New Infections (F)

New infections enter the system through the infected compartment ( $I$ ) as follows:

1. Infection arises in the  $I$  compartment from susceptible individuals through transmission:  $\frac{\beta S}{1 + \alpha'I}$ .
2. No new infection occurs directly in the cancer compartment ( $C$ ) directly .
3. The new infection function  $F$  includes only the infected compartment:

$$F = \begin{bmatrix} \frac{\beta S}{1 + \alpha'I} & 0 \\ 0 & 0 \end{bmatrix}.$$

### Transition Matrix (V)

The transition matrix captures the rates of progression, recovery, and death out of infected compartments ( $I$  and  $C$ ):

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

The inverse of the transition matrix is:

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

## Next-Generation Matrix and Basic Reproduction Number

$$FV^{-1} = \begin{bmatrix} \frac{\beta S_0}{\delta + \gamma + \mu} & 0 \\ 0 & 0 \end{bmatrix}.$$

Thus, the basic reproduction number is:

$$R_0 = \frac{\beta S_0}{\delta + \gamma + \mu}.$$

Substituting the disease-free equilibrium value  $S_0 = \frac{\Lambda}{\mu}$ , we get:

$$R_0 = \frac{\beta \Lambda}{\mu(\delta + \gamma + \mu)}.$$

## 6 Stability analysis for a disease-free and Endemic equilibrium

### 6.1 Local stability

**Theorem 6.1.** *The disease-free equilibrium  $E_0$  of the model is locally asymptotically stable if  $R_0 < 1$  and unstable if  $R_0 > 1$ .*

*Proof.* The Jacobian matrix at  $E_0$  is given by:

$$J(E_0) = \begin{bmatrix} -\mu & -\frac{\beta \Lambda}{\mu} & 0 & \alpha \\ 0 & \frac{\beta \Lambda}{\mu} - (\delta + \gamma + \mu) & 0 & 0 \\ 0 & \delta & -(\xi + \mu) & 0 \\ 0 & \gamma & 0 & -(\alpha + \mu) \end{bmatrix}.$$

The characteristic roots are:

$$\begin{aligned} \lambda_1 &= -\mu (< 0), \\ \lambda_2 &= \frac{\beta \Lambda}{\mu} - (\delta + \gamma + \mu), \\ \lambda_3 &= -(\xi + \mu) (< 0), \\ \lambda_4 &= -(\alpha + \mu) (< 0). \end{aligned}$$

For stability, real parts of all eigenvalues should be negative. So for the stability of  $E_0$ ,  $\lambda_2$  must be negative i.e.,  $\lambda_2 = \frac{\beta \Lambda}{\mu} - (\delta + \gamma + \mu) < 0 \Rightarrow \frac{\beta \Lambda}{\mu} < (\delta + \gamma + \mu)$  which gives the condition:

$$R_0 = \frac{\beta \Lambda}{\mu(\delta + \gamma + \mu)} < 1$$

In summary, when  $\lambda_2 < 0$ , the disease cannot invade or persist in the population, and the system settles at the disease-free equilibrium. Understanding this threshold helps guide public health interventions to keep  $R_0$  below 1, effectively eradicating the infection.

Conversely, when  $\lambda_2 > 0$  and  $R_0 > 1$ , the disease-free equilibrium  $E_0$  becomes unstable.

□

**Theorem 6.2.** *The endemic equilibrium  $E_1(S^*, I^*, C^*, R^*)$  is locally asymptotically stable if  $R_0 > 1$ , and unstable if  $R_0 < 1$ .*

*Proof.* The Jacobian matrix at  $E_1(S^*, I^*, C^*, R^*)$  is given by:

$$J(E_1) = \begin{bmatrix} -\frac{\beta I^*}{1+\alpha' I^*} - \mu & -\frac{\beta S^*}{(1+\alpha' I^*)^2} & 0 & \alpha \\ \frac{\beta I^*}{1+\alpha' I^*} & \frac{\beta S^*}{(1+\alpha' I^*)^2} - (\gamma + \delta + \mu) & 0 & 0 \\ 0 & \delta & -(\zeta + \mu) & 0 \\ 0 & \gamma & 0 & -(\alpha + \mu) \end{bmatrix}.$$

The characteristic equation of  $J(E_1)$  is:

$$\lambda^4 + a_1 \lambda^3 + a_2 \lambda^2 + a_3 \lambda + a_4 = 0,$$

$$a_1 = -(a_{11} + a_{22} + a_{33} + a_{44}),$$

$$a_2 = (a_{33}a_{44} + a_{11}a_{44} + a_{11}a_{22} - a_{12}a_{21} + a_{11}a_{33} + a_{22}a_{44} + a_{22}a_{33}),$$

$$a_3 = -(a_{22}a_{33}a_{44} + a_{11}a_{33}a_{44} + a_{11}a_{22}a_{44} - a_{12}a_{21}a_{44} + a_{14}a_{21}a_{42} + a_{11}a_{22}a_{33} - a_{12}a_{21}a_{33}),$$

$$a_4 = a_{11}a_{22}a_{33}a_{44} - a_{12}a_{21}a_{33}a_{44} + a_{14}a_{21}a_{33}a_{42},$$

$$a_{11} = -\frac{\beta I^*}{1+\alpha' I^*} - \mu, a_{12} = -\frac{\beta S^*}{(1+\alpha' I^*)^2}, a_{14} = \alpha, a_{21} = \frac{\beta I^*}{1+\alpha' I^*}, a_{22} = \frac{\beta S^*}{(1+\alpha' I^*)^2} - (\gamma + \delta + \mu),$$

$$a_{32} = \delta, a_{33} = -(\zeta + \mu), a_{42} = \gamma, a_{44} = -(\alpha + \mu).$$

We observe that if  $R_0 > 1$ , the following conditions (Routh-Hurwitz criterion) hold:

$$\begin{aligned} a_1 &> 0, & a_2 &> 0, \\ a_3 &> 0, & a_4 &> 0, \\ a_1 a_2 a_3 &> a_3^2 + a_1^2 a_4. \end{aligned}$$

Thus, all the roots of the characteristic equation have negative real parts, implying that the endemic equilibrium is locally asymptotically stable when  $R_0 > 1$ .  $\square$

## 6.2 Global stability

**Theorem 6.3.** *The disease-free equilibrium  $E_0$  of model (2.1) is globally asymptotically stable if  $R_0 < 1$ .*

*Proof.* To establish the global stability of  $E_0$ , we construct a Lyapunov function:

$$V(t) = I(t) + aC(t),$$

where  $a > 0$  is a constant to be determined. Differentiating  $V(t)$  with respect to time, we obtain:

$$\frac{dV}{dt} = \frac{dI}{dt} + a \frac{dC}{dt}.$$

From the given system:

$$\frac{dI}{dt} = \frac{\beta SI}{1 + \alpha' I} - (\gamma + \delta + \mu)I,$$



$$\frac{dC}{dt} = \delta I - (\xi + \mu)C.$$

Substituting these into  $\frac{dV}{dt}$ :

$$\frac{dV}{dt} = \frac{\beta SI}{1 + \alpha' I} - (\gamma + \delta + \mu)I + a(\delta I - (\xi + \mu)C).$$

At  $E_0 = (S_0, 0, 0, 0)$ , where  $S_0 = \frac{\Lambda}{\mu}$ , we use  $R_0 = \frac{\beta \Lambda}{\mu(\delta + \gamma + \mu)}$ .

Rewriting  $\frac{dV}{dt}$ :

$$\begin{aligned} \frac{dV}{dt} &= \left( \frac{\beta S_0}{1 + \alpha' I} - (\delta + \gamma + \mu) + a\delta \right) I - a(\xi + \mu)C \\ &\leq [\beta S_0 - (\delta + \gamma + \mu) + a\delta] I \\ &= \left[ \beta \frac{\Lambda}{\mu} - (\delta + \gamma + \mu) + a\delta \right] I \\ &= [(R_0 - 1)(\gamma + \delta + \mu) + a\delta] I. \end{aligned}$$

Now, choosing  $a = R_0 - 1$ , we obtain:

$$\frac{dV}{dt} = (R_0 - 1)(2\delta + \gamma + \mu)I.$$

Since  $R_0 < 1$ , it follows that  $\frac{dV}{dt} < 0$ , which ensures that the disease-free equilibrium  $E_0$  is globally asymptotically stable by LaSalle's Invariance Principle.

Thus when  $R_0 < 1$ , the infection will eventually die out, and the population will return to the disease-free equilibrium.  $\square$

**Theorem 6:** The endemic equilibrium  $E_1$  of our model is globally asymptotically stable, provided the following conditions hold:

$$\begin{aligned} I &> I^*, & R &> R^*, & SI^* &< S^* I, \\ 2 - \frac{C^*}{C} - \frac{R^*}{R} &< 0, & 1 + I - I^* - \frac{S^*}{S} &< 0 \end{aligned}$$

*Proof.* We construct a Lyapunov function to establish the global stability of  $E_1$ :

$$\begin{aligned} V(t) &= \left( S - S^* - S^* \ln \frac{S}{S^*} \right) + \left( I - I^* - I^* \ln \frac{I}{I^*} \right) + \frac{\alpha + \mu}{\delta} \left( C - C^* - C^* \ln \frac{C}{C^*} \right) \\ &\quad + \frac{\alpha + \mu}{\gamma} \left( R - R^* - R^* \ln \frac{R}{R^*} \right) + \frac{\alpha}{2\gamma} (R - R^*)^2. \end{aligned}$$

Differentiating  $V(t)$ , we have:

$$\begin{aligned} \frac{dV}{dt} &= \left( 1 - \frac{S^*}{S} \right) \frac{dS}{dt} + \left( 1 - \frac{I^*}{I} \right) \frac{dI}{dt} + \frac{\alpha + \mu}{\delta} \left( 1 - \frac{C^*}{C} \right) \frac{dC}{dt} + \frac{\alpha + \mu}{\gamma} \left( 1 - \frac{R^*}{R} \right) \frac{dR}{dt} + \frac{\alpha}{\gamma} (R - R^*) \frac{dR}{dt} \\ \Rightarrow \frac{dV}{dt} &= \left( 1 - \frac{S^*}{S} \right) \left( \frac{\beta S^* I^*}{1 + \alpha' I^*} - \frac{\beta SI}{1 + \alpha' I} - \mu(S - S^*) + \alpha(R - R^*) \right) + (I - I^*) \left( \frac{\beta S}{1 + \alpha' I} - \frac{\beta S^*}{1 + \alpha' I^*} \right) \end{aligned}$$

$$\begin{aligned}
& +(\alpha+\mu) \left(1 - \frac{C^*}{C}\right) (I - I^*) - \frac{(\alpha+\mu)(\zeta+\mu)(C - C^*)^2}{\delta C} + (\alpha+\mu) \left(1 - \frac{R^*}{R}\right) (I - I^*) - \frac{(\alpha+\mu)^2(R - R^*)^2}{R\gamma} \\
& + \alpha(R - R^*) (I - I^*) - \frac{\alpha(\alpha+\mu)(R - R^*)^2}{\gamma},
\end{aligned}$$

$$\text{since } \Lambda = \frac{\beta S^* I^*}{1+\alpha' I^*} + \mu S^* - \alpha R^*, \quad \frac{\beta S^*}{1+\alpha' I^*} = \gamma + \delta + \mu, \quad \delta I^* - (\zeta + \mu) C^* = 0, \quad \gamma I^* - (\alpha + \mu) R^* = 0$$

$$\begin{aligned}
\Rightarrow \frac{dV}{dt} & \leq \left(1 - \frac{S^*}{S}\right) \left(\frac{\beta S^* I^*}{1+\alpha' I^*} - \frac{\beta S I}{1+\alpha' I} - \mu(S - S^*) + \alpha(R - R^*)\right) + (I - I^*) \left(\frac{\beta S}{1+\alpha' I} - \frac{\beta S^*}{1+\alpha' I^*}\right) \\
& + (\alpha + \mu) \left(1 - \frac{C^*}{C}\right) (I - I^*) + (\alpha + \mu) \left(1 - \frac{R^*}{R}\right) (I - I^*) + \alpha(R - R^*) (I - I^*), \\
\Rightarrow & \leq -\beta(SI - S^* I^*) \left(1 - \frac{S^*}{S}\right) - \alpha' \beta I I^* \frac{(S - S^*)^2}{S} + \beta(S - S^*)(I - I^*) + \alpha' \beta (I - I^*)(SI^* - S^* I) - \mu \frac{(S - S^*)^2}{S} \\
& + (\alpha + \mu)(I - I^*) \left(2 - \frac{C^*}{C} - \frac{R^*}{R}\right) + \alpha(R - R^*) \left(1 + I - I^* - \frac{S^*}{S}\right), \text{ since } \frac{1}{1+\alpha' I} \leq 1, \quad \frac{1}{1+\alpha' I^*} \leq 1 \\
\Rightarrow & = -\beta I^* \frac{(S - S^*)^2}{S} - \alpha' \beta I I^* \frac{(S - S^*)^2}{S} + \alpha' \beta (I - I^*)(SI^* - S^* I) - \mu \frac{(S - S^*)^2}{S} \\
& + (\alpha + \mu)(I - I^*) \left(2 - \frac{C^*}{C} - \frac{R^*}{R}\right) + \alpha(R - R^*) \left(1 + I - I^* - \frac{S^*}{S}\right).
\end{aligned}$$

$\therefore \frac{dV}{dt} < 0$  if we take  $I > I^*, R > R^*, SI^* < S^* I, 2 - \frac{C^*}{C} - \frac{R^*}{R} < 0$  and  $1 + I - I^* - \frac{S^*}{S} < 0$  and  $\frac{dV}{dt} = 0$  at  $S = S^*, I = I^*, C = C^*, R = R^*$ .

Hence, by LaSalle's Invariance Principle,  $E_1(S^*, I^*, C^*, R^*)$  is globally asymptotically stable under the conditions  $\{I > I^*, R > R^*, SI^* < S^* I, 2 - \frac{C^*}{C} - \frac{R^*}{R} < 0, 1 + I - I^* - \frac{S^*}{S} < 0\}$ .

□

## 7 Transcritical Bifurcation Analysis

A transcritical bifurcation is a type of local bifurcation where two fixed points collide and exchange their stability. This occurs when a parameter crosses a critical value, causing a qualitative change in the behavior of the system's fixed points.

In our study, this occurs when the disease-free equilibrium  $E_0$  and the endemic equilibrium  $E_1$  exchange stability when they cross the line  $R_0 = 1$ .

- For  $R_0 < 1$ , only  $E_0$  is stable.

- For  $R_0 > 1$ ,  $E_1$  becomes stable.

To analyze the bifurcation, we examine the stability and existence of equilibrium at  $R_0 = 1$  using the Jacobian matrix and center manifold theory.

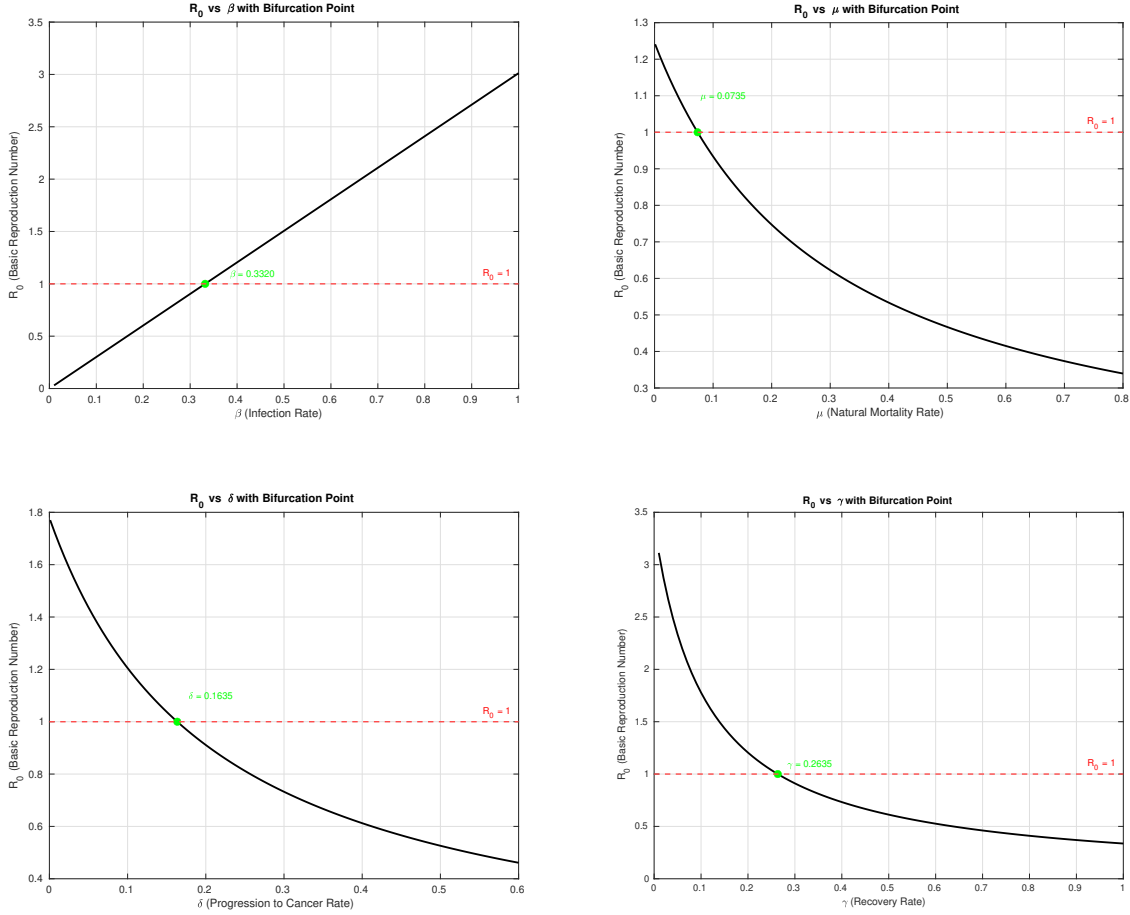


Figure 1: Transcritical bifurcation diagrams with respect to system parameters

## Stability regions of parameters for the disease-free and Endemic Equilibrium

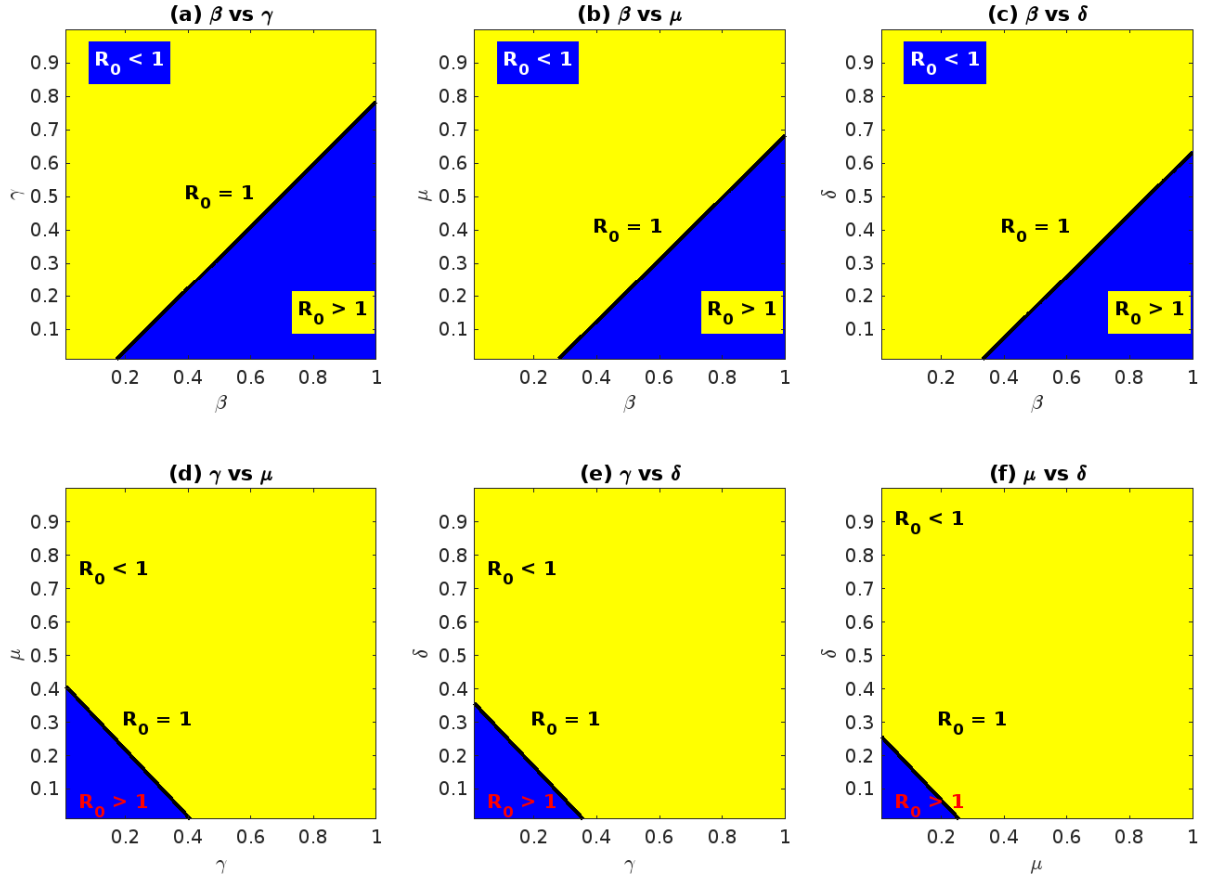


Figure 2: Two parameters bifurcation diagrams

## 8 Sensitivity analysis

Sensitivity analysis helps us understand how changes in model parameters affect the output of a mathematical model. In epidemiological models (like yours for HPV and cervical cancer), this tells us which parameters have the most influence on things like the basic reproduction number or endemic equilibrium.

### Local sensitivity index

We compute the sensitivity indices of the basic reproduction number  $R_0$  to identify the parameters with the most significant impact. This helps determine which factors should be targeted to improve intervention strategies. The normalized forward sensitivity index of a variable  $L$  that depends on the differentiability of a parameter  $p$  is defined as:

$$\Upsilon_{R_0}^p = \frac{p}{R_0} \times \frac{\partial R_0}{\partial p}.$$

Including the immunity loss parameter  $\alpha$ , the sensitivity indices of  $R_0$  with respect to the model parameters become:

$$\begin{aligned}
\Upsilon_{R_0}^\beta &= 1, & (\text{Transmission rate}) \\
\Upsilon_{R_0}^\Lambda &= 1, & (\text{Recruitment rate}) \\
\Upsilon_{R_0}^\gamma &= -\frac{\gamma}{\delta + \gamma + \mu}, & (\text{Recovery rate, without } \alpha) \\
\Upsilon_{R_0}^\delta &= -\frac{\delta}{\delta + \gamma + \mu}, & (\text{Progression rate to cancer}) \\
\Upsilon_{R_0}^\mu &= -\frac{\delta + \gamma + 2\mu}{\delta + \gamma + \mu}, & (\text{Natural mortality rate})
\end{aligned}$$

Parameter	Description	Values (year) <sup>-1</sup>
$\gamma$	Recovery rate due to natural immunity	0.2
$\delta$	Progression rate of HPV to cervical cancer	0.008
$\mu$	Natural rate of mortality	0.012

Table 3: Estimated parameter values and description of the model

Parameter	Sensitivity index
$\Upsilon_{R_0}^\beta$	1
$\Upsilon_{R_0}^\Lambda$	1
$\Upsilon_{R_0}^\gamma$	-0.90
$\Upsilon_{R_0}^\delta$	-0.036
$\Upsilon_{R_0}^\mu$	-1.05

Table 4: Sensitivity indices of  $\mathcal{R}_0$  with respect to parameters given in Table 3

The sensitivity analysis of the basic reproduction number  $R_0$  with respect to model parameters shows that the transmission rate  $\beta$  and recruitment rate  $\Lambda$  have the greatest influence, each with a sensitivity index of 1. This means that a 1% increase in either parameter leads to a 1% increase in  $R_0$ , since individuals who progress to the cancer class  $C$  are no longer contributing to new infections thus reducing the infectious population. Both the recovery rate  $\gamma$  and the natural mortality rate  $\mu$  also have a negative impact on  $R_0$ , implying that faster recovery or higher death rates suppress disease transmission. In contrast, the immunity loss rate  $\alpha$  has no effect on  $R_0$ , as its sensitivity index is zero.

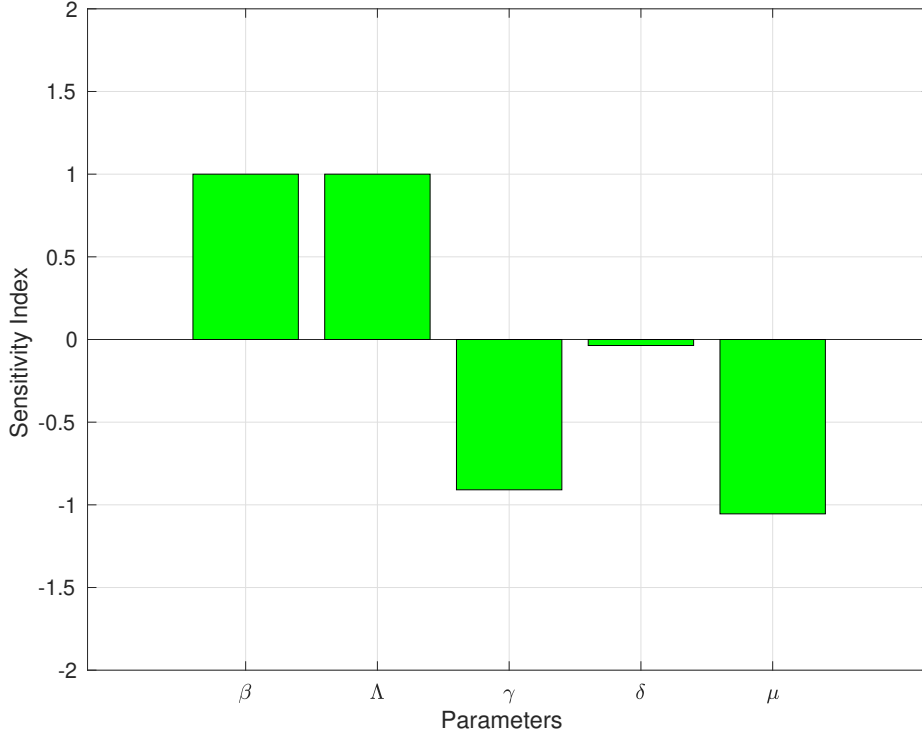


Figure 3: Sensitivity indices of  $R_0$  with respect to model parameters

## Partial Rank Correlation Coefficients (PRCC)

Parameter	Description	Values (year) <sup>-1</sup>
$\Lambda$	Recruitment rate into the susceptible individuals	(5, 40)
$\beta$	Transmission rate of contact with individuals	(0.1, 1.0)
$\alpha'$	Saturation factor	(0.005, 0.02)
$\gamma$	Recovery rate due to natural immunity	(0.01, 1.0)
$\delta$	Progression rate of HPV to cervical cancer	(0.001, 0.6)
$\xi$	Death rate of individuals with cervical cancer	(0.1, 0.25)
$\mu$	Natural rate of mortality	(0.01, 0.8)
$\alpha$	Rate of loss of immunity	(0.01, 0.2)

Table 5: Estimated parameter values and description of the model (2.1)

The PRCC analysis the main factors driving disease transmission. The recruitment rate ( $\Lambda$ ) and the transmission rate ( $\beta$ ) emerge as the most influential parameters, suggesting that controlling new entries in the susceptible population and reducing contact-based transmission are the most effective ways to reduce  $R_0$ . In contrast, parameters such as the mortality rate ( $\mu$ ) and the progression rate ( $\delta$ ) have a minimal impact, emphasizing that while these factors are important for individual health outcomes, they do not significantly alter the dynamics of broader spread of the disease.

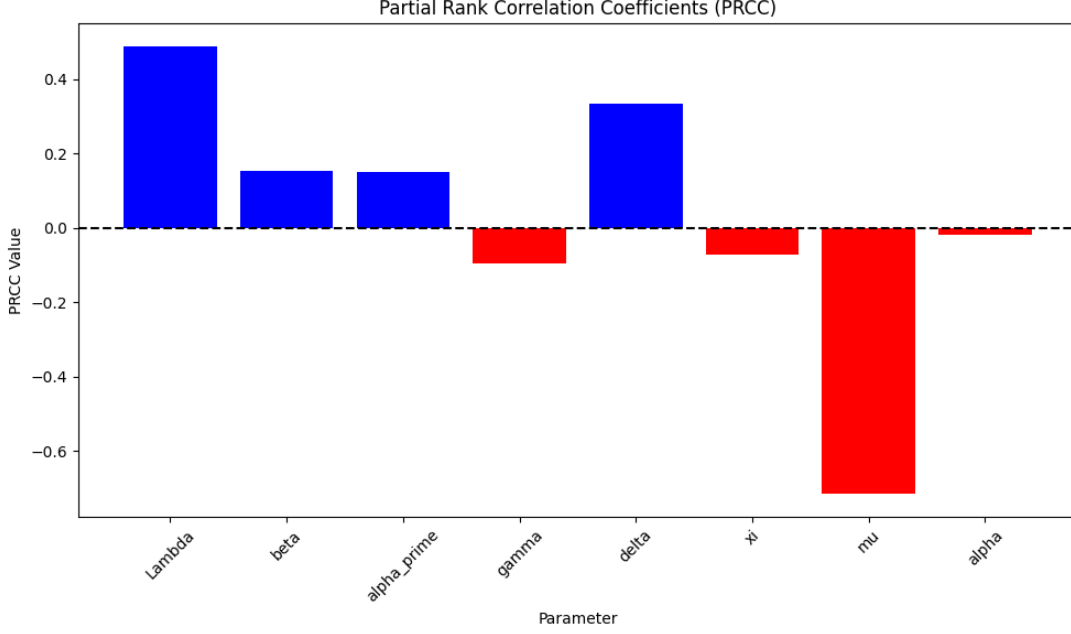


Figure 4: PRCC results capturing the sensitivity indices of parameters with  $R_0$

## 9 Numerical simulations

In this section, we perform numerical simulations to meticulously examine the intricate dynamics of the deterministic model (2.1) to substantiate the theoretical insights expounded in the previous sections. Through careful selection of parameter values, we embark on a comprehensive exploration and analysis of the system's complete dynamical profile, encompassing aspects such as stability analysis. To execute numerical computations, we harness the computational capabilities offered by MATLAB, MATCONT and MATHEMATICA software tools.

### Time Series for disease-free equilibrium

Here, we analyze the stability behavior of the Disease-Free Equilibrium (DFE) using the updated parameter values that satisfy the condition  $\mu > 0.0765$ , while maintaining similar system dynamics.

#### Parameter Values:

$$\Lambda = 36, \quad \beta = 0.30, \quad \mu = 0.08, \quad \alpha = 0.12, \quad \delta = 0.18, \quad \gamma = 0.4, \quad \xi = 0.2, \quad \alpha' = 0.01.$$

The basic reproduction number  $R_0$  for this model is given by:

$$R_0 = \frac{\tilde{S} \cdot \beta}{\gamma + \mu + \delta}, \quad \text{where } \tilde{S} = \frac{S_0}{N_0}.$$

Substituting the values:

$$\tilde{S} = \frac{421.896}{451.815} \approx 0.9338, \quad \text{and } \gamma + \mu + \delta = 0.4 + 0.08 + 0.18 = 0.66,$$

$$\Rightarrow R_0 = \frac{0.9338 \cdot 0.30}{0.66} \approx 0.4246 < 1.$$

Thus, the basic reproduction number is below 1, suggesting that the infection will eventually die out.

The disease-free equilibrium is:

$$E_0 = (S^*, I^*, C^*, R^*) = (S^*, 0, 0, 0),$$

$$\text{where } S^* = \frac{\Lambda}{\mu} = \frac{36}{0.08} = 450.$$

**Eigenvalues of the Jacobian at DFE:**

$$\lambda_1 = -\mu = -0.08,$$

$$\lambda_2 = \frac{\beta\Lambda}{\mu N_0} - (\gamma + \mu + \delta) = -0.3613,$$

$$\lambda_3 = -(\delta + \mu + \xi) = -(0.18 + 0.08 + 0.2) = -0.46,$$

$$\lambda_4 = -(\alpha + \mu) = -(0.12 + 0.08) = -0.20.$$

Since all eigenvalues are negative, the DFE  $E_0$  is locally asymptotically stable under the modified parameter regime as well.

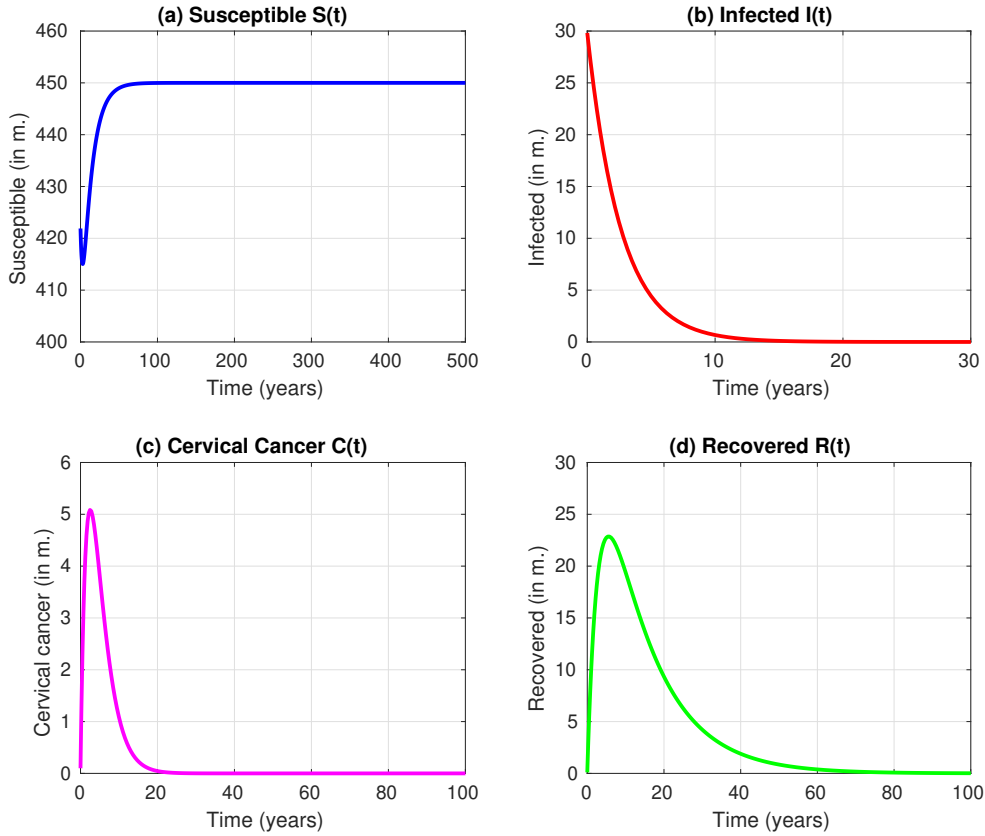


Figure 5: Stability analysis for Disease free Equilibrium  $E_0(450, 0, 0, 0)$  with initial conditions  $(421.896, 29.819, 0.0991, 0.1)$



## Time series for endemic equilibrium

Now, the numerical simulation for the Endemic Equilibrium (EE) point corresponding to the following parameter values:

$$\Lambda = 8.8, \quad \beta = 0.41, \quad \mu = 0.012, \quad \alpha = 0.012, \quad \delta = 0.008, \quad \gamma = 0.2, \quad \xi = 0.001, \quad \alpha' = 0.5714$$

The basic reproduction number is calculated as:

$$R_0 = \frac{(S_0/N_0) \cdot \beta}{\gamma + \mu + \delta} \approx 1.7453 > 1.$$

Thus, the endemic equilibrium point is approximately:

$$E_1(S^*, I^*, C^*, R^*) \equiv E_1(403.79, 12.85, 18.24, 296.16).$$

The eigenvalues of the Jacobian matrix at  $E_1$  are:

$$\begin{aligned} \lambda_1 &= -0.0211 + 0.0141i, \\ \lambda_2 &= -0.0211 - 0.0141i, \\ \lambda_3 &= -0.0194, \\ \lambda_4 &= -0.012. \end{aligned}$$

Since all eigenvalues have negative real parts, the endemic equilibrium  $E_1$  is locally asymptotically stable. Therefore, any small perturbations will decay over time and the system will return to equilibrium.

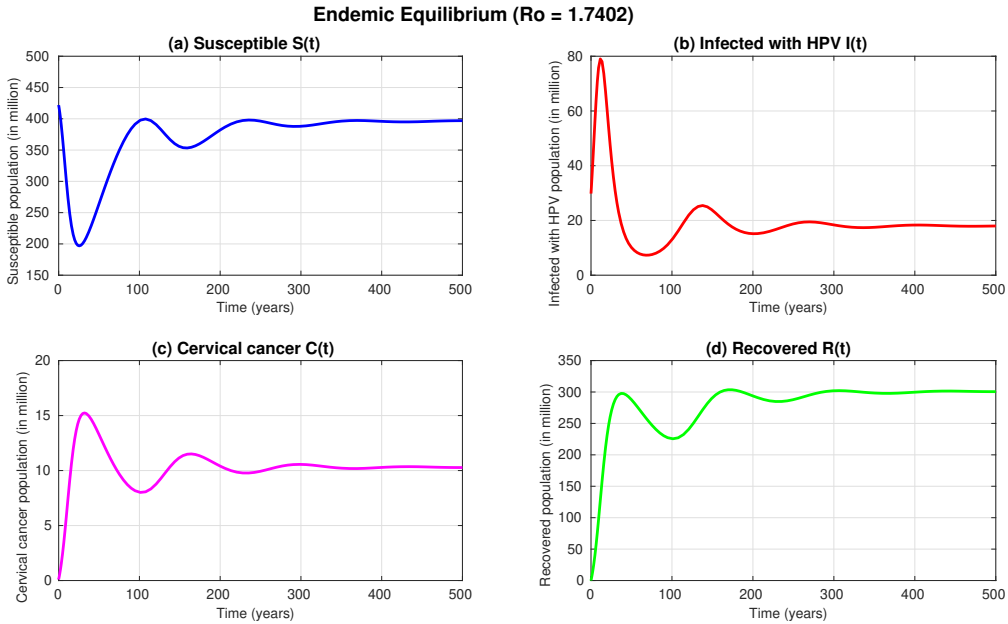


Figure 6: Stability analysis for Endemic Equilibrium  $E_1(403.79, 12.85, 18.24, 296.16)$  with initial conditions  $(421.896, 29.819, 0.0991, 0.1)$

## 10 Conclusion

- This project developed a mathematical model to study the spread of HPV infection and its progression to cervical cancer using a system of differential equations.
- The basic reproduction number  $R_0$  was derived to determine the conditions for disease persistence or elimination.
- Stability analysis showed that:
  - When  $R_0 < 1$ , the disease-free equilibrium (DFE) is globally stable, meaning the infection dies out.
  - When  $R_0 > 1$ , an endemic equilibrium (EE) appears, indicating the infection persists in the population.
- A bifurcation analysis at  $R_0 = 1$  confirmed a transcritical bifurcation, where the stability of equilibria shifts as  $R_0$  crosses the threshold.
- Numerical simulations illustrated the time evolution of different population groups (susceptible, infected, cancer cases, and recovered individuals), validating the theoretical findings.
- The study emphasizes that reducing HPV transmission (e.g., through vaccination and treatment) can lower  $R_0$  and prevent cervical cancer cases.
- Future improvements could include:
  - Incorporating vaccination strategies and age-structured models.
  - Analyzing seasonal effects and external interventions.
  - Extending the model to study co-infections with other diseases.
- Overall, this project highlights how mathematical modeling helps understand disease dynamics and supports public health strategies to control HPV and cervical cancer.

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