Epidemiology For Cervical Cancer Prevention And Assess The Impact Of Pre-Vaccinated Indivisuals: Mathematical Modelling Analysis

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Abstract **- In this paper we have developed and analyzed a non-linear transmission mathematical model in the compartmental epidemic system of infectious disease with the assumption that the population is in the homogeneous environment and all the susceptible individuals are vaccinated properly, and to assess the impact of vaccination and progression to cervical cancer. In this we discussed an SIQCR epidemic infectious disease model with non-linear incidence rate. The value of reproduction number is defined and it is obtained that the disease-free equilibrium point is stable if R01. The linear and global stability for the model is also discussed. Finally, a numerical solution is given for the proposed epidemic model in support of the result.**

keywords **- HPV (Human Papillomavirus), Cervical Cancer, Epidemic, Infectious Disease, Pre-Cancerous Stage, Stability.**

I. INTRODUCTION

Every year, in excess of 300 000 people pass on of cervical disease. The greater part a million people are diagnosed. Every minute, one individual is diagnosed. Cervical disease is one of the greatest dangers to human wellbeing. Every demise is a catastrophe, and can be anticipated. The majority of these people are not diagnosed early enough, and need access to life-sparing treatment. Studies have demonstrated that avoidance and early treatment of cervical malignancy are additionally exceedingly practical [1]. As indicated by WHO (World Health Organization), Cervical cancer is the second most common cancer in human living in less developed regions with an estimated 570 000 new cases in 2018 (84% of the new cases worldwide). In 2018, around 311 000 individuals kicked the bucket from cervical cancer; over 85% of these deaths occurring in low- and middle-income nations. Cervical cancer is a standout amongst the most preventable and curable forms of cancer, as long as it is detected early and managed effectively. New diagnoses can be reduced in two ways, HPV vaccination and screening of the cervix with follow on treatment of early changes before cancer appears. Comprehensive cervical cancer control includes primary prevention (vaccination against HPV), secondary prevention (screening and treatment of pre-cancerous lesions), tertiary prevention (diagnosis and treatment of invasive cervical cancer) and palliative care. Cervical cancer can be cured if diagnosed at an early stage [2].

Human papillomavirus (HPV) is a gathering of infections or group of viruses that are incredibly basic around the world. There are in excess of 100 kinds of HPV, of which at least 14 are cancer-causing (otherwise called high hazard type). HPV is predominantly transmitted through sexual contact and the vast majority are tainted with HPV not long after the beginning of sexual action. Cervical cancer growth is brought about by explicitly obtained contamination with particular kinds of HPV. Two HPV types (16 and 18) cause 70% of cervical cancers and pre-carcinogenic cervical lesions. [3] Human papillomavirus (HPV) is the most well-known viral contamination of the conceptive tract. Most sexually active individuals will be tainted eventually in their lives and some might be over and over infected.There are as of now 3 vaccines securing against both HPV 16 and 18, which are known to cause at least 70% of cervical cancers. The third vaccine secures against three extra oncogentic HPV types, which cause a further 20% of cervical cancers. Given that the vaccines which are just securing against HPV 16 and 18 likewise have some cross-protection against different less common HPV types which cause cervical cancer, WHO considers the three antibodies (vaccines) similarly defensive against cervical disease. Two of the antibodies additionally secure against HPV types 6 and 11, which cause anogenital moles. [4] Clinical preliminaries and post-promoting observation have demonstrated that HPV immunizations are extremely protected and compelling in counteracting diseases with HPV infections.HPV antibodies work best whenever managed preceding introduction to HPV. Accordingly, WHO prescribes to inoculate young individuals, matured somewhere in the range of 9 and 14 years, when most have not begun sexual action [5].

Mathematical modelling has turned out to be significant tools in examining the spread and control of irresistible illnesses. Mathematical models consider primary factors that oversee advancement of disease, for example, transmission and recuperation rates and anticipate how the infection will spread over some stretch of time. It is notable that the spread of numerous irresistible maladies can be counteracted by immunization of the susceptible population [6]. Moreover, a few diseases furnish recouped people with a short or long immunity against re-contamination. Immunity can be achieved through focused immunization. Immunization is one of the procedures to control irresistible diseases. One can research under what conditions a given specialist can attack a (somewhat) vaccinated population, i.e., how large a fraction of the population must be maintained immunized in control to keep the operator from building up[7]. Mathematical models including inoculation go for settling on an immunization

technique and deciding changes in qualitative behavior that could result from such a control measure. The model we propose will be analyzed qualitatively to decide the ideal antibody inclusion level expected to successfully control or destroy the sickness.

The present examination is progressively reasonable as it incorporates natural recovery, which has not been given much unmistakable quality already. Motivated by the work of Capasso and Serio, in this paper, we consider a SIQCR pandemic model with nonlinear saturation occurrence rate. For the most part, a model contains a disease-free equilibrium and one more endemic equilibrium. The stability of a disease-free steady state just as the presence of other non-trifling equilibria can be resolved utilizing the purported basic reproduction number, which quantities how many secondary infections appear from a single infected exposed in a population of susceptible. At the point when the basic reproduction number is less than unity, the disease-free equilibrium is locally asymptotically stable, and, therefore the disease dies out after some period of times. Similarity, when the endemic equilibrium is a global attractor, epidemiologically means that the disease will prevail and persist in the population. The aim of this paper is to propose an epidemic model, to investigate its global dynamics and predict the optimal vaccination coverage needed to insure the disease eradication from the population, when all susceptible individuals are properly vaccinated.

II. Formulation Of Mathematical Model

In this part, we shall formulate the dynamic model system as in [8, 9] with saturation incidence rate of the infection.Here, we proposed a SIQCR epidemic mathematical model of the assumed situation which is governed by the following ordinary differential equations:

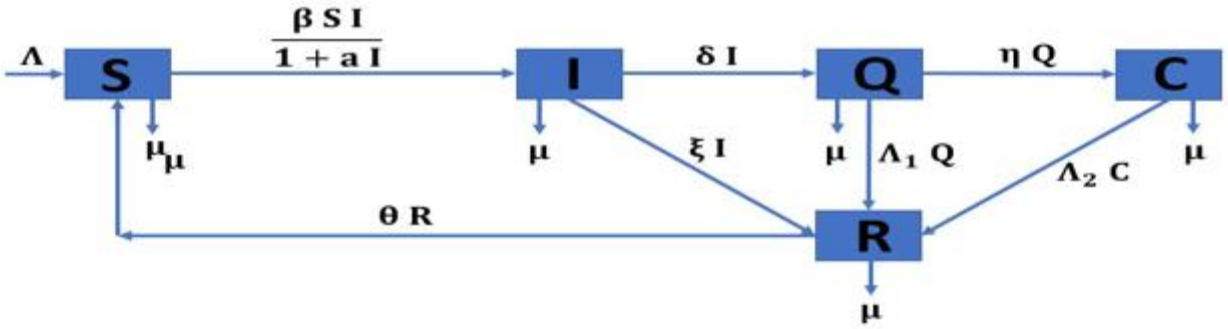

Figure 1: Schematic flow of proposed mathematical model

$$\frac{dS}{dt} = \Lambda - \frac{\beta SI}{1+aI} - \mu S + \theta R, \tag{1}$$

$$\frac{dI}{dt} = \frac{\beta SI}{1+aI} - \delta I - \xi I - \mu I, \tag{2}$$

$$\frac{dQ}{dt} = \delta E - \mu Q - \Lambda_1 Q - \eta Q, \tag{3}$$

$$\frac{dC}{dt} = \eta Q - \mu C - \Lambda_2 C, \tag{4}$$

$$\frac{dR}{dt} = \Lambda_1 Q + \Lambda_2 C + \xi I - \mu R - \theta R, \tag{5}$$

with the following initial conditions:

$$S(0) = S_0 > 0, \quad I(0) = I_0 > 0, \quad Q(0) = Q_0 > 0, \quad C(0) = C_0 > 0, \quad R(0) = R_0 > 0.$$

where N is whole population at the time t and $N = S + I + Q + C + R$,. All the parameters have positive identity. The definitions of all the parameters are outlined in Table 1.

Table 1: Descriptions of parameters used in this proposed model system (1)-(5)

Parameters	Definition	Dimension
S	Susceptible population	——
I	Infectious population	——
Q	Pre-cancered population	——
C	Cervical cancered population	——
R	Recovered population	——
Λ	Susceptible's recruitment rate	$days^{-1}$
β	Coefficient of transmission for infected individuals	$days^{-1}$
$\frac{1}{a}$	Constant of half-saturation for infected individuals	——
μ	Natural death rate	$days^{-1}$
θ	Transfer rate for recovered individuals to susceptible	$days^{-1}$
ξ	Rate of recovered for infectious individuals	$days^{-1}$
δ	Rate of Pre-cancered for infectious individuals	$days^{-1}$
η	Rate of cancered individuals for pre-cancered individuals	$days^{-1}$
Λ_1	Rate of recovery for pre-cancered individuals	$days^{-1}$
Λ_2	Rate of recovery for cancered individuals	$days^{-1}$

III. Analysis Of The Model

In this part, we have analyzed R_0 the basic reproduction number, equilibrium points for all the feasible states, local and global stability for both the states (disease-free and endemic).

Suppose that the size of the whole population is N verifies $\frac{dN}{dt} = \Lambda - \mu N$, thus $N(t) \to \frac{\Lambda}{\mu}$, as $t \to \infty$. Hence, feasibly biological state

$$\Omega = \left\{(S,\ I,\ Q,\ C,\ R): 0 \le S,\ I,\ Q,\ C,\ R,\ S+I+Q+C+R \le \frac{\Lambda}{\mu}\right\},$$

positive which are invariant for the model system (1)-(5).

Basic Reproduction Number

The next generation matrix for the model system (1)-(5) is,

$$K = \mathrm{FV}^{-1} = \begin{bmatrix} \frac{\beta S^0}{\xi+\delta+\mu} & 0 & 0] \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}.$$

Further, the radius of spectral R_0 of matrix $K = \mathrm{FV}^{-1}$, is R_0 of the system model, which is, $R_0 = \rho(\mathrm{FV}^{-1})$, thus

$$R_0 = \frac{\beta S^0}{\xi+\delta+\mu}. \tag{6}$$

Since,

$$S_0 = \frac{\Lambda}{\mu}, \tag{7}$$

$$R_0 = \frac{\beta\Lambda}{(\mu)(\xi+\delta+\mu)}. \tag{8}$$

Interior Equilibrium Points

Here, we analyze that the model system (1)-(5) also have endemic equilibrium or interior equilibrium, which is given as,

$$\bar{E} = (S^*, I^*, Q^*, C^*, R^*),$$

where,

$$S^* = \frac{(\delta+\mu+\xi)[a\Lambda(\theta+\mu)(\eta+\Lambda_1+\mu)(\Lambda_2+\mu)+\mu[\delta[(\theta+\Lambda_1+\mu)(\Lambda_2+\mu)+\eta(\theta+\Lambda_2+\mu)]+(\eta+\Lambda_1+\mu)(\Lambda_2+\mu)(\theta+\mu+\xi)]]}{\mu[a(\theta+\mu)(\eta+\Lambda_1+\mu)(\Lambda_2+\mu)(\delta+\mu+\xi)+\beta[\delta[(\theta+\Lambda_1+\mu)(\Lambda_2+\mu)+\eta(\theta+\Lambda_2+\mu)]+(\eta+\Lambda_1+\mu)(\Lambda_2+\mu)(\theta+\mu+\xi)]]}$$

$$I^* = \frac{(\theta+\mu)(\eta+\Lambda_1+\mu)(\Lambda_2+\mu)(-\beta\Lambda+\mu(\delta+\mu+\xi))}{\mu[a(\theta+\mu)(\eta+\Lambda_1+\mu)(\Lambda_2+\mu)(\delta+\mu+\xi)+\beta[\delta[(\theta+\Lambda_1+\mu)(\Lambda_2+\mu)+\eta(\theta+\Lambda_2+\mu)]+(\eta+\Lambda_1+\mu)(\Lambda_2+\mu)(\theta+\mu+\xi)]]},$$

$$Q^* = \frac{\delta(\theta+\mu)(\Lambda_2+\mu)(-\beta\Lambda+\mu(\delta+\mu+\xi))}{\mu[a(\theta+\mu)(\eta+\Lambda_1+\mu)(\Lambda_2+\mu)(\delta+\mu+\xi)+\beta[\delta[(\theta+\Lambda_1+\mu)(\Lambda_2+\mu)+\eta(\theta+\Lambda_2+\mu)]+(\eta+\Lambda_1+\mu)(\Lambda_2+\mu)(\theta+\mu+\xi)]]},$$

$$C^* = \frac{\delta\eta(\theta+\mu)(-\beta\Lambda+\mu(\delta+\mu+\xi))}{\mu[a(\theta+\mu)(\eta+\Lambda_1+\mu)(\Lambda_2+\mu)(\delta+\mu+\xi)+\beta[\delta[(\theta+\Lambda_1+\mu)(\Lambda_2+\mu)+\eta(\theta+\Lambda_2+\mu)]+(\eta+\Lambda_1+\mu)(\Lambda_2+\mu)(\theta+\mu+\xi)]]},$$

$$R^* = \frac{[\delta(\eta+\Lambda_1)\Lambda_2+\delta\Lambda_1\mu+(\eta+\Lambda_1+\mu)(\Lambda_2+\mu)\xi](-\beta\Lambda+\mu(\delta+\mu+\xi))}{\mu[a(\theta+\mu)(\eta+\Lambda_1+\mu)(\Lambda_2+\mu)(\delta+\mu+\xi)+\beta[\delta[(\theta+\Lambda_1+\mu)(\Lambda_2+\mu)+\eta(\theta+\Lambda_2+\mu)]+(\eta+\Lambda_1+\mu)(\Lambda_2+\mu)(\theta+\mu+\xi)]]},$$

According to above equations, we can say that the equilibrium points for endemic state are exist if and only if $R_0 > 1$.

Local Stability Analysis

We can assumed that the total population is to be constant $N = N^0 = \frac{\Lambda}{\mu}$. Then, the normalized dynamical system is given by:

$$\frac{dS}{dt} = \Lambda(1+\frac{\theta}{\mu}) - (\mu+\theta)S - \frac{\beta SI}{1+aI} - \theta I - \theta Q - \theta C, \tag{9}$$

$$\frac{dI}{dt} = \frac{\beta SI}{1+aI} - \xi I - \delta I - \mu I, \tag{10}$$

$$\frac{dQ}{dt} = \delta I - \mu Q - \Lambda_1 Q - \eta Q, \tag{11}$$

$$\frac{dC}{dt} = \eta Q - \mu C - \Lambda_2 C, \tag{12}$$

with the initial conditions:

$$S(0) = S_0 > 0, \qquad I(0) = I_0 > 0, \qquad Q(0) = Q_0 > 0, \qquad C(0) = C_0 > 0.$$

The local stability for disease-free equilibrium and endemic equilibrium are analyzed as follows:

a. For Disease-Free Equilibrium

The variational matrix for disease-free equilibrium is given as,

$$J_0 = \begin{bmatrix} -(\mu+\theta) & \frac{-\beta\Lambda}{\mu} - \theta & -\theta & -\theta \\ 0 & \frac{\beta\Lambda}{\mu} - \delta - \xi - \mu & 0 & 0 \\ 0 & \delta & -(\mu+\Lambda_1+\eta) & 0 \\ 0 & 0 & \eta & -(\mu+\Lambda_2) \end{bmatrix}.$$

By solving this given matrix we get the all four roots of J_0, which are follows as,

$$\lambda = (-\theta - \mu), \lambda = (-\mu - \Lambda_1 - \eta), \lambda = (-\mu - \Lambda_2), \lambda = (-\mu + \delta + \xi - \frac{\beta\Lambda}{\mu})$$

By all the four roots, we can say that the model system (9-12) is locally asymptotically stable for the disease-free equilibrium.

b. For Endemic Equilibrium

The variational matrix for endemic equilibrium is given as,

$$J_0 = \begin{bmatrix} -(\mu + \theta + \frac{\beta I}{1+aI}) & \frac{-\beta S}{(1+aI)^2} - \theta & -\theta & -\theta \\ \frac{\beta I}{1+aI} & \frac{\beta S}{(1+aI)^2} - \delta - \xi - \mu & 0 & 0 \\ 0 & \delta & -(\mu + \Lambda_1 + \eta) & 0 \\ 0 & 0 & \eta & -(\mu + \Lambda_2) \end{bmatrix}.$$

Now, By solving this we get the characteristics equation of J is,

$$\lambda^4 + \lambda^3 A_1 + \lambda^2 A_2 + \lambda^1 A_3 + A_4 = 0,$$

where, we can get the value of A_1, A_2, A_3 and A_4 easily. Now, for the all four roots of the characteristics equation, we have to apply the Routh-Hurwitz Criterion,

$$A_1 A_2 A_3 > (A_3)^2 + (A_1)^2 A_4,$$

where, $A_1 > 0$, $A_2 > 0$, $A_3 > 0$, and $A_4 > 0$.

By the above discussion, we can say that the model system (9-12) is locally asymptotically stable for the endemic equilibrium.

Global Stability Analysis

a. For Disease-Free Equilibrium

We analyze the global stability of disease-free equilibrium by the method given by Castillo-Chavez, which gives two conditions for the global stability of DFE, which are as follows:

Let $Z = (I,\ Q)$ and $X = (S)$, and

$$Q_0 = (X^0,\ 0), where \quad X^0 = \frac{\Lambda}{\mu}. \tag{13}$$

Then,

$$\frac{dX}{dt} = F(X, \quad Z) = \Lambda(1 + \frac{\theta}{\mu}) - (\mu + \theta)S - \frac{\beta SI}{1 + aI} - \theta I - \theta Q - \theta C.$$

At $S = S^0$, $G(X,\ 0) = 0$ and $\frac{dX}{dt} = F(X,\ 0) = \Lambda(1 + \frac{\theta}{\mu}) - (\mu + \theta)X$.

As $X \to X^0$, $t \to \infty$. Therefore, $X = X^0 (= S^0)$ is g.a.s.

Now,

$$G(X,Z) = \begin{bmatrix} \beta S^0 - (\mu + \xi + \delta) & 0 & 0 \\ \delta & -(\mu + \Lambda_1 + \eta) & 0 \\ 0 & \eta & -(\mu + \Lambda_2) \end{bmatrix} \begin{bmatrix} I \\ Q \\ C \end{bmatrix} - \begin{bmatrix} \beta S^0 I - \frac{\beta SI}{1 + aI} \\ 0 \\ 0 \end{bmatrix},$$

which is, $G(X,\ Z) = BZ - \hat{G}(X,\ Z)$,

Thus both the conditions are satisfied, therefore the DFE E^0 is globally asymptotically stable.

b. For Endemic Equilibrium

We analyze the global stability of endemic equilibrium by Lyapunov's Direct Method of Stability, which is as follows:

Consider a positive definite function:

$$V_1 = \frac{1}{2}(D_1 S^2 + D_2 I^2 + D_3 Q^2 + D_4 C^2), \tag{14}$$

Then using the system (9)-(12) in $\frac{dV_1}{dt}$, we get,

$$\frac{dV_1}{dt} = D_1(\Lambda S + \frac{\theta\Lambda S}{\mu} - \mu S^2 - \theta S^2 - \theta SI - \theta SQ - \theta SC) + D_2(-\xi I^2 - \delta I^2 - \mu I^2) + D_3(\delta IQ - \mu Q^2 - \Lambda_1 Q^2 - \eta Q^2) + D_4(\eta QC - \mu C^2 - \Lambda_2 C^2), \tag{15}$$

Now using the inequality $\pm 2ab \le (a^2 + b^2)$ and also using region Ω on the right hand side of the above equation, we get:

$$\frac{dV_1}{dt} \le -[(\frac{b_{11}S^2}{3} - b_{12}SI + \frac{b_{22}I^2}{4}) + (\frac{b_{11}S^2}{2} - b_{13}SQ + \frac{b_{33}Q^2}{3}) + (\frac{b_{11}S^2}{2} - b_{14}SC + \frac{b_{44}C^2}{2}) + (\frac{b_{22}I^2}{4} - b_{23}IQ + \frac{b_{33}Q^2}{2}) + (\frac{b_{33}Q^2}{2} - b_{34}QC + \frac{b_{44}C^2}{2}), \tag{16}$$

where,

$$b_{11} = D_1(\mu + \theta - \frac{\beta\Lambda}{2\mu}), b_{22} = D_2(\xi + \delta + \mu - \frac{\beta\Lambda}{2\mu}), b_{33} = D_3(\mu + \Lambda_1 + \eta),$$
$$b_{44} = D_4(\mu + \Lambda_2), b_{12} = D_1\theta, b_{13} = D_1\theta, b_{14} = D_1\theta, b_{23} = D_3\delta, b_{34} = D_4\eta.$$

Hence by Lyapunov's direct method of stability, we find that the required conditions for global stability of endemic equilibrium are:

$(1)[\mu + \theta - \frac{\beta\Lambda}{2\mu}] > 0.$

$(2)[\mu + \xi + \delta - \frac{\beta\Lambda}{2\mu}] > 0.$

$(3)[\mu + \theta - \frac{\beta\Lambda}{2\mu}][\mu + \xi + \delta - \frac{\beta\Lambda}{2\mu}] > [\theta^2].$

Thus, we show that endemic equilibrium point $\bar{E}$ is globally asymptotically stable under the above-mentioned conditions.

IV. NUMERICAL SIMULATION

In this part, we will discuss the result by numerical simulation of the model with the help of the parametric values given in the previously researched paper namely, "Epidemiology of cervical cancer with special focus in India" [10].

(1) When the infection rate $\beta = 0.004$, we get the effective reproduction number $R_0 = 0.128 < 1$. The disease free equilibrium $E^0(8,\ 0,\ 0,\ 0,\ 0)$ is globally asymptotically stable (See Figure 2).

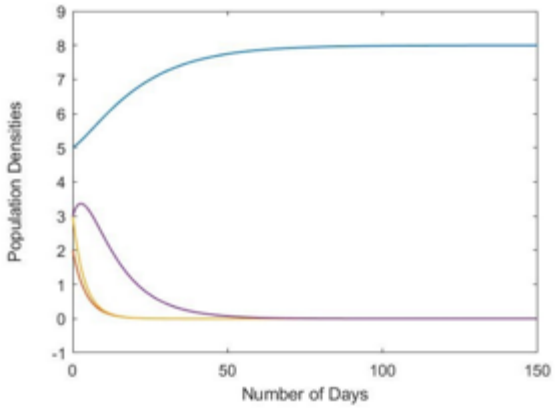

Figure 2: Population densities at infection rate $\beta = 0.004$.

(2) When the infection rate $\beta = 0.04$, we get the effective reproduction number $R_0 = 1.28 > 1$. The endemic equilibrium $\bar{E}(30.8024,\ 5.07162,\ 1.53685,\ 3.41523,\ 12.7787)$ is globally asymptotically stable under the above conditions. (See Figure 3).

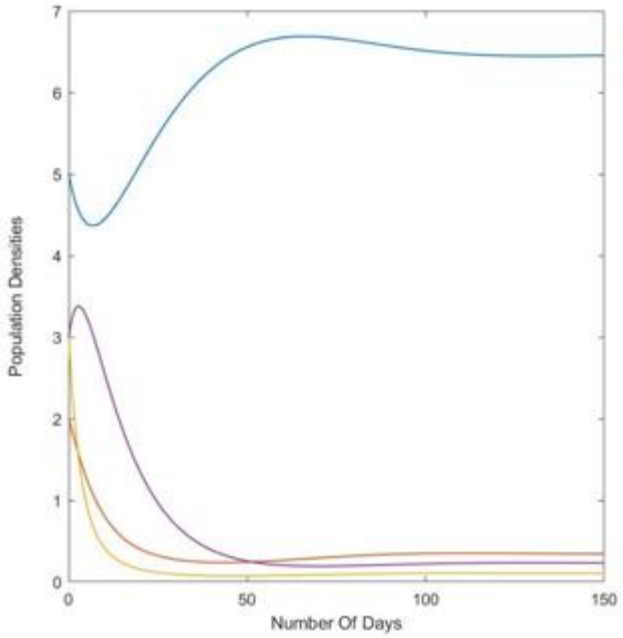

Figure 3: Population densities at infection rate $\beta = 0.04$.

V. CONCLUSION

In this paper, we discussed an epidemic infectious disease model for cervical cancer with non-linear saturation incidence rate. This model exists in two non-negative feasible steady states, like as, the endemic equilibrium and the disease-free equilibrium. Further, the increase in the infection rate obtains from the basic reproduction number (R_0). The qualitative features of the model depend on R_0. Also, determined the linear and non-linear stability conditions for both the equilibrium of the system.Numerical Simulation has done for the proposed model which takes previously researched parametric values to support our systematic findings. Given the importance of our model for understanding the biology, epidemiology, and policy implications of HPV infection and cervical carcinogenesis, serious consideration should be given to the development of a consensus model, for general use.

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