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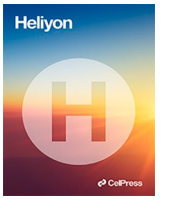

Research article

In-host density-dependent model of high-risk HPV virions, basal cells, lymphocytes t-cells incorporating functional responses

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ABSTRACT

Cervical cancer is one of the most common types of cancer and it is caused mostly by high-risk Human Papillomavirus (HPV) and continues to spread at an alarming rate. While HPV impacts have been investigated before, there are currently only a scanty number of mathematical models that account for HPV's dynamic role in cervical cancer. The objectives were to develop an in-host density-dependent deterministic model for the dynamics implications of basal cells, virions, and lymphocytes incorporating immunity and functional responses. Analyze the model using techniques of epidemiological models such as basic reproduction number and simulate the model using Matlab ODE solver. Six compartments are considered in the model that is; Susceptible cells (S), Infected cells (I), Precancerous cells (P), Cancerous cells (C), Virions (V), and Lymphocytes (L). Next generation matrix (NGM), survival function, and characteristic polynomial method were used to determine the basic reproduction number denoted as R_0. R_0 was obtained using three methods because NGM has some weaknesses hence the need for the other two methods. The findings from this research indicated that Disease-Free Equilibrium point is locally asymptotically stable whenever $R_0^* < 1$ and globally asymptotically stable if $R_0^* \leq 1$ and the Endemic Equilibrium is globally asymptotically stable if $R_0^* > 1$. The results obtained shows that the progression rate of precancerous cells to cancerous cells (θ) has the most direct impact on the model. The model was able to estimate the longevity of a patient as 10 days when (θ) increases by 0.08. The findings of this research will help healthcare providers, public health authorities, and non-governmental health groups in creating effective prevention strategies to slow the development of cervical cancer. More research should be done to determine the exact number of cancerous cells that can lead to the death of a cervical cancer patient since this paper estimated a proportion of 75%.

1. Introduction

According to Ref. [1], cervical cancer arises from the uncontrolled, invasive proliferation of epithelial cells in the cervix, the area of the uterus that attaches to the vagina. Human Papillomavirus (HPV) is the main cause of cervical cancer, and in over 90 % of instances,

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HPV infection contributes to the development of cancer [1]. Small double-stranded DNA viruses with a diameter of 52–55 nm are known as human papillomaviruses (HPV) [2]. There are more than 100 varieties of Human Papillomavirus, but the types that cause cervical cancer are high-risk HPV 16 and 18 [3,4]. Sexual contact between people can spread the sexually transmitted virus HPV [5]. This is often through a cut, abrasion, or a small tear in the skin and sexual activity without protection [6]. Some of the risk factors of cervical cancer include tobacco usage, harmful alcohol consumption, overweight, obesity, age, the individual's sex, and genetic or inherited factors, exposure to carcinogens in the environment, such as chemicals, radiation, and infectious agents [7] (see Figs. 7–15).

The dynamics of HPV to cervical cancer are clearly shown in Fig. 1 [8].

One of the main causes of morbidity and death worldwide is cervical cancer. According to a 2018 World Health Organization (WHO) fact sheet, approximately 311,000 women worldwide lost their lives to cervical cancer in 2018, making it the fourth most common malignancy among women globally and a global health concern [9]. In 2020 the estimated number of deaths worldwide was 342,000. Focusing on women's health is necessary to achieve Sustainable Development Goals (SDG) targets 3.4 and 5, which are to lower premature mortality from non-communicable diseases (NCDs) by a third by 2030 compared to 2015 levels, to enhance mental health and well-being, and to achieve gender equality and empower all women and girls, respectively [10]. The estimated number of secondary infections triggered by an index case in a community that is fully susceptible is known as the basic reproduction number, or R_0 [11]. Methods used to calculate R_0 include the survival function, the next generation method, the Jacobian matrix's eigenvalues, the presence of the endemic equilibrium, and the characteristic polynomial's constant term [12]. A description of a system using mathematical terminology and instruments is called a mathematical model. In the natural sciences, such as biology and epidemiology, mathematical models play a crucial role. They support our efforts to discover new information about a system, arrange and interpret biological data, and ascertain the system's reaction behavior. Daniel Bernoulli's smallpox model from the 1760s marked the beginning of mathematical modeling of infectious illness. Since then, numerous infectious diseases have been simulated through the development of mathematical models, including influenza, HIV, TB, malaria, and tuberculosis to mention a few. These mathematical models were designed to address an array of unresolved questions [13].

To provide some insights into this study, this section brings to light relevant literature. In particular, literature that is based on mathematical modeling of Human Papillomavirus dynamics. Finally, the focus is directed on current research that will attempt to fill the gap in the literature.

[1]formulated an HPV-induced cervical cancer model with six compartments including, Susceptible cells (S), Infected cells (I), Cancerous cells (C), Dendritic cell population (D), CTL population (T), and HPV (V) to explain how a combination of drugs can treat cervical cancer [14].developed an SIPVC model consisting of five compartments which are susceptible, infected, precancerous, cancerous cells, and HPV to the features of HPV infectious and cancer disease.

Other compartments which were used to model the dynamics of HPV to cervical cancer include; SIVPC, SIVPC, SIVPCM, SITR, $SI_{HPV}I_{UC}I_{CC}$, $S(t)V(t)E(t)I_u(t)C(t)R(t)$, SIVPC where S-susceptible, I-infected, V-virus, P-precancerous, C- cancerous, T-treated and R-recovered, E−exposed [6,15–20], respectively.

Those studies missed critical aspects such as; a density-dependent population, functional responses, and the maximum proportion of cancerous cells that can cause an individual to die and also the trio-interaction of basal cells, virions, and lymphocytes. To achieve this, a new mathematical model is formulated; an in-host density-dependent deterministic model of basal cells, virions, and lymphocyte dynamics and their relation to cervical cancer. The study analyzes the model using epidemiological techniques and simulates it using an inbuilt Matlab ODE solver. The paper is organized as follows: Section 2 is on Model Formulation, Section 3 is on Model analysis and Section 4 is on Conclusion and recommendations. The findings of this research will help healthcare providers, public health authorities, and non-governmental health groups in creating effective prevention strategies to slow the development of cervical cancer.

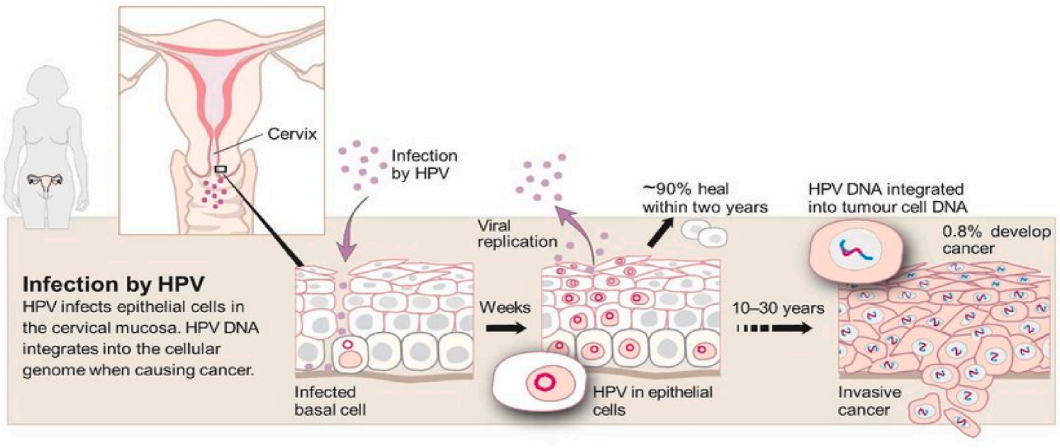

Fig. 1. Progression of cervical cancer by HPV.

2. Model formulation

In this study, first-order nonlinear ordinary differential equations are used to create a logistic deterministic model for the effects of the Human Papillomavirus. The model of HPV infection and cancer development has considered 6 compartments namely: S-Susceptible (normal) cells, I-Infected cells, V-Free virus, P-Precancerous cells, C-Cancerous cells, and L- Lymphocytes cells. The model is analyzed in terms of positivity, equilibrium points, and their stabilities, and the basic reproduction number is determined using the next-generation matrix method, survival function, and the constant term of a characteristic polynomial.

This study assumes that: the number of cervical epithelial cells remains roughly constant, the epithelium is replaced every 4–5 days [16], all the epithelium cells are susceptible, the basal cell population grows logistically, with an intrinsic growth rate and a carrying capacity. There is significance to the recovery from natural immunity and Human Papillomavirus infection is the strongest risk factor for cervical cancer. Besides the common assumptions of any epidemiological model, the following are additional assumptions.

i. $\frac{\tau_2 S}{S+BV}$ is Arditi-Ginzburg function predator (virions) density can also influence individual (Prey/Basal Cells) consumption rate, an effect termed predator dependence. The ratio of prey density to predator density will determine how virions attack Basal cells.
ii. $\frac{CP^2}{D^2+P^2}$ is a saturation function in which precancerous cells progress to cancerous cells based on Holling type III response.
iii. $\frac{EM}{F+M}$ is based on Holling type II response on the assumption that the rate of infected basal cell recovery increases with the immunity level, but saturates at some maximum level M.

The parameters and state variables are summarized in the table below.

Some parameter values in Table 1 were obtained from different literature while others were estimated using the maximum likelihood estimation method (see Table 2).

The equations are derived from the model flow chart as follows;

$$\frac{dS}{dt} = r_1 S\left(1 - \frac{N}{K_1}\right) - \frac{\tau_2 SV}{S+BV} + \frac{EM}{F+M} I - \delta_1 S, \tag{1}$$

$$\frac{dI}{dt} = r_1 I\left(1 - \frac{N}{K_1}\right) + \frac{\tau_2 SV}{S+BV} - \beta I - \frac{EM}{F+M} I - \eta_1 I - \delta_1 I, \tag{2}$$

$$\frac{dP}{dt} = r_1 P\left(1 - \frac{N}{K_1}\right) + \beta I - \Theta \frac{CP^2}{D^2+P^2} - \eta_2 P - \delta_1 P, \tag{3}$$

$$\frac{dC}{dt} = \left\{ r_1 C\left(1 - \frac{N}{K_1}\right) + \Theta \frac{CP^2}{D^2+P^2} - \eta_3 C - \delta_1 C \right\}\left(1 - \frac{C}{K_4}\right), \tag{4}$$

Table 1
Parameter and state variables description.

Parameter	Description	Value	Reference
r_1	Mitosis division rate of basal cells	0.8506	[21]
r_2	Division rate virions	0.011	Estimated
r_3	Division rate lymphocytes	0.902	Estimated
K_1	Carrying capacity of basal cells	10,000,000	Estimated
K_2	Carrying capacity of virions	100,000	Estimated
K_3	Carrying capacity of lymphocytes	50,000	Estimated
K_4	The population of cancerous cells that causes a person to die	6,500,000	Estimated
τ_2	The rate of infection of susceptible cells by the virions	0.000001	[15]
β	Progression rate from infected cells to precancerous cells	0.0082	[17]
Θ	Progression rate from precancerous cells to cancerous cells	0.01	[21]
$\eta 1 = \eta 2 = \eta 3$	Induced death rate of I, P and C	0.005	[21]
δ_1	The apoptosis rate of basal cells	0.0048	[22]
δ_2	The apoptosis rate of virions	0.0021	[22]
δ_3	The apoptosis rate of lymphocytes	0.0005	Estimated
D	Half-saturation concentration for the progression from P to C	10^5	[23]
$\omega_1 = \omega_2 = \omega_3$	Number of virions that are produced by I, P and C	1000	[24]
M	The autoimmune rate of I to S	0.00003333	[22]
α_1	Contact rate	0.0002	Estimated
ϵ	Rate at which the virions are killed by the lymphocytes	0.90005	Estimated
τ_1	Rate at which virions are eliminated as they attack normal cells	0.0005	Estimated
$S(t)$	Susceptible basal cells with time		
$I(t)$	Infected basal cells with time		
$P(t)$	Precancerous basal cells with time		
$C(t)$	Cancerous basal cells with time		
$V(t)$	Virions with time		
$L(t)$	Lymphocytes with time		

Table 2
Table of sensitivity indices.

Parameter	Next Generation Matrix.	Survival Function.	Constant term of the characteristic polynomial.
F	0.993351	0.0000346813344295621	0.993351
M	− 0.99463	− 0.00003468133442956 2096	− 0.99463
K_1	− 0.0000176205	0.026674154887992983	− 0.000158879
r_1	1	0.9879380508173314	3
r_2	0	$5.883416249394072 \times 10^{-7}$	1
B	-1.05469×10^{-10}	− 0.000099212399239203786	-1.05469×10^{-10}
δ_1	6.17395×10^{-6}	− 0.22125138109693612	− 0.979586
δ_2	0	− 0.12494859329913026	0.00799353
η_1	6.43119×10^{-6}	− 0.047374582684402054	6.43119×10^{-10}
η_2	0	− 0.29268294620149876	− 0.510204
η_3	0	− 0.1764099056748374	− 0.510204
S	− 176.208	− 0.011490780279154997	− 529.625
E	1	0	− 1
L	0	0	0.00135933
K_4	0	− 0.0006712604976524636	-6.36864×10^{-10}
ϵ	0	$-2.188287319016677 \times 10^{-11}$	6.36864×10^{-10}
τ_1	0	− 0.011499992678394202	− 1.00799
I	0	0.005348560226721884	0
ω_3	0	0.001337140056680471	0
ω_2	0	0.004813704204049696	0
ω_1	0	0.005348560226721884	0
K_2	0	0.00029487161100197416	0
D	0	0.04629077249233771	0
P	0	− 0.01364474132726996	0
C	0	− 0.025823926384812002	0
θ	0	− 0.027832326961018047	0
E	0	− 0.00003491252020486956	0
β	0	− 0.08646595437424326	0
V	0	− 0.011241531993419006	0
N	0	− 0.026674154887992983	0

$$\frac{dV}{dt} = \{r_2 V + \omega_1 \eta_1 I + \omega_2 \eta_2 P + \omega_3 \eta_3 C\}\left(1 - \frac{V}{K_2}\right) - \tau_1 SV - \epsilon \frac{L}{L + K_4} V - \delta_2 V, \tag{5}$$

$$\frac{dL}{dt} = r_3 L\left(1 - \frac{L}{K_3}\right) - \alpha_1 LV - \delta_3 L. \tag{6}$$

with initial conditions $S(0) \geq 0,\ I(0) \geq 0,\ P(0) \geq 0,\ C(0) \geq 0, V(0) \geq 0,\ L(0) \geq 0.$;

3. Results and discussion

This section is organized as follows: 3.1. Model analysis and 3.2 Model simulation.

3.1. Model analysis

This sub-section is organized as follows: **3.1.1** Existence and positive in variance, **3.1.2.** Boundedness of the solution, **3.1.3** Disease-free equilibrium point, **3.1.4** Basic reproduction number, **3.1.5** Endemic equilibrium, **3.1.6** Stability analysis, and **3.1.7** Bifurcation analysis.

3.1.1. Existence and positive invariance

Theorem 1. Solutions of the model equations (1)–(6) together with the initial conditions $S(0) \geq 0, I(0) \geq 0, P(0) \geq 0, C(0) \geq 0, V(0) \geq 0, L(0) \geq 0$ are always positive or the model variables S (t), I(t), P(t), C(t), V(t) and L(t) all positive for all t and will remain in R_6^+ [6].

Proof. .

For the sake of analysis

$$\frac{dS}{dt} = r_1 S(1 - k_1 N) - \frac{\tau_2 SV}{S + BV} + \Omega_1 I - \delta_1 S, \tag{7}$$

$$\frac{dI}{dt} = r_1 I(1 - k_1 N) + \frac{\tau_2 S}{S + BV} - \Omega_2 I, \tag{8}$$

$$\frac{dP}{dt} = r_1 P(1 - k_1 N) + \beta I - \Theta \frac{CP^2}{D^2 + P^2} - \Omega_3 P, \tag{9}$$

$$\frac{dC}{dt} = \left\{ r_1 C(1 - k_1 N) + \Theta \frac{CP^2}{D^2 + P^2} - \Omega_4 C \right\} (1 - k_4 C), \tag{10}$$

$$\frac{dV}{dt} = \{ r_2 V + \omega_1 \eta_1 I + \omega_2 \eta_2 P + \omega_3 \eta_3 C \}(1 - k_2 V) - \tau_1 SV - \epsilon \frac{L}{L + K_4} V - \delta_2 V, \tag{11}$$

$$\frac{dL}{dt} = r_3 L(1 - k_3 L) - \alpha_1 LV - \delta_3 L, \tag{12}$$

Where $\frac{1}{K_1} = k_1; \frac{1}{K_2} = k_2; \frac{1}{K_3} = k_3; \frac{EM}{F+M} = \Omega_1; \Omega_2 = \beta + \Omega_1 + \eta_1 + \delta_1; \Omega_3 = \eta_2 + \delta_1$;

$/\Omega_4 = \eta_3 + \delta_1$, to reduce the number of parameters, therefore;

For $t > 0$, let $W = (s(t), i(t), p(t), n(t), v(t), l(t))^T$ and $F(W) = \left(F1(W), F2(W), F3(W), F4(W), F5(W), F6(W)\right)^T$,where $F1(W) = r_1 S(1 - k_1 N) - \frac{\tau_2 SV}{S+BV} + \Omega_1 I - \delta_1 S$, $F2(W) = r_1 I(1 - k_1 N) + \frac{\tau_2 SV}{S+BV} - \Omega_2 I, F3(W) = r_1 P(1 - k_1 N) + \beta I - \Theta \frac{CP^2}{D^2+P^2} - \Omega_3 P, F4(W) = \left\{ r_1 C(1 - k_1 N) + \Theta \frac{CP^2}{D^2+P^2} - \Omega_4 C \right\}(1 - k_4 C), F5(W) = \{ r_2 V + \omega_1 \eta_1 I + \omega_2 \eta_2 P + \omega_3 \eta_3 C \}(1 - k_2 V) - \tau_1 SV - \epsilon \frac{L}{L+K_4} V - \delta_2 V, F6(W) = r_3 L(1 - k_3 L) - \alpha_1 LV - \delta_3 L$. Then, system (1)–(6) can be written as $\frac{dQ}{dt} = F(W)$ where $F : C_+ \rightarrow (R)^6_+$ with $W(0) = W_0 \epsilon\, R^6_+$. Thus, the function W is locally Lipschitzian and completely stable on R^6_+.

Therefore, the solution of the system with non-negative initial conditions exists and is unique. It is also evident that these solutions exist for all $t > 0$ and are non-negative, hence the region R^6_+ is an invariant domain of the system [25].

3.1.2. Boundedness of the solution

For the system to be mathematically meaningful, it is necessary to show that its state variables are positive and bounded for all t. That is, the solution of the system with a positive initial value will remain positive for all $t \geq 0$.

Theorem 2. The positive solutions of the system of model equations (1)–(6) are bounded. That is, the model variables S(t), I(t), P(t), C (t), V(t) and L(t) are bounded for all t [6].

Proof.

$$N(t) = S(t) + I(t) + P(t) + C(t) \tag{13}$$

By differentiating equation (13) gives,

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dI}{dt} + \frac{dP}{dt} + \frac{dC}{dt} \tag{14}$$

$$\frac{dN}{dt} = r_1 S\left(1 - \frac{N}{K_1}\right) - \delta_1 S + r_1 I\left(1 - \frac{N}{K_1}\right) - \eta_1 I - \delta_1 I + r_1 P\left(1 - \frac{N}{K_1}\right) - \eta_2 P - \delta_1 P + r_1 C\left(1 - \frac{N}{K_1}\right) - \eta_3 C - \delta_1 C\left(1 - \frac{C}{K_4}\right) \tag{15}$$

$$\frac{dN}{dt} = r_1 N\left(1 - \frac{N}{K_1}\right) - \left(\delta_1 S + \eta_1 I + \delta_1 I + \eta_2 P + \delta_1 P + \eta_3 C + \delta_1 C\left(1 - \frac{C}{K_4}\right)\right) \tag{16}$$

$$\frac{dN}{dt} \leq r_1 N\left(1 - \frac{N}{K_1}\right)$$

By using the separation of variables of inequality, we have

$$\frac{dN}{N\left(1 - \frac{N}{K_1}\right)} \leq r_1 dt \tag{17}$$

On integrating both sides (17) and applying the initial conditions to get the value of A and finally substituting the value of A, we have

$$N(t) \leq \frac{K_1}{1 + \left(\frac{K_1}{N(0)} - 1\right) e^{-rt}}. \tag{18}$$

Introducing limits, $\lim_{t\to\infty} N(t) \le K_1$.Implying that $0 \le N(t) \le K_1$.

Also for, $V(t)$.

$$\frac{dV}{dt} = \{r_2 V + \omega_1\eta_1 I + \omega_2\eta_2 P + \omega_3\eta_3 C\}\left(1 - \frac{V}{K_2}\right) - \tau_1 SV - \epsilon\frac{L}{L+K_4}V - \delta_2 V. \tag{19}$$

$$Let\ r_2 V + \omega_1\eta_1 I + \omega_2\eta_2 P + \omega_3\eta_3 C = r_4 V \tag{20}$$

$$\frac{dV}{dt} = r_4 V\left(1 - \frac{V}{K_2}\right) - \tau_1 SV - \epsilon\frac{L}{L+K_4}V - \delta_2 V, then, \frac{dV}{dt} \le r_4 V\left(1 - \frac{V}{K_2}\right) \tag{21}$$

By separating variables (21), integrating and applying initial conditions and limits we obtained $\lim_{t\to\infty} V(t) \le K_2$.Therefore; $V(t) \le K_2$. Implying that, $0 \le V(t) \le K_2$.

Similarly, $L(t)$, $\frac{dL}{dt} \le r_3 L\left(1 - \frac{L}{K_3}\right)$. Therefore; $L(t) \le \frac{K_3}{1+\left(\frac{K_3}{L(0)}-1\right)e^{-rt}}$. On applying the limits as $t\to\infty$, it follows that; $0 \le L(t) \le K_3$.

3.1.3. Disease-free equilibrium point (DFE)

Theorem 3. The system of equations (1)–(6) has disease-free equilibrium point (E^0) obtained as; $E^0 = (S^0, I^0, P^0, C^0, V^0, L^0) = \left(\frac{K_1(r_1-\delta_1)}{r_1}, 0, 0, 0, 0, \frac{K_3}{r_3}(r_3 - \delta_3)\right)$.

Proof. .

DFE of system (1)–(6) is obtained by setting the right-hand side to zero and equating the infectious classes to zero $I = 0, P = 0, C = 0, A = 0$ *and* $V = 0$ [26].

Solving, we obtained. $S^0 = 0$ and $S^0 = \frac{K_1(r_1-\delta_1)}{r_1}$ $L^0 = 0$ and $L^0 = \frac{K_3(r_3-\delta_3)}{r_3}$. The set, $S^0 = L^0 = 0$ was not biologically meaningful because it is not feasible to have a cervix with no basal cells and Lymphocytes. Hence $S^0 = \frac{K_1(r_1-\delta_1)}{r_1}$ and $L^0 = \frac{K_3(r_3-\delta_3)}{r_3}$. Hence the disease free equilibrium point of the system of equations (1)–(8) was obtained as:

$$E^0 = (S^0, I^0, P^0, C^0, V^0, L^0) = \left(\frac{K_1(r_1-\delta_1)}{r_1}, 0, 0, 0, 0, \frac{K_3}{r_3}(r_3 - \delta_3)\right).$$

3.1.4. Basic reproduction number ($\mathbf{R_0}$)

There are numerous controversies surrounding the method of calculating basic reproduction number (R_0) because it has been proven that each method produces a unique estimate of (R_0) hence posing a challenge to stakeholders on how best to control the dynamics of a disease [12]**.** Although most studies have evaluated R_0 using the next-generation method, it estimates R_0 as an average regardless of whether the population is of human or host cells. It also lacks some uniqueness [12]. To address the challenges of those methods, this study determined R_0 using three methods for comparative purpose: Sub-Sub section **3.1.4.1** next-generation matrix, **3.1.4.2** Survival Function and **3.1.4.3** constant term of characteristic polynomial.

3.1.4.1. Using next generation matrix. **Theorem 4.** The basic reproduction number , $R_0 = \frac{(M+F)(K_1 - S^0)\gamma_1}{K_1(M\beta + F\beta + ME + M\delta_1 + F\delta_1 + M\eta_1 + F\eta_1)}$ by Next-generation method.

Proof. .

To obtain basic reproduction number, we use next generation matrix method proposed by Kermack and Diekmann [27]. Let non-negative matrix f and non-singular matrix v represent new infections terms and transfer of infections terms respectively. Thus

$$f = \begin{bmatrix} r_1 I\left(1 - \frac{N}{K_1}\right) + \frac{\tau_2 SV}{S+BV} \\ r_1 P\left(1 - \frac{N}{K_1}\right) \\ r_1 C\left(1 - \frac{N}{K_1}\right)\left(1 - \frac{C}{K_4}\right) \\ r_1 V + \omega_1\eta_1 I + \omega_2\eta_2 P + \omega_3\eta_3 C\left(1 - \frac{V}{K_2}\right) \end{bmatrix}; v = \begin{bmatrix} \beta I + \frac{EM}{F+M} I + \eta_2 I + \delta_1 I \\ -\beta I + \frac{\theta CP^2}{D^2+P^2} + \eta_2 P + \delta_1 P \\ \left(-\frac{\theta CP^2}{D^2+P^2} + \eta_3 C + \delta_1 C\right)\left(1 - \frac{C}{K_4}\right) \\ \tau_1 SV + \frac{\epsilon LV}{L+K_4} + \delta_2 V \end{bmatrix}$$

At E^0 point, Jacobian matrices of f and v was evaluated to find out matrices F and V respectively,

$$F=\begin{bmatrix}\left(1-\frac{S^0}{K_1}\right)\gamma_1 & 0 & 0 & \frac{-\beta S^0 V\tau_2}{S_2}\\ 0 & \left(1-\frac{S^0}{K_1}\right)\gamma_1 & 0 & 0\\ 0 & 0 & \left(1-\frac{S^0}{K_1}\right)\gamma_1 & 0\\ \eta_1\omega_1 & \eta_2\omega_2 & \eta_3\omega_3 & \gamma_2\end{bmatrix};V=\begin{bmatrix}\beta+\frac{EM}{F+M}+\delta_1+\eta_1 & 0 & 0 & 0\\ -\beta & \delta_1+\eta_2 & 0 & 0\\ 0 & 0 & \delta_1+\eta_3 & 0\\ 0 & 0 & 0 & \frac{L^0\epsilon}{L^0+K_5}+\delta_2+\tau_1 S^0 V\end{bmatrix}$$

At E^0 point, FV^{-1}, was obtained as, $\begin{bmatrix}\frac{\left(1-\frac{S^0}{K_1}\right)r_1}{\frac{MQ}{F+M}+\beta+\delta_1+\eta_1} & 0 & 0 & 0\\ 0 & \frac{\left(1-\frac{S^0}{K_1}\right)r_1}{\delta_1+\eta_2} & 0 & 0\\ 0 & 0 & \frac{\left(1-\frac{S^0}{K_1}\right)r_1}{\delta_1+\eta_3} & 0\\ 0 & 0 & 0 & \frac{r_2}{\frac{L^0\epsilon}{L^0+K_5}+\delta_2+\tau_1 S^0 V}\end{bmatrix}$;

The four eigenvalues of FV^{-1} at E^0 were: $\frac{(K_1-S^0)\gamma_1}{K_1(\delta_1+\eta_3)}$, $\frac{(K_1-S^0)\gamma_1}{K_1(\delta_1+\eta_2)}$, $\frac{(M+F)(K_1-S^0)\gamma_1}{K_1(M\beta+F\beta+ME+M\delta_1+F\delta_1+M\eta_1+F\eta_1)}$ *and* $\frac{(L^0+K_4)\gamma_2}{\epsilon L^0+\delta_2 L^0+K_4\delta_2}$.

By inspection method (which was be verified by numerical method too) the dominant eigenvalue represents the R_0 [27]. Hence

$$R_0=\frac{(M+F)(K_1-S^0)\gamma_1}{K_1(M\beta+F\beta+ME+M\delta_1+F\delta_1+M\eta_1+F\eta_1)}$$

3.1.4.2. Basic reproduction number by survival function. **Theorem 5.** The basic reproduction number

$$R_0=\frac{r_1\left(1-\frac{N}{K_1}\right)+\frac{\tau_2 SV}{S+BV}}{\beta+\frac{EM}{F+M}+\eta_1+\delta_1}+\frac{r_1\left(1-\frac{N}{K_1}\right)}{\frac{\theta CP}{D^2+P^2}+\eta_2+\delta_2}+\frac{r_1\left(1-\frac{N}{K_1}\right)}{\left((\eta_3+\delta_1)\left(1-\frac{C}{K_4}\right)\right)}+\frac{(r_2V+\omega_1\eta_1 I+\omega_2\eta_2 P+\omega_3\eta_3 C)\left(1-\frac{V}{K_2}\right)}{\frac{\epsilon L}{L+K_4}+\delta_2+\tau_1 SV}$$

by the method proposed by Ref. [28]. Where $N(0), S(0), V(0), P(0), C(0), I(0)$ *and* $L(0)$ are assumed to be constant terms at the beginning of the epidemic. For numerical computation, in this study, we assumed those constant values to be the initial conditions of the model.

Proof. .

Evaluation of R_0 using the survival function method is considered to be a more accurate method. One benefit of the survival function approach is that it consistently yields the average number of secondary basal cells infected by one infected basal cell in the same class [12]. It also takes into account the different attributes of the population, therefore, the basic reproduction number using the survival function is given by; $R_0=\int_0^\infty (k\times b\times p)dt$ where:k = rate at which an individual in that class causes an infection.,b = probability at which an infected individual remains in the same class to cause an infection. p = probability that an infected case will enter that class [28].

Considering the infectious classes (I, P, C, and V), and $\boldsymbol{N}, S, V, P, C, I$ *and* L are assumed to be constant terms at the beginning of the epidemic, evaluating R_0 of equations (2)–(5), the basic reproduction number was obtained by summing them [12] that is,

$$\left\{r_1\left(1-\frac{N}{K_1}\right)+\frac{\tau_2 SV}{S+BV}\right\}\int_0^\infty e^{-\left(\beta+\frac{EM}{F+M}+\eta_1+\delta_1\right)T_A}dT_A+\left\{r_1\left(1-\frac{N}{K_1}\right)\right\}\int_0^\infty e^{-\left(\frac{\theta CP}{D^2+P^2}+\eta_2+\delta_2\right)T_A}dT_A$$
$$+\left\{r_1\left(1-\frac{N}{K_1}\right)\right\}\int_0^\infty e^{-\left((\eta_3+\delta_1)\left(1-\frac{C}{K_4}\right)\right)T_A}dT_A+\left\{(r_2V+\omega_1\eta_1 I+\omega_2\eta_2 P+\omega_3\eta_3 C)\left(1-\frac{V}{K_2}\right)\right\}\int_0^\infty e^{-\left(\frac{\epsilon L}{L+K_4}+\delta_2+\tau_1 SV\right)T_A}dT_A$$

On integration, $\left\{r_1\left(1-\frac{N}{K_1}\right)+\frac{\tau_2 SV}{S+BV}\right\}\left[-\frac{e^{-\left(\beta+\frac{EM}{F+M}+\eta_1+\delta_1\right)T_A}}{\beta+\frac{EM}{F+M}+\eta_1+\delta_1}\right]_0^\infty+\left\{r_1\left(1-\frac{N}{K_1}\right)\right\}\left[-\frac{e^{-\left(\frac{\theta CP}{D^2+P^2}+\eta_2+\delta_2\right)T_A}}{\frac{\theta CP}{D^2+P^2}+\eta_2+\delta_2}\right]_0^\infty+\left\{r_1\left(1-\frac{N}{K_1}\right)\right\}$

$\left[-\frac{e^{-\left((\eta_3+\delta_1)\left(1-\frac{C}{K_4}\right)\right)T_A}}{\left((\eta_3+\delta_1)\left(1-\frac{C}{K_4}\right)\right)}\right]_0^\infty + \left\{(r_2V+\omega_1\eta_1I+\omega_2\eta_2P+\omega_3\eta_3C)\left(1-\frac{V}{K_2}\right)\right\}\left[\frac{e^{-\left(\frac{\epsilon L}{L+K_4}+\delta_2+\tau_1SV\right)T_A}}{\frac{\epsilon L}{L+K_4}+\delta_2+\tau_1SV}\right]_0^\infty$. Putting the limits the basic reproduction number is obtained as:

$$R_0=\frac{r_1\left(1-\frac{N}{K_1}\right)+\frac{\tau_2SV}{S+BV}}{\beta+\frac{EM}{F+M}+\eta_1+\delta_1}+\frac{r_1\left(1-\frac{N}{K_1}\right)}{\frac{\theta CP}{D^2+P^2}+\eta_2+\delta_2}+\frac{r_1\left(1-\frac{N}{K_1}\right)}{\left((\eta_3+\delta_1)\left(1-\frac{C}{K_4}\right)\right)}+\frac{(r_2V+\omega_1\eta_1I+\omega_2\eta_2P+\omega_3\eta_3C)\left(1-\frac{V}{K_2}\right)}{\frac{\epsilon L}{L+K_4}+\delta_2+\tau_1SV}$$

3.1.4.3. Basic reproduction number by evaluating the constant term of the characteristic polynomial. **Theorem 6.** The basic reproduction number

$R_0=\frac{(F+M)\left(S^0-K_1\right)^3\left(L^0+K_4\right)r_1^3r_2}{K_1^3(F\beta+M(Q+\beta)+(F+M)(\delta_1+\eta_1))(\delta_1+\eta_2)(\delta_1+\eta_3)\left(L^0\epsilon+\left(L^0+K_4\right)(\delta_2+S\tau_1)\right)}$ by method evaluating the constant term of the characteristic polynomial [12].

Proof. .

For comparison purposes, there is a need to determine the basic reproduction number using the constant term of a characteristic polynomial. When λ max = 0, the constant term of the characteristic polynomial will be zero [12]. However, the reverse is not true, as the polynomial could have both zero and positive roots. The characteristic polynomial by Next generation matrix (FV^{-1}) is of the form $b_4\lambda^4+b_3\lambda^3+b_2\lambda^2+b_1\lambda+b_0=0$, where the expressions of b_4, b_3, b_2, b_1 *and* b_0 are found in the appendix in section 4. The study [12] proposes the following conditions.

Let b_0 represent R_0, then $b_0=0$ is a threshold if $b_j\geq 0$ for all j. Some sufficient conditions include; non-constant coefficients all being positive and $b_j\geq 0$ under the constraint $b_0=0$ (so that the largest eigenvalue at $b_0=0$ is 0). This method is significantly easier to use than finding the largest eigenvalue, although verifying that $b_j=0$ necessarily corresponds to the largest eigenvalue can become complicated for some models [12].

$$R_0=\frac{(F+M)\left(S^0-K_1\right)^3\left(L^0+K_4\right)r_1^3r_2}{K_1^3(F\beta+M(Q+\beta)+(F+M)(\delta_1+\eta_1))(\delta_1+\eta_2)(\delta_1+\eta_3)\left(L^0\epsilon+\left(L^0+K_4\right)(\delta_2+S\tau_1)\right)}\ .$$

3.1.5. Endemic equilibrium

By setting the system of equations to zero and evaluating the state variables, the endemic equilibrium points would be in the form:

$(EEP)=(S^*,I^*,P^*,C^*,V^*,L^*)$

From; $\left\{r_1C^*\left(1-\frac{N}{K_1}\right)+\Theta\frac{C^*P^{*2}}{D^2+P^{*2}}-\eta_3C^*-\delta_1C^*\right\}\left(1-\frac{C^*}{K_4}\right)=0;$

It follows that; $C^*=K_4$;

The endemic equilibrium point exists at $C^*=K_4$ and since the equations are highly non-linear, it was not tractable to solve them explicitly.

From; $r_1P^*\left(1-\frac{N}{K_1}\right)+\beta I^*-\Theta\frac{C^*P^{*2}}{D^2+P^{*2}}-\eta_2P^*-\delta_1P^*=0;$

It implies that; $P^*=\frac{-C\theta K_1\pm\sqrt{C^2\theta^2K_1^2-4(\beta K_1-Nr_1+K_1r_1-K_1\delta_1-K_1\eta_2)\left(D^2\beta K_1-D^2Nr_1+D^2K_1r_1-D^2K_1\delta_1-D^2K_1\eta_2\right)}}{2(-\beta K_1+Nr_1-K_1r_1+K_1\delta_1+K_1\eta_2)}$;

From; $\{r_2V^*+\omega_1\eta_1I^*+\omega_2\eta_2P^*+\omega_3\eta_3C^*\}\left(1-\frac{V^*}{K_2}\right)-\tau_1SV-\epsilon\frac{L^*}{L^*+K_4}V^*-\delta_2V^*=0$

$$V^*=\frac{K_2\left(\frac{L\epsilon}{K_4}-r_2+\frac{J\eta_1\omega_1}{K_2}+\frac{P\eta_2\omega_2}{K_2}+\frac{T\eta_3\omega_3}{K_2}+\sqrt{\frac{4r_2(J\eta_1\omega_1+P\eta_2\omega_2+T\eta_3\omega_3)}{K_2}+\left(-\frac{L\epsilon}{K_4}+r_2-\frac{J\eta_1\omega_1}{K_2}-\frac{P\eta_2\omega_2}{K_2}-\frac{T\eta_3\omega_3}{K_2}\right)^2}\right)}{2r_2}$$

Substituting the value of P^*, C^* *and* V^* to;

$r_1I^*\left(1-\frac{N}{K_1}\right)+\frac{\tau_2S^0V}{S+BV^*}-\beta I^*-\frac{EM}{F+M}I^*-\eta_1I^*-\delta_1I^*>0$ and solving for I^*, we get the value of $I^*=-\frac{\tau_2M}{\left(S+BV\right)\left(-\frac{EM}{F+M}-\beta+\left(1-\frac{X}{K_1}\right)r_1-\delta_1-\eta_1\right)}$;

From $r_3L^*\left(1-\frac{L^*}{K_3}\right)-\alpha_1L^*V^*-\delta_3;$

$$L^*=\frac{K_3(r_3-V\delta_1-\delta_3)}{r_3}$$

Theorem 7. The necessary and sufficient conditions for existence is $R_0 > 1, \frac{dI}{dt} > 0, \frac{dP}{dt} > 0, \frac{dC}{dt} > 0$ *and* $\frac{dV}{dt} > 0$ [29].

3.1.6. Stability analysis

3.1.6.1. Local stability of disease-free equilibrium point. **Theorem 2.** The Disease Free Equilibrium of the system (1)-(6) is locally asymptomatic stable whenever $R_0 < 1$.

Proof. .

The relative stability of the system can be determined by the Routh-Hurwitz criterion of stability without having to solve each equation.

Determining Jacobian Matrix of system (1)–(6) at Disease Free Equilibrium is obtained;

$$[\, R_1 \quad R_2 \quad R_3 \quad R_4 \quad R_5 \quad R_6 \,]^T$$

$$R_1 = \begin{bmatrix} -\delta_1 - k_1 r_1 S^0(1 - k_1 S^0) & \Omega_1 - k_1 r_1 S^0(1 - k_1 S^0) & -k_1 r_1 S^0(1 - k_1 S^0) & -k_1 r_1 S^0(1 - k_1 S^0) & \frac{\tau_2 B}{S^0} & 0 \end{bmatrix}$$

$$R_2 = \begin{bmatrix} 0 & (1 - k_1 S^0) r_1 - \Omega_2 & 0 & 0 & -\frac{\tau_2 B}{S^0} & 0 \end{bmatrix}$$

$$R_3 = [\, 0 \quad \beta \quad (1 - k_1 S^0) r_1 - \Omega_3 \quad 0 \quad 0 \quad 0 \,]$$

$$R_4 = [\, 0 \quad 0 \quad 0 \quad (1 - k_1 S^0) r_1 - \Omega_4 \quad 0 \quad 0 \,]$$

$$R_5 = \begin{bmatrix} 0 & \eta_1 \omega_1 & \eta_2 \omega_2 & \eta_3 \omega_3 & -\frac{\epsilon L^0}{L^0 + K_4} + r_2 - \delta_2 - \tau_1 S^0 & 0 \end{bmatrix}$$

$$R_6 = [\, 0 \quad 0 \quad 0 \quad 0 \quad -\alpha_1 L^0 \quad -\delta_3 - k_3 r_3 L^0(1 - k_3 L^0) \,]$$

The characteristic polynomial is obtained as $a_0\lambda^6 + a_1\lambda^5 + a_2\lambda^4 + a_3\lambda^3 + a_4\lambda^2 + a_5\lambda + a_6 = 0,$ where the expression $a_i, i = 1$ for system (1)–(6) are in appendix section 2. The Routh table for the coefficients was also derived in the appendix in section 1.

From the characteristic polynomial, the values $a_2, a_4, a_6, b_1, c_1, d_1$ *and* e_1 are determined using Mathematica Software and expressed in terms of Ro. By Routh-Hurwitz Criteria for stability, system (1)–(6) is locally asymptotically stable at DFE whenever Ro < 1 if and only if $a_2 > 0, a_4 > 0, a_6 > 0, b_1 > 0, c_1 > 0, d_1 > 0, e_1 > 0$ are satisfied and otherwise unstable [26]. The values of $a_2, a_4, a_6, b_1, c_1, d_1$ *and* e_1 have been expressed in the appendix.

3.1.6.2. Global stability of disease-free equilibrium point. The global stability of disease-free equilibrium is investigated using the Castillo-Chavez Metzler Matrix method. $\frac{dX}{dt} = F(X, Z)$; $\frac{dZ}{dt} = G(X, Z)$, $G(X, 0) = 0$ Where; $X = (S, L)\ \varepsilon R_2^+$ denote non-infectious cervical cancer compartments and $Z = (I, P, C, V)\ \varepsilon\ R_4^+$ denote the infectious cervical cancer compartments $Eo = (X^*, 0)$ represents the disease-free equilibrium of the system if this point satisfies following conditions.

i. $\frac{dX}{dt} = (X, 0),$ Where X* is globally asymptotically stable.
ii. $\frac{dZ}{dt} = DzG(X, 0)Z - G(X, Z) \geq 0$ for all X,Z $\in \Omega$, then we can conclude that Eo is locally asymptotically stable if the following theorems hold.

Theorem; The equilibrium point $Eo = (X^*, 0)$ of the system [1–6] is globally asymptotically stable if $R_0^* \leq 1$ and the conditions (i) and (ii) are satisfied, otherwise unstable. From equation (1) two vectors function G (X, Z) and F (X,Z), we consider systems $\frac{dX}{dt} = (X, 0) = 0$ Letting $A = D_z G(X^*, 0),$ which is the Jacobian of $\hat{G}$(X,Z) taken in (I, P, C, V) and evaluated at (X*,0) such that the matrix A is given by;

$$AZ = \begin{bmatrix} (\beta_1 S^0 - k_1)E + \eta_1\beta_1 S^0 I + \eta_2\beta_1 S^0 T + \eta_3\beta_1 S^0 C \\ \rho E - k_2 I \\ \omega I - k_3 T \\ \gamma I + \alpha T - k_4 C \end{bmatrix} \quad G(X, Z) = \begin{bmatrix} (\lambda_1 + \lambda_2)S - k_1 E \\ \rho E - k_2 I \\ \omega I - k_3 T \\ \gamma I + \alpha T - k_4 C \end{bmatrix}$$

But $\hat{G}(X, Z) = AZ - G(X, Z)$, This reduces to $\hat{G}(X, Z) = \begin{bmatrix} \hat{G_1}(X, Y) \\ \hat{G_2}(X, Y) \\ \hat{G_3}(X, Y) \\ \hat{G_4}(X, Y) \end{bmatrix} = \begin{bmatrix} (\beta_1(E + \eta_1 I + \eta_2 T + \eta_3 C)(S^0 - S) - \lambda_2 S \\ 0 \\ 0 \\ 0 \end{bmatrix};$

Thus, if then the disease-free equilibrium (E^0) is globally stable and unstable otherwise. The susceptible is bounded as, $S \leq S^0$.Thus,

DFE, E^0 is globally asymptomatically stable if and only if $\left(\beta_1(E+\eta_1 I+\eta_2 T+\eta_3 C)\left(S^0-S\right)\geq \lambda_2 S\right.$ [26,29,30].

3.1.6.3. Global stability analysis of endemic equilibrium point. Lyapunov functions are mathematical tools used to study the stability of dynamical systems. Different Lyapunov functions are employed for global stability analysis such as; quadratic, non-quadratic, radial basis functions, composite and piecewise Lyapunov functions. This study adopted composite Lyapunov function.

$$L=\sum b_i\left(x_i-x_i^*\ ln\ x_i\right)$$

The function L is said to be positive definite if it satisfies the following conditions.

i) Strict positivity: $L>0$ for all $x\neq 0$.
ii) Zero at origin: $L(0)=0$.

Where b_i the constant is selected such that $b_i>0$, x_i is the population of the ith compartment and x_i^* is the endemic equilibrium point.

$$L=b_1(S-S^*\ ln\ S)+b_2(I-I^*\ ln\ I)+b_3(P-P^*\ ln\ P)+b_4(C-C^*\ ln\ C)+b_5(V-V^*\ ln\ V)+b_3(L-L^*\ ln\ L)$$

$$\frac{dL}{dt}=b_1\left(1-\frac{S^*}{S}\right)\frac{dS}{dt}+b_2\left(1-\frac{I^*}{I}\right)\frac{dI}{dt}+b_3\left(1-\frac{C^*}{C}\right)\frac{dC}{dt}+b_4\left(1-\frac{P^*}{P}\right)\frac{dP}{dt}+b_5\left(1-\frac{V^*}{V}\right)\frac{dV}{dt}+b_6\left(1-\frac{L^*}{L}\right)\frac{dL}{dt}$$

$$\begin{aligned}\frac{dL}{dt}=&b_1\left(1-\frac{S^*}{S}\right)\left\{r_1S(1-k_1N)-\frac{\tau_2S}{S+BV}+\Omega_1I-\delta_1S\right\}+b_2\left(1-\frac{I^*}{I}\right)\left\{r_1I(1-k_1N)+\frac{\tau_2S}{S+BV}\right.\\&\left.-\Omega_2I\right\}+b_3\left(1-\frac{C^*}{C}\right)\left\{\left\{r_1C(1-k_1N)+\Theta\frac{CP^2}{D^2+P^2}-\Omega_4C\right\}(1-k_4C)\right\}+b_4\left(1-\frac{P^*}{P}\right)\left\{r_1P(1-k_1N)+\beta I-\Theta\frac{CP^2}{D^2+P^2}\right.\\&\left.-\Omega_3P\right\}+b_5\left(1-\frac{V^*}{V}\right)\left\{\{r_2V+\omega_1\eta_1I+\omega_2\eta_2P+\omega_3\eta_3C\}(1-k_2V)-\tau_1SV-\epsilon\frac{L}{L+K_4}V-\delta_2V\right\}+b_6\left(1-\frac{L^*}{L}\right)\{r_3L(1-k_3L)\\&-\alpha_1LV-\delta_3L\}\end{aligned}$$

After solving we obtain the value of X and Y as follows.

$$\begin{aligned}X=&b_1r_1S+b_1\Omega_1I+bS^*r_1K_1N+\frac{bS^*\tau_2}{S+BV}+bS^*\delta_1+b_2r_1I+b_2\tau_2S+b_2I^*K_1N+b_2I^*\Omega_2+b_3r_1C+b_3\frac{\theta CP^2}{D^2+P^2}\\&+b_3r_1C^2K_1K_4N+b_3\Omega_4C^2K_4+b_3K_1NC^*+b_3\Omega_4C^*+b_3K_4CC^*r_1+b_3\frac{\theta C^*CP^2K_4}{D^2+P^2}+b_4r_1P+b_4\beta I+b_4r_1PK_1NK_4C\\&+b_4\frac{\theta CP^2}{D^2+P^2}K_4C+b_4\Omega_4C^2K_4+b_4\frac{P^*}{P}\left(r_1PK_1N+\frac{\theta CP^2}{D^2+P^2}+\Omega_4C+r_1PK_4C+\beta ICK_4+b_5\left(r_2V+\omega_1\eta_1I+\omega_2\eta_2P\right.\right.\\&\left.\left.+\omega_3\eta_3C+\omega_2\eta_2PK_2V+b_5\frac{V^*}{V}\left(r_2K_2V^2+\omega_1\eta_1IK_2V+\omega_3\eta_3CK_2V+\tau_1SV+\frac{\epsilon LV}{L+K_4}+\delta_2V\right)+b_6r_3L+b_6\frac{L^*}{L}\left(r_3L^2K_3+\alpha_1LV+\delta_3L\right)\right.\end{aligned}$$

$$\begin{aligned}Y=&-br_1SK_1N-\frac{bS\tau_2}{S+BV}-bS\delta_1-bS^*r_1-\frac{bS^*\Omega_1I}{S}-b_2r_1IK_1N-b_2\Omega_2I-b_2I^*r_1-b_2\frac{I^*}{I}\frac{S\tau_2}{S+BV}-b_3r_1CK_1N-b_3\Omega_4\ C\ -b_3r_1C^2K_4\\&-b_3\frac{\theta C^2P^2K_4}{D^2+P^2}-b_3C^*-b_3\frac{\theta C^*P^2}{D^2+P^2}-b_3C^*\Omega_4CK_4-b_3C^*K_1CK_4r_1-b_4\left(r_1PK_1N+\frac{\theta CP^2}{D^2+P^2}+\Omega_4C+r_1PK_4C+\beta\ I\ K_4C\right)\\&-\ b_4\frac{P^*}{P}\left(r_1P+\beta\ I+r_1PK_1NK_4C+\frac{\theta CP^2}{D^2+P^2}K_4C\right)-b_5\left(r_2K_2V^2+\omega_1\eta_1IK_2V+\omega_3\eta_3CK_2V+\tau_1SV+\frac{\epsilon LV}{L+K_4}+\delta_2V\right)\\&-b_5\frac{V^*}{V}(r_2V+\omega_1\eta_1I+\omega_2\eta_2P+\omega_3\eta_3C+\omega_2\eta_2PK_2V)-b_6\left(r_3L^2K_3+\alpha_1LV+\delta_3L\right)-\ b_6L^*r_3\end{aligned}$$

By inspection method $X>Y$, therefore this result shows that cervical cancer would persist whenever $X>Y$ irrespective of the initial conditions, and if $Y>X$ the disease will die out irrespective of initial conditions. The global stability for EEP exists for people without underlying health conditions, hence implying that the global stability for EEP for system (1–6) [29].

3.1.7. Bifurcation analysis

Most mathematical models often undergo bifurcation which makes the control of most diseases difficult. Utilizing the center manifold theory, the likelihood of population hopf bifurcation was investigated. The renaming of variables is done simply by letting, $S=x_1, I=x_2, P=x_3, C=x_4, V=x_5, L=x_6$;

Using vector notation;

$$x=x_1,x_2,x_3,x_4,x_5,x_6$$

System (1)–(6) is written as,

$\frac{dx}{dt} = F(x)$ where $F = \left(f_1, f_2 f_3, f_4, f_5, f_6\right)^T$, It follows that:

$$\frac{d_{x_1}}{dt} = p_1 = r_1 f_1\left(1 - \frac{N}{K_1}\right) - \frac{\tau_2 f_1 f_5}{f_1 + B f_5} + \frac{EM}{F+M} f_2 - \delta_1 f_1$$

$$\frac{dx_2}{dt} = p_2 = r_1 f_2\left(1 - \frac{N}{K_1}\right) + \frac{\tau_2 f_1 f_5}{f_1 + B f_5} - \beta f_2 - \frac{EM}{F+M} f_2 - \eta_1 f_2 - \delta_1 f_2$$

$$\frac{dx_3}{dt} = p_3 = r_1 f_3\left(1 - \frac{N}{K_1}\right) + \beta f_2 - \Theta \frac{f_4 {f_3}^2}{D^2 + {f_3}^2} - \eta_2 f_3 - \delta_1 f_3.$$

$$\frac{dx_4}{dt} = p_4 = \left\{ r_1 f_4\left(1 - \frac{N}{K_1}\right) + \Theta \frac{f_4 {f_3}^2}{D^2 + {f_3}^2} - \eta_3 f_4 - \delta_1 f_4 \right\}\left(1 - \frac{f_4}{K_4}\right).$$

$$\frac{dx_5}{dt} = p_5 = \left\{ r_2 f_5 + \omega_1 \eta_1 f_2 + \omega_2 \eta_2 f_3 + \omega_3 \eta_3 f_4 \right\}\left(1 - \frac{f_5}{K_2}\right) - \tau_1 f_1 f_5 - \epsilon \frac{f_6}{f_6 + K_4} f_5 - \delta_2 f_5.$$

$$\frac{dx_6}{dt} = p_6 = r_3 f_6\left(1 - \frac{f_6}{K_3}\right) - \alpha_1 f_6 f_5 - \delta_3 f_6.$$

Jacobian solved at DFE,

$\mathrm{E}^0 = (\mathrm{S}^0, \mathrm{I}^0, \mathrm{P}^0, \mathrm{C}^0, \mathrm{V}^0, \mathrm{L}^0) = \left(\frac{K_1(r_1 - \delta_1)}{r_1}, 0, 0, 0, 0, \frac{K_3}{r_3}(r_3 - \delta_3)\right)$, in a case, where $R_0^* = 1$ and further, suppose that $r_1 = r_1^*$ is a bifurcation parameter, then solving for r_1^* from $R_0^* = 1$ we get,

$$r_1^* = \frac{K_1(MQ + F\beta + M\beta + F\delta_1 + M\delta_1 + F\eta_1 + M\eta_1)}{(F+M)(K_1 - S^0)}$$

Gives

$$\begin{bmatrix} A_1 & A_2 \\ A_3 & A_4 \end{bmatrix}$$

Where;

$$A_1 = \begin{bmatrix} \left(1 - \frac{S^0}{K_1}\right) r_1^* - \frac{r_1^* S^0}{K_1} - \delta_1 & \frac{ME}{F+M} - \frac{r_1^* S^0}{K_1} & -\frac{r_1^* S^0}{K_1} \\ 0 & -\frac{ME}{F+M} - \beta + \left(1 - \frac{S^0}{K_1}\right) r_1^* - \delta_1 - \eta_1 & 0 \\ 0 & \beta & \left(1 - \frac{S^0}{K_1}\right) r_1^* - \delta_1 - \eta_2 \end{bmatrix}$$

It can easily be shown that, Jacobian of the system

$$A_2 = \begin{bmatrix} -\frac{r_1^* S^0}{K_1} & \frac{\tau_2 B}{S^0} & 0 \\ 0 & -\frac{\tau_2 B}{S^0} & 0 \\ 0 & 0 & 0 \end{bmatrix} \quad A_3 = \begin{bmatrix} 0 & 0 & 0 \\ 0 & \eta_1 \omega_1 & \eta_2 \omega_2 \\ 0 & 0 & 0 \end{bmatrix}$$

$$A_4 = \begin{bmatrix} \left(1 - \frac{S^0}{K_1}\right) r_1^* - \delta_1 - \eta_3 & 0 & 0 \\ \eta_3 \omega_3 & \frac{\epsilon L^0}{L^0 + K_4} + r_2 - \delta_2 - \tau_1 S^0 & 0 \\ 0 & -\alpha_1 L^0 & \left(1 - \frac{L^0}{K_3}\right) r_3 - \frac{r_3 L^0}{K_3} - \delta_3 \end{bmatrix}$$

It has been proved that at least one of the eigenvalues of the matrix is a simple zero eigenvalue [26]. Therefore, the bifurcation of the system can be evaluated using the Castillo-Chavez theorem.

Let $u = \left(u_1, u_2, u_3, u_4, u_5, u_6\right)^T$ be the right eigenvector and $v = (v_1, v_3, v_4, v_5, v_6)^T$ be the left eigenvector linked with zero eigenvalues of the Jacobian matrix near $r_1 = r_1^*$, of the system.

Solving the system of the equations, we obtain;

$$u_1 = 0, u_2 = \frac{u_3\beta - u_5(\eta_1\omega_1)}{\Omega_1 + \beta + (S^0k_1 - 1) - \delta_1 - \eta_1}, u_3 = \frac{-u_5(\eta_3\omega_3)}{(1 - S^0k_1)r_1 - \eta_3}, u_4 = \frac{-u_5(\eta_3\omega_3)}{(1 - S^0k_1)r_1 - \eta_4}$$

$$u_5 = \frac{u_2 - \frac{\tau_2 B}{S^0} + u_6\alpha_1 L^0}{\frac{\varepsilon L^0}{L^0 + k_4} + r_2 - \delta_2 - \tau_1 S^0} = \frac{u_2 - \frac{\tau_2 B}{S^0}}{\frac{\varepsilon L^0}{L^0 + k_4} + r_2 - \delta_2 - \tau_1 S^0}, u_6 = 0$$

$$v_1 = \frac{-(\eta_1 - r_1 S^0 k_1)v_2 + v_3 r_1 S^0 k_1 - r_1 S^0 k_1 v_4 + v_5\frac{\tau_2 B}{S^0}}{(1 - S^0k_1)r_1 - r_1 S^0 k_1 - \delta_1} = \frac{v_3 r_1 S^0 k_1 + v_5\frac{\tau_2 B}{S^0}}{(1 - S^0k_1)r_1 - r_1 S^0 k_1 - \delta_1}, v_2 = 0$$

$$v_3 = \frac{\left((S^0k_1 - 1)r_1 + \eta_{1+\delta_1} + \Omega_1 + \beta\right)v_2 + v_5\frac{\tau_2 B}{S^0}}{(1 - S^0k_1)r_1 - \eta_3} = \frac{v_5\frac{\tau_2 B}{S^0}}{(1 - S^0k_1)r_1 - \eta_3}, v_4 = 0, v_5 = \frac{-(\eta_2\omega_2)v_3 - (\eta_3\omega_3)v_4}{\frac{\varepsilon L^0}{K_4 + L^0} + r_2 - \delta_2 - \tau_1 S^0}$$

$$= \frac{-(\eta_2\omega_2)v_3}{\frac{\varepsilon L^0}{K_4 + L^0} + r_2 - \delta_2 - \tau_1 S^0}, v_6 = \frac{v_5\alpha_1 L}{\left((1 - L^0k_1)r_3 - \frac{r_3 L^0}{k_3} - \delta_3\right)}.$$

Let p_k be the kth component of p and

$$a = \sum_{k,ij=1}^{n} v_k u_i u_j \frac{\partial^2 p_k}{\partial f_i \partial f_j}(0,0) \text{ and } b = \sum_{k,ij=1}^{n} v_k u_i \frac{\partial^2 p_k}{\partial f_i \partial r_1^*}(0,0)$$

then the local dynamics of the system around the equilibrium point (0,0) is totally determined by the signs of a and b [31].

On evaluating the values of a and b which are found in the appendix in section 3, we conclude that since, $a < 0$ and $b < 0$, when $r_1^* < 0$ with $|r_1^*| \ll 1, (0,0)$ is unstable; when $0 < r_1^* \ll 1, (0,0)$ is then asymptotically stable and there exists a positive unstable equilibrium.

3.2. Numerical simulation

MATLAB2019a is utilized in numerical simulation to illustrate the non-linear ODE's dynamic behavior in system (1)–(6). The simulations are run with the initial conditions and parameter values (taken from the literature review and graphically depicted) in Table 1.

The graphs obtained from simulations are interpreted as follows.

The immunity level for the infected cells varied from M = 0.0000333 to M = 0.000000000000001333 and M = 0.9333 while the other parameters were constant. From Fig. 2 it shows that increasing the immunity level it reduces the number of infected cells. This indicates that eating a balanced diet can boost the immunity level which fights the virus reducing the number of infected cells.

The infection rate for the infected cells was varied from $\gamma_{2=}$ 0.000001 to $\gamma_{2=}$ 0.5000001 while the other parameters were held constant. From Fig. 3 it indicates that when the rate of infection was increased the number of infected cells increased.

The Progression rate from Precancerous cells to Cancerous cells varied from θ = 0.000001 to θ = 0.101 while the other parameters were held constant. Fig. 4 shows that when the progression rate was decreased it increased the pre-cancerous cells while when it was increased it significantly reduced the number of pre-cancerous cells.

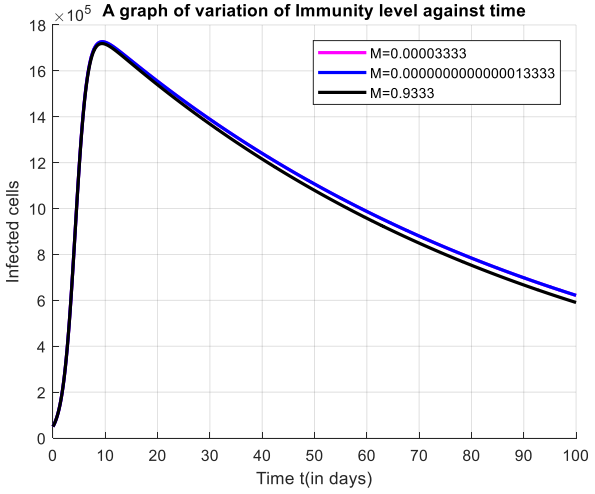

Fig. 2. A graph of variation of Immunity level against time.

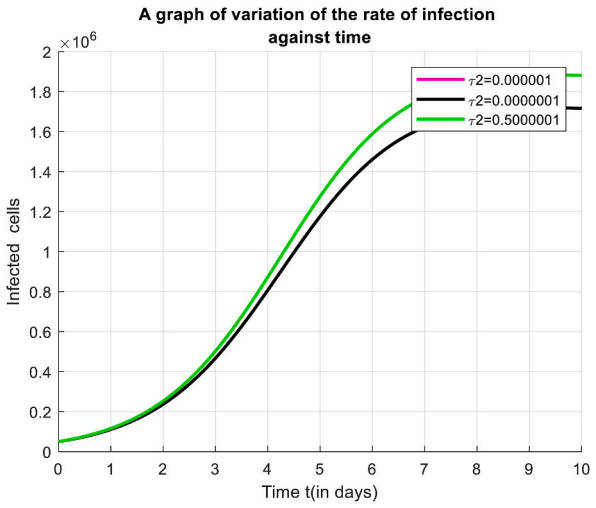

Fig. 3. A graph of variation of the rate of infection against time

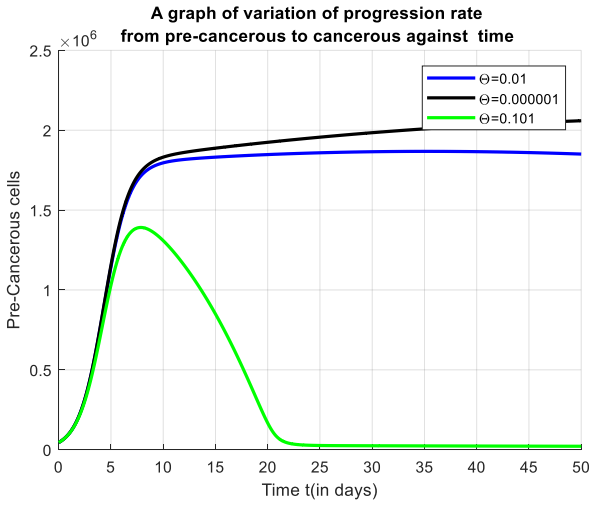

Fig. 4. A graph of variation of progression rate from pre-cancerous to cancerous against time.

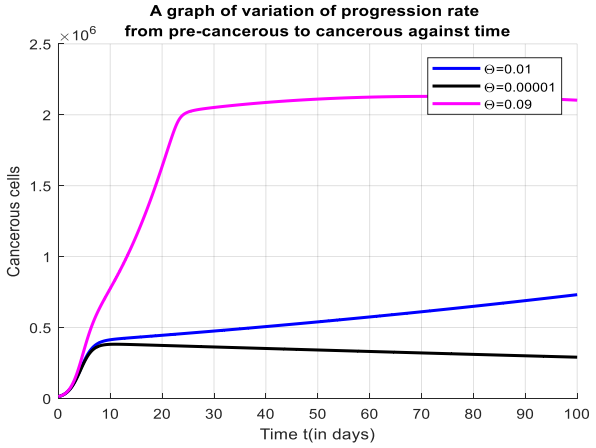

Fig. 5. A graph of variation of progression rate from pre-cancerous to cancerous against time

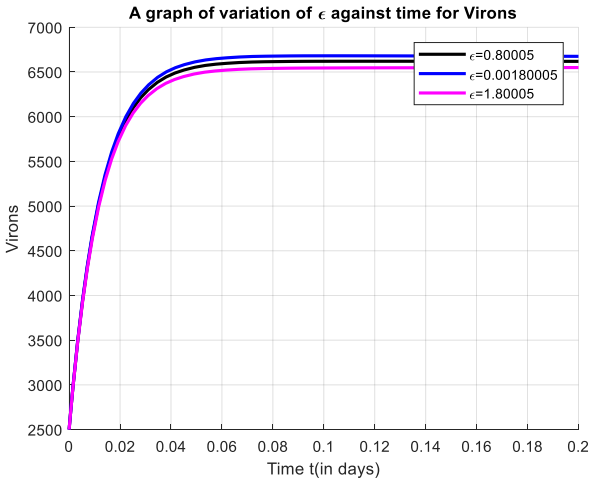

Fig. 6. A graph of variation of $\in$ against time for Virions.

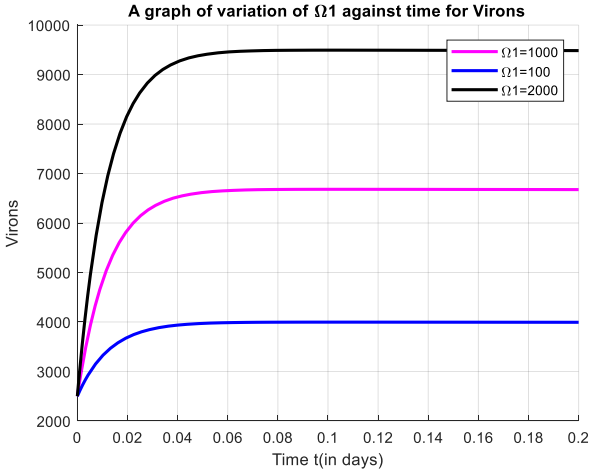

Fig. 7. A graph of variation of Ω_1 against time for Virions

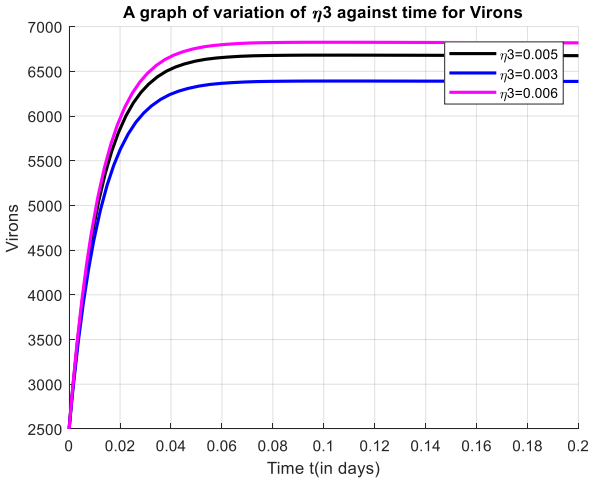

Fig. 8. A graph of Variation of η^3 against time for Virons

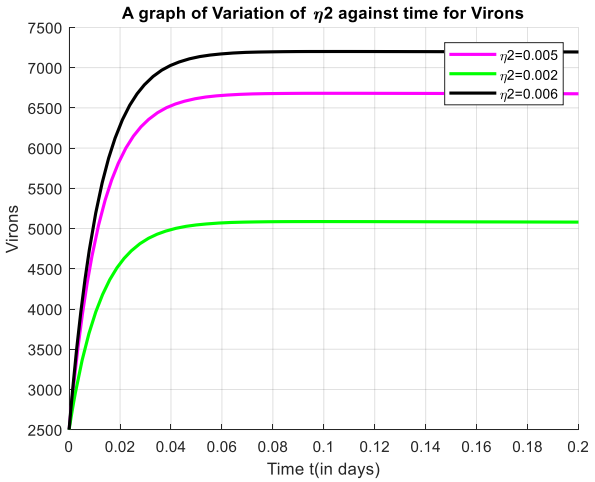

Fig. 9. A graph of Variation of η2 against time for Virons.

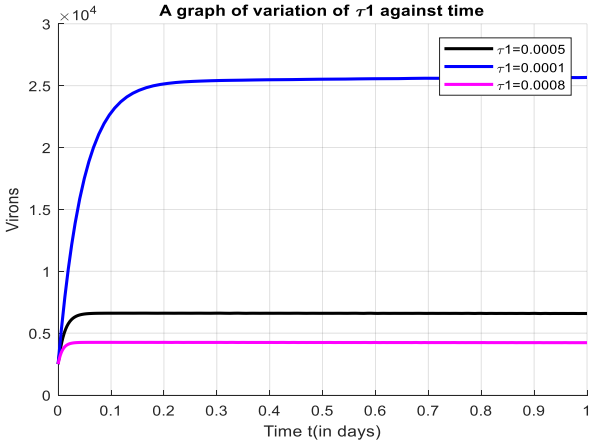

Fig. 10. A graph of Variation of τ1 against time

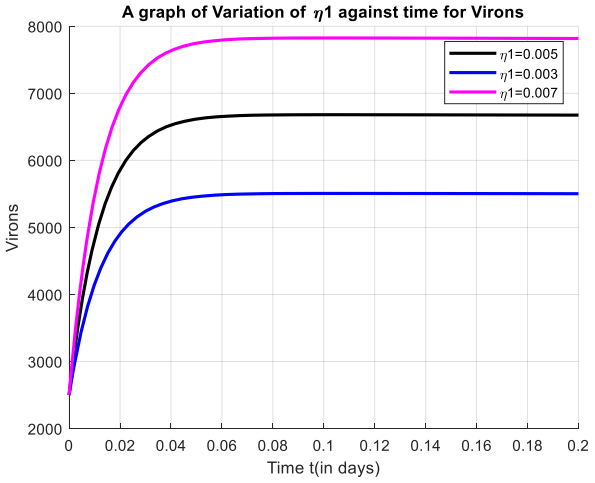

Fig. 11. A graph of variation of η1 against time for Virons

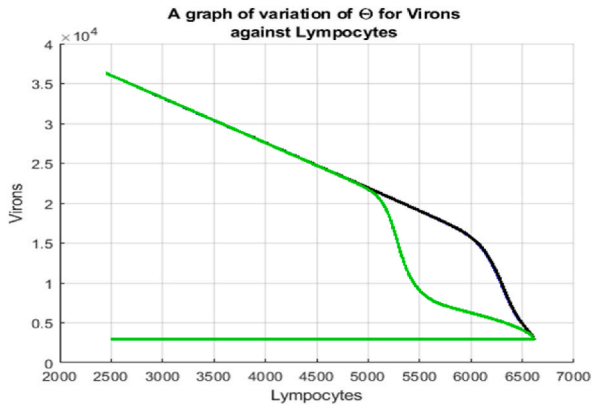

Fig. 12. A graph of Variation of θ for Virons against Lympocytes.

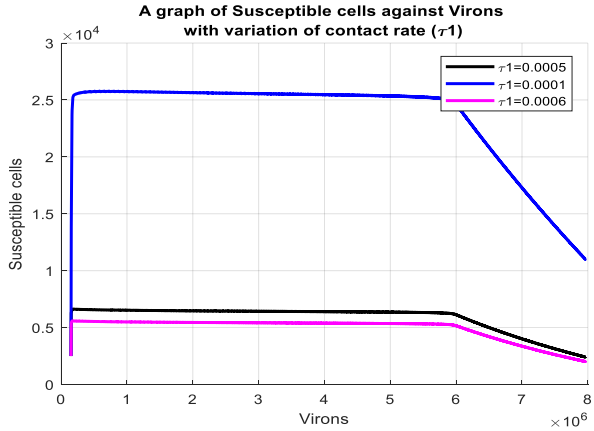

Fig. 13. A graph of Susceptible cells against Virons with variation of contact rate (τ1)

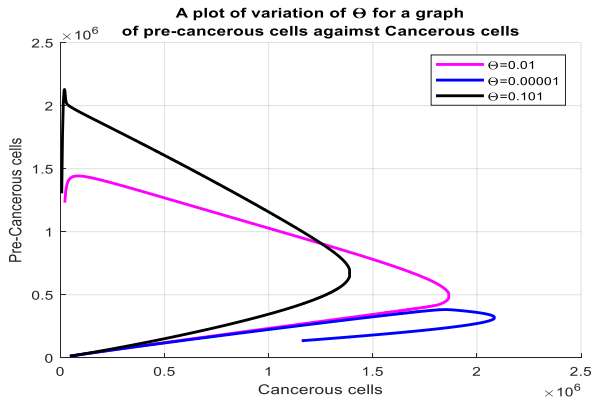

Fig. 14. A plot of variation of θ for a graph of pre-cancerous cells against cancerous cells.

The progression rate from Precancerous cells to Cancerous cells was varied for Cancerous cells while the other parameters were held constant. The results as represented by Fig. 5indicate that when the rate was reduced it decreased the number of cancerous cells while when it was increased, the population of cancerous cells increased (see Fig. 6).

3.3. Sensitivity analysis of the model

The relationship below provides the sensitivity index of the model parameter;

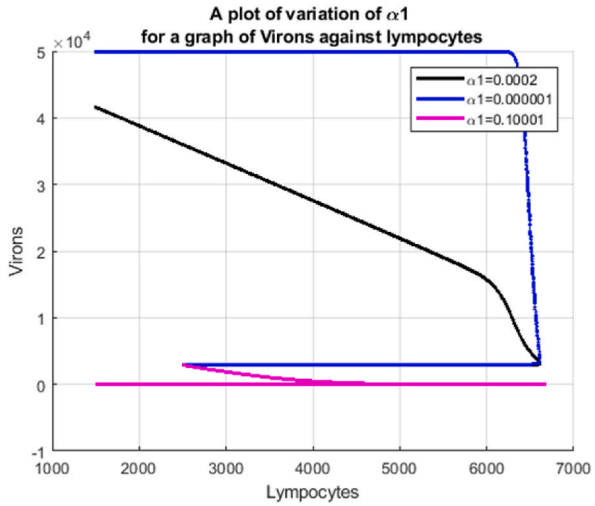

Fig. 15. A plot of variation of α1 for a graph of Virons against Lympocytes

$$S_X^{R_o} = \frac{\partial R_o}{\partial X} * \frac{X}{R_o}$$

Sensitivity analysis for the whole model is as follows.

From the sensitivity indices table above, r_1 is the most positive parameter implying that it is directly related to the dynamics of high-risk HPV to cervical cancer. To reduce the risk of cervical cancer r_1 should be decreased while, S being the most negative means that it is inversely related to the dynamics of HPV to cervical cancer. Increasing the value of S reduces the risk of the disease.

4. Discussion

Based on the analysis done, we discovered that the model was bounded and fell within the positive region; the DFE persisted even in the absence of the disease; the endemic equilibrium point was present when $R_0 > 1$; and the local stability of the DFE is unstable when $R_0^* > 1$ and locally asymptotically stable when $R_0^* < 1$. When $R_0 > 1$, the global stability of EEP is asymptotically stable. Additional examination was conducted utilizing the simplified system of the model (1)–(6), demonstrating that the Disease Free Equilibrium's global stability is asymptotically stable if $R_0^* < 1$ and the lack of backward bifurcation indicates that is feasible to completely eradicate cervical cancer. The reproduction number was found to have a numerical value of $-7.2485210 \times 10^{-6}$, which was used to simulate the model. It was observed that increasing parameter γ_2 increased the number of infected cells hence increasing the risk to cervical cancer while decreasing M reduced the number of infected cells hence the need to focus on a balanced diet so as to boost the immunity levels. It was shown that θ has the most direct impact and the model was able to estimate that a patient can die within 10 days when $\theta = 0.01$, however, the patient can live up to 20 days when $\theta = 0.09$.

5. Conclusion

In the presence of immunity and functional responses, this work aimed to construct an in-host density-dependent deterministic model for the dynamics of basal cells, virions, and lymphocytes and their consequences for cervical cancer. The general (SIVPC) model by Ref. [1] was adjusted for our investigation to include the maximum number of malignant cells that can result in a patient's death. A system of six first-order non-linear ordinary differential equations that explain the dynamics of HPV to cervical cancer helped to achieve this goal in section 2. In this work, the survival function, method of characteristic polynomial, next-generation matrix, positivity and boundedness of the solution, equilibrium points, and basic reproduction number were used to examine the behavior of the deterministic model. The Routh-Hurwitz criteria for stability were used to determine the local stability of the DFE, while the Castillo-Chavez approach was used to determine the global stability of the EEP. Bifurcation analyses were also produced. Additionally, sensitivity indices for the model's system were calculated using the next-generation matrix, survival function, and characteristic polynomial, depending on the reproduction number. Also, sensitivity indices for the system of the model was performed based on the reproduction number using three methods which are next-generation matrix, survival function, and characteristic polynomial.

The model suggests a proportion of 75% of cancerous cells that can lead to the death of a cervical cancer patient however, future studies should focus to obtaining the real data for the proportion of cancerous cells that can lead to the death of a patient.

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We recognize the University of Embu for granting me a full scholarship to pursue my master's degree.

Data availability statement

Data used was a secondary data which was obtained from literature review.

CRediT authorship contribution statement

Elosy Makena: Writing – review & editing, Writing – original draft, Methodology. **Cyrus Gitonga Ngari:** Supervision. **Patrick Mwangi Kimani:** Supervision. **Jeremiah Savali Kilonzi:** Software.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix

Section 1.

The characteristic polynomial of the above matrix is given as;

$$a_0\lambda^6 + a_1\lambda^5 + a_2\lambda^4 + a_3\lambda^3 + a_4\lambda^2 + a_5\lambda + a_6 = 0,$$

Where constant $a_0, a_1, a_2, a_3, a_4, a_5, a_6$ are determined using Mathematica software as;

Routh Table

Label				
λ^6	1	a_2	a_4	a_6
λ^5	a_1	a_3	a_5	0
λ^4	b_1	b_2	b_3	0
λ^3	c_1	c_2	0	0
λ^2	d_1	d_2	0	0
λ^1	e_1	0	0	0
λ^0	f_1	0	0	0

Where,

$$b_1 = \frac{-\begin{vmatrix} 1 & a_2 \\ a_1 & a_3 \end{vmatrix}}{a_1} = \frac{a_1a_2 - a_3}{a_1} \quad b_2 = \frac{-\begin{vmatrix} 1 & a_4 \\ a_1 & a_5 \end{vmatrix}}{a_1} = \frac{a_1a_4 - a_5}{a_1} \quad b_3 = \frac{-\begin{vmatrix} 1 & a_6 \\ a_1 & 0 \end{vmatrix}}{a_1} = a_6$$

$$c_1 = \frac{-\begin{vmatrix} a_1 & a_3 \\ b_1 & b_2 \end{vmatrix}}{b_1} = \frac{b_1a_3 - a_1b_2}{b_1} \quad c_2 = \frac{-\begin{vmatrix} a_1 & a_5 \\ b_1 & b_3 \end{vmatrix}}{b_1} = \frac{b_1a_5 - a_1b_3}{b_1} \quad d_1 = \frac{-\begin{vmatrix} b_1 & b_2 \\ c_1 & c_2 \end{vmatrix}}{c_1} = \frac{c_1b_2 - b_1c_2}{c_1}$$

$$d_2 = \frac{-\begin{vmatrix} b_1 & b_3 \\ c_1 & 0 \end{vmatrix}}{c_1} = b_3 \quad e_1 = \frac{-\begin{vmatrix} c_1 & c_2 \\ d_1 & d_2 \end{vmatrix}}{d_1} = \frac{d_1c_2 - c_1d_2}{d_1} \quad f_1 = -\begin{vmatrix} d_1 & d_2 \\ e_1 & 0 \\ d_1 & \end{vmatrix} = \frac{d_2e_1}{d_1}$$

Section 2.

$$a_1 = \frac{1}{S^0\left(L^0+K_4\right)}\left(S^0\left(\epsilon L^0 - L^0 r_2 - K_4 r_2 + L^0\delta_2 + K_4\delta_2 + \left(-L^0 - K_4\right)\left(r_1 - S^0 k_1 r_1 + \left(1 - S^0 k_1\right)r_1 - \Omega_2 - \Omega_3\right)\right) - S^0\left(L^0 + K_4\right)\left(\left(1 - S^0 k_1\right)r_1 - \Omega_4\right) + S^0\left(L^0 + K_4\right)\left(\delta_1 + \delta_3 + k_3\left(1 - L^0 k_3\right)r_3 L^{0'} + k_1 r_1 S^{0'} - S^0 k_1^2 r_1 S^{0'}\right)\right)$$

$$a_2 = \frac{1}{S\left(L^0+K_4\right)}\Bigg(-AB\left(-L^0 - K_4\right)\eta_1\omega_1 + S^0\Bigg(\left(-L^0 - K_4\right)\left(-r_1 + S^0 k_1 r_1 + \Omega_2\right)\left(\left(1 - S^0 k_1\right)r_1 - \Omega_3\right) + \left(-L^0\epsilon + L^0 r_2 + K_4 r_2 - L^0\delta_2 - K_4\delta_2\right)\left(r_1 - S^0 k_1 r_1 + \left(1 - S^0 k_1\right)r_1 - \Omega_2 - \Omega_3\right)\Bigg) - S^0\Bigg(L^0\epsilon - L^0 r_2 - K_4 r_2 + L^0\delta_2 + K_4\delta_2 + \left(-L^0 - K_4\right)\left(r_1 - S^0 k_1 r_1 + \left(1 - S^0 k_1\right)r_1 - \Omega_2 - \Omega_3\right)\Bigg)\left(\left(1 - S^0 k_1\right)r_1 - \Omega_4\right) + \Bigg(S^0\Bigg(L^0\epsilon - L^0 r_2 - K_4 r_2 + L^0\delta_2 + K_4\delta_2 + \left(-L^0 - K_4\right)\left(r_1 - S^0 k_1 r_1 + \left(1 - S^0 k_1\right)r_1 - \Omega_2 - \Omega_3\right)\Bigg) - S^0\left(L^0 + K_4\right)\left(\left(1 - S^0 k_1\right)r_1 - \Omega_4\right)\Bigg)\left(\delta_1 + \delta_3 + k_3\left(1 - L^0 k_3\right)r_3 L^{0'} + k_1 r_1 S^{0'} - S^0 k_1^2 r_1 S^{0'}\right) + S^0\left(L^0 + K_4\right)\left(-\delta_3 - k_3\left(1 - L^0 k_3\right)r_3 L^{0'}\right)\left(-\delta_1 - k_1 r_1 S^{0'} + S^0 k_1^2 r_1 S^{0'}\right)\Bigg)$$

$$a_3 = \frac{1}{S^0\left(L^0+K_4\right)}\Bigg(\tau_2 B\Bigg(\beta\left(L^0 + K_4\right)\eta_2\omega_2 + \left(-L^0 - K_4\right)\eta_1\omega_1\left(\left(1 - S^0 k_1\right)r_1 - \Omega_3\right)\Bigg) + S^0\left(-L^0\epsilon + L^0 r_2 + K_4 r_2 - L^0\delta_2 - K_4\delta_2\right)\left(-r_1 + S^0 k_1 r_1 + \Omega_2\right)\Bigg(\left(\left(1 - S^0 k_1\right)r_1 - \Omega_3\right) + \Bigg(\tau_2 B\left(-L^0 - K_4\right)\eta_1\omega_1 - S^0\left(\left(-L^0 - K_4\right)\left(-r_1 + S^0 k_1 r_1 + \Omega_2\right)\left(\left(1 - S^0 k_1\right)r_1 - \Omega_3\right) + \left(-L^0\epsilon + L^0 r_2 + K_4 r_2 - L^0\delta_2 - K_4\delta_2\right)\left(r_1 - S^0 k_1 r_1 + \left(1 - S^0 k_1\right)r_1 - \Omega_2 - \Omega_3\right)\right)\Bigg)\Bigg(\left(\left(1 - S^0 k_1\right)r_1 - \Omega_4\right) + \Bigg(-AB\left(-L^0 - K_4\right)\eta_1\omega_1 + S^0\left(\left(-L^0 - K_4\right)\left(-r_1 + S^0 k_1 r_1 + \Omega_2\right)\left(\left(1 - S^0 k_1\right)r_1 - \Omega_3\right) + \left(-L^0\epsilon + L^0 r_2 + K_4 r_2 - L^0\delta_2 - K_4\delta_2\right)\left(r_1 - S^0 k_1 r_1 + \left(1 - S^0 k_1\right)r_1 - \Omega_2 - \Omega_3\right)\right) - S^0\left(L^0\epsilon - L^0 r_2 - K_4 r_2 + L^0\delta_2 + K_4\delta_2 + \left(-L^0 - K_4\right)\left(r_1 - S^0 k_1 r_1 + \left(1 - S^0 k_1\right)r_1 - \Omega_2 - \Omega_3\right)\right)\Bigg)\left(\left(1 - S^0 k_1\right)r_1 - \Omega_4\right)\Bigg)\left(\delta_1 + \delta_3 + k_3\left(1 - L^0 k_3\right)r_3 L^{0'} + k_1 r_1 S^{0'} - S^0 k_1^2 r_1 S^{0'}\right) + \Bigg(S^0\Bigg(L^0\epsilon - L^0 r_2 - K_4 r_2 + L^0\delta_2 + K_4\delta_2 + \left(-L^0 - K_4\right)\left(r_1 - S^0 k_1 r_1 + \left(1 - S^0 k_1\right)r_1 - \Omega_2 - \Omega_3\right)\Bigg) - S^0\left(L^0 + K_4\right)\left(\left(1 - S^0 k_1\right)r_1 - \Omega_4\right)\Bigg)\left(-\delta_3 - k_3\left(1 - L^0 k_3\right)r_3 L^{0'}\right)\left(-\delta_1 - k_1 r_1 S^{0'} + S^0 k_1^2 r_1 S^{0'}\right)\Bigg)$$

$$a_4=\frac{1}{S^0\left(L^0+K_4\right)}((-AB(\beta\left(L^0+K_4\right)\eta_2\omega_2+\left(-L^0-K_4\right)\eta_1\omega_1((1-S^0k_1\Big)r_1-\Omega_3\Big))-S^0\Big(-L^0\epsilon+L^0r_2+K_4r_2-L^0\delta_2-K_4\delta_2\Big)\Big(-r_1+S^0k_1r_1+\Omega_2\Big)\Big(\Big(1-S^0k_1\Big)r_1-\Omega_3\Big)\Big)\Big(\Big(1-S^0k_1\Big)r_1-\Omega_4\Big)+\Big(AB\Big(\beta\Big(L^0+K_4\Big)\eta_2\omega_2+\Big(-L^0-K_4\Big)\eta_1\omega_1((1-S^0k_1\Big)r_1-\Omega_3\Big)\Big)+S^0\Big(-L^0\epsilon+L^0r_2+K_4r_2-L^0\delta_2-K_4\delta_2\Big)\Big(-r_1+S^0k_1r_1+\Omega_2\Big)\Big(\Big(1-S^0k_1\Big)r_1-\Omega_3\Big)+\Big(AB\Big(-L^0-K_4\Big)\eta_1\omega_1-S^0((-L^0-K_4\Big)\Big(-r_1+S^0k_1r_1+\Omega_2\Big)\Big(\Big(1-S^0k_1\Big)r_1-\Omega_3\Big)+\Big(-L^0\epsilon+L^0r_2+K_4r_2-L^0\delta_2-K_4\delta_2\Big)\Big(r_1-S^0k_1r_1+\Big(1-S^0k_1\Big)r_1-\Omega_2-\Omega_3\Big)\Big)\Big)\Big(\Big(1-S^0k_1\Big)r_1-\Omega_4\Big)\Big)\Big(\delta_1+\delta_3+k_3\Big(1-L^0k_3\Big)r_3L^{0'}+k_1r_1S^{0'}-S^0k_1^2r_1S^0\Big)+\Big(-AB\Big(-L^0-K_4\Big)\eta_1\omega_1+S^0((-L^0-K_4\Big)\Big(-r_1+S^0k_1r_1+\Omega_2\Big)\Big(\Big(1-S^0k_1\Big)r_1-\Omega_3\Big)+\Big(-L^0\epsilon+L^0r_2+K_4r_2-L^0\delta_2-K_4\delta_2\Big)\Big(r_1-S^0k_1r_1+\Big(1-S^0k_1\Big)r_1-\Omega_2-\Omega_3\Big)\Big)-S^0\Big(L^0\epsilon-L^0r_2-K_4r_2+L^0\delta_2+K_4\delta_2+\Big(-L^0-K_4\Big)\Big(r_1-S^0k_1r_1+\Big(1-S^0k_1\Big)r_1-\Omega_2-\Omega_3\Big)\Big)\Big(\Big(1-S^0k_1\Big)r_1-\Omega_4\Big)\Big)\Big(-\delta_3-k_3\Big(1-L^0k_3\Big)r_3L^{0'}\Big)\Big(-\delta_1-k_1r_1S^{0'}+S^0k_1^2r_1S^{0'}\Big)\Big)$$

$$a_5=\frac{1}{S^0\left(L^0+K_4\right)}((-\tau_2AB\Big(\beta\Big(L^0+K_4\Big)\eta_2\omega_2+\Big(-L^0-K_4\Big)\eta_1\omega_1((1-S^0k_1\Big)r_1-\Omega_3\Big)\Big)-S^0\Big(-L^0\epsilon+L^0r_2+K_4r_2-L^0\delta_2-K_4\delta_2\Big)\Big(-r_1+S^0k_1r_1+\Omega_2\Big)\Big(\Big(1-S^0k_1\Big)r_1-\Omega_3\Big)\Big)\Big(\Big(1-S^0k_1\Big)r_1-\Omega_4\Big)\Big(\delta_1+\delta_3+k_3\Big(1-L^0k_3\Big)r_3L^{0'}+k_1r_1S^{0'}-S^0k_1^2r_1S^{0'}\Big)+\Big(\tau_2B\Big(\beta\Big(L^0+K_4\Big)\eta_2\omega_2+\Big(-L^0-K_4\Big)\eta_1\omega_1((1-S^0k_1\Big)r_1-\Omega_3\Big)\Big)+S^0\Big(-L^0\epsilon+L^0r_2+K_4r_2-L^0\delta_2-K_4\delta_2\Big)\Big(-r_1+S^0k_1r_1+\Omega_2\Big)\Big(\Big(1-S^0k_1\Big)r_1-\Omega_3\Big)+\Big(\tau_2B\Big(-L^0-K_4\Big)\eta_1\omega_1-S^0((-L^0-K_4\Big)\Big(-r_1+S^0k_1r_1+\Omega_2\Big)\Big(\Big(1-S^0k_1\Big)r_1-\Omega_3\Big)+\Big(-L^0\epsilon+L^0r_2+K_4r_2-L^0\delta_2-K_4\delta_2\Big)\Big(r_1-S^0k_1r_1+\Big(1-S^0k_1\Big)r_1-\Omega_2-\Omega_3\Big)\Big)\Big)\Big(\Big(1-S^0k_1\Big)r_1-\Omega_4\Big)\Big)\Big(-\delta_3-k_3\Big(1-L^0k_3\Big)r_3LL^{0'}\Big)\Big(-\delta_1-k_1r_1S^0S^{0'}+S^0k_1^2r_1S^{0'}\Big)\Big)$$

$$a_6=\frac{1}{S^0\left(L^0+K_4\right)}\Big(-\tau_2B\Big(\beta\Big(L^0+K_4\Big)\eta_2\omega_2+\Big(-L^0-K_4\Big)\eta_1\omega_1((1-S^0k_1\Big)r_1-\Omega_3\Big)\Big)-S^0\Big(-L^0\epsilon+L^0r_2+K_4r_2-L^0\delta_2-K_4\delta_2\Big)\Big(-r_1+S^0k_1r_1+\Omega_2\Big)\Big(\Big(1-S^0k_1\Big)r_1-\Omega_3\Big)\Big)\Big(\Big(1-S^0k_1\Big)r_1-\Omega_4\Big)\Big(-\delta_3-k_3\Big(1-L^0k_3\Big)r_3L^{0'}\Big)\Big(-\delta_1-k_1r_1S^{0'}+S^0k_1^2r_1S^{0'}\Big)$$

By Routh-Hurwitz criteria for stability, system (1)–(6) is locally asymptomatically stable at disease-free equilibrium $\left(E^0\right)$ if and only if $a_1>0, a_2>0, a_4>0, a_6>0, b_1>0, c_1>0, d_1>0$ *and* $e_1>0$ are satisfied and otherwise unstable.

Section 3.

The bifurcation results of a and b values are as follows;

$$
\begin{aligned}
a = & -\frac{2(-AB+u_2)v_3\eta_2\omega_2\left(-\frac{\epsilon f_6}{f_6+K_4}+\left(1-\frac{f_5}{K_2}\right)r_2-\delta_2+\left(1-\frac{f_5}{K_2}\right)\eta_1\omega_1-\frac{f_5r_2+f_2\eta_1\omega_1+f_3\eta_2\omega_2+f_4\eta_3\omega_3}{K_2}\right)(\beta u_3-u_5[\eta_1\omega_1])}{\left(\frac{\epsilon}{1+k_4}+r_2-\delta_2\right)\left(\frac{\epsilon}{1+K_4}+r_2-\delta_2\right)(-1+\beta+k_1-\delta_1-\eta_1+\Omega_1)} \\
& +\frac{2(-AB+u_2)v_3\eta_2\omega_2\left(-\frac{\epsilon f_6}{f_6+K_4}+\left(1-\frac{f_5}{K_2}\right)r_2-\delta_2+\left(1-\frac{f_5}{K_2}\right)\eta_2\omega_2-\frac{f_5r_2+f_2\eta_1\omega_1+f_3\eta_2\omega_2+f_4\eta_3\omega_3}{K_2}\right)u_5[\eta_3\omega_3]}{\left(\frac{\epsilon}{1+k_4}+r_2-\delta_2\right)\left(\frac{\epsilon}{1+K_4}+r_2-\delta_2\right)((1-k_1)r_1-\eta_3)} \\
& +\frac{2(-AB+u_2)v_3\eta_2\omega_2\left(-\frac{\epsilon f_6}{f_6+K_4}+\left(1-\frac{f_5}{K_2}\right)r_2-\delta_2+\left(1-\frac{f_5}{K_2}\right)\eta_3\omega_3-\frac{f_5r_2+f_2\eta_1\omega_1+f_3\eta_2\omega_2+f_4\eta_3\omega_3}{K_2}\right)u_5[\eta_3\omega_3]}{\left(\frac{\epsilon}{1+k_4}+r_2-\delta_2\right)\left(\frac{\epsilon}{1+K_4}+r_2-\delta_2\right)((1-k_1)r_1-\eta_4)} \\
& -\frac{2ABv_5\left(\beta+\frac{2\theta f_3^3f_4}{\left(D^2+f_3^2\right)^2}-\frac{2\theta f_3f_4}{D^2+f_3^2}+1\left[1-\frac{N}{K_1}\right]r_1-\delta_1-\eta_2\right)(\beta u_3-u_5[\eta_1\omega_1])u_5[\eta_3\omega_3]}{((1-k_1)r_1-\eta_3)^2(-1+\beta+k_1-\delta_1-\eta_1+\Omega_1)} \\
& -\frac{2AB\left(\beta-\frac{\theta f_3^2}{D^2+f_3^2}\right)v_5(\beta u_3-u_5[\eta_1\omega_1])u_5[\eta_3\omega_3]}{((1-k_1)r_1-\eta_3)}+\frac{2v_3\eta_2\omega_2\left(\left(1-\frac{f_5}{K_2}\right)\eta_1\omega_1+\left(1-\frac{f_5}{K_2}\right)\eta_2\omega_2\right)(\beta u_3-u_5[\eta_1\omega_1])u_5[\eta_3\omega_3]}{\left(\frac{\epsilon}{1+K_4}+r_2-\delta_2\right)((1-k_1)r_1-\eta_3)(-1+\beta+k_1-\delta_1-\eta_1+\Omega_1)} \\
& +\frac{2v_3\eta_2\omega_2\left(\left(1-\frac{f_5}{K_2}\right)\eta_1\omega_1+\left(1-\frac{f_5}{K_2}\right)\eta_3\omega_3\right)(\beta u_3-u_5[\eta_1\omega_1])u_5[\eta_3\omega_3]}{\left(\frac{\epsilon}{1+K_4}+r_2-\delta_2\right)((1-k_1)r_1-\eta_4)(-1+\beta+k_1-\delta_1-\eta_1+\Omega_1)} \\
& +\frac{2ABv_5\left(-\frac{\theta f_3^2}{D^2+f_3^2}+\frac{2\theta f_3^3f_4}{\left(D^2+f_3^2\right)^2}-\frac{2\theta f_3f_4}{D^2+f_3^2}+1\left[1-\frac{N}{K_1}\right]r_1-\delta_1-\eta_2\right)u_5[\eta_3\omega_3]^2}{((1-k_1)r_1-\eta_3)^2((1-k_1)r_1-\eta_4)}-\frac{2v_3\eta_2\omega_2\left(\left(1-\frac{f_5}{K_2}\right)\eta_2\omega_2+\left(1-\frac{f_5}{K_2}\right)\eta_3\omega_3\right)u_5[\eta_3\omega_3]^2}{\left(\frac{\epsilon}{1+K_4}+r_2-\delta_2\right)((1-k_1)r_1-\eta_3)((1-k_1)r_1-\eta_4)} \\
& -\left.\frac{2(-\tau_2B+u_2)(-k_1r_1v_4+\tau_2Bv_5+v_2(k_1r_1-\eta_1))u_5[\eta_1\omega_1]\left(\frac{eM}{F+M}+\frac{\tau_2Bf_1}{\left(f_1+Bf_5\right)^2}-\frac{r_1f_1'\left[1-\frac{f_1+f_2+f_3+f_4}{K_1}\right]}{K_1}\right)}{((1-k_1)r_1-k_1r_1-\delta_1)}\right\}
\end{aligned}
$$

$$b=\frac{2\Theta f_3^3 f_4}{\left(D^2+f_3^2\right)^2}-\frac{2\Theta f_3 f_4}{D^2+f_3^2}-\delta_1-\eta_2+\frac{(-AB+u_2)(k_1r_1v_3+ABv_5)\left(\frac{ABf_1}{\left(f_1+Bf_5\right)^2}+f_1\left[1-\frac{f_1+f_2+f_3+f_4}{K_1}\right]\right)}{((1-k_1)r_1-k_1r_1-\delta_1)}+f_3\Bigg[1$$
$$-\frac{f_1+f_2+f_3+f_4}{K_1}\Bigg]+\frac{AB(-AB+u_2)v_5f_3\left[1-\frac{f_1+f_2+f_3+f_4}{K_1}\right]}{\left(\frac{c}{1+k_4}+r_2-\delta_2\right)((1-k_1)r_1-\eta_3)}+\frac{AB\left(\beta+f_3\left(1-\frac{f_1+f_2+f_3+f_4}{K_1}\right)-\frac{f_3r_1}{K_1}\right)v_5(\beta u_3-u_5[\eta_1\omega_1])}{((1-k_1)r_1-\eta_3)}$$
$$-\frac{(k_1r_1v_3+ABv_5)u_5[\eta_3\omega_3]\left(f_1\left[1-\frac{f_1+f_2+f_3+f_4}{K_1}\right]-\frac{r_1{f_1}'\left[1-\frac{f_1+f_2+f_3+f_4}{K_1}\right]}{K_1}\right)}{((1-k_1)r_1-k_1r_1-\delta_1)}$$
$$-\frac{(k_1r_1v_3+ABv_5)u_5[\eta_3\omega_3]\left(f_1\left[1-\frac{f_1+f_2+f_3+f_4}{K_1}\right]-\frac{r_1{f_1}'\left[1-\frac{f_1+f_2+f_3+f_4}{K_1}\right]}{K_1}\right)}{((1-k_1)r_1-k_1r_1-\delta_1)}$$
$$+\frac{(k_1r_1v_3+ABv_5)(\beta u_3-u_5[\eta_1\omega_1])\left(\frac{eM}{F+M}+f_1\left[1-\frac{f_1+f_2+f_3+f_4}{K_1}\right]-\frac{r_1{f_1}'\left[1-\frac{f_1+f_2+f_3+f_4}{K_1}\right]}{K_1}\right)}{((1-k_1)r_1-k_1r_1-\delta_1)}$$
$$-\frac{ABr_1v_5u_5[\eta_3\omega_3]\left(1\left[1-\frac{f_1+f_2+f_3+f_4}{K_1}\right]-\frac{{f_3}'\left[1-\frac{f_1+f_2+f_3+f_4}{K_1}\right]}{K_1}\right)}{((1-k_1)r_1-\eta_3)^2}-\frac{ABv_5u_5[\eta_3\omega_3]\left(-\frac{\Theta f_3^2}{D^2+f_3^2}+f_3\left[1-\frac{f_1+f_2+f_3+f_4}{K_1}\right]-\frac{r_1{f_3}'\left[1-\frac{f_1+f_2+f_3+f_4}{K_1}\right]}{K_1}\right)}{((1-k_1)r_1-\eta_3)}$$

Section 4.

$$b_4=1;$$

$$b_3=r_1\left(-\frac{1}{\frac{MQ}{F+M}+\beta+\delta_1+\eta_1}-\frac{1}{\delta_1+\eta_2}-\frac{1}{\delta_1+\eta_3}+\frac{S\left(\frac{1}{\frac{MQ}{F+M}+\beta+\delta_1+\eta_1}+\frac{1}{\delta_1+\eta_2}+\frac{1}{\delta_1+\eta_3}\right)}{K_1}\right)-\frac{r_2}{\frac{L\epsilon}{L+K_4}+\delta_2+S\tau_1}$$

$$b_2=r_1\left(\frac{(S-K_1)^2r_1(F\beta+M(Q+\beta)+(F+M)(3\delta_1+\eta_1+\eta_2+\eta_3))}{K_1^2(F\beta+M(Q+\beta)+(F+M)(\delta_1+\eta_1))(\delta_1+\eta_2)(\delta_1+\eta_3)}+\frac{r_2\left(\frac{1}{\frac{MQ}{F+M}+\beta+\delta_1+\eta_1}+\frac{1}{\delta_1+\eta_2}+\frac{1}{\delta_1+\eta_3}+\frac{S\left(-\frac{1}{\frac{MQ}{F+M}+\beta+\delta_1+\eta_1}-\frac{1}{\delta_1+\eta_2}-\frac{1}{\delta_1+\eta_3}\right)}{K_1}\right)}{\frac{L\epsilon}{L+K_4}+\delta_2+S\tau_1}\right)$$

$$b_1 = -\frac{r_1^3}{\left(\frac{MQ}{F+M}+\beta+\delta_1+\eta_1\right)(\delta_1+\eta_2)(\delta_1+\eta_3)}+\frac{S^3r_1^3}{K_1^3\left(\frac{MQ}{F+M}+\beta+\delta_1+\eta_1\right)(\delta_1+\eta_2)(\delta_1+\eta_3)}$$
$$-\frac{3S^2r_1^3}{K_1^2\left(\frac{MQ}{F+M}+\beta+\delta_1+\eta_1\right)(\delta_1+\eta_2)(\delta_1+\eta_3)}+\frac{3Sr_1^3}{K_1\left(\frac{MQ}{F+M}+\beta+\delta_1+\eta_1\right)(\delta_1+\eta_2)(\delta_1+\eta_3)}$$
$$-\frac{r_1^2r_2}{\left(\frac{MQ}{F+M}+\beta+\delta_1+\eta_1\right)(\delta_1+\eta_2)\left(\frac{L\epsilon}{L+K_4}+\delta_2+S\tau_1\right)}-\frac{S^2r_1^2r_2}{K_1^2\left(\frac{MQ}{F+M}+\beta+\delta_1+\eta_1\right)(\delta_1+\eta_2)\left(\frac{L\epsilon}{L+K_4}+\delta_2+S\tau_1\right)}$$
$$+\frac{2Sr_1^2r_2}{K_1\left(\frac{MQ}{F+M}+\beta+\delta_1+\eta_1\right)(\delta_1+\eta_2)\left(\frac{L\epsilon}{L+K_4}+\delta_2+S\tau_1\right)}-\frac{r_1^2r_2}{\left(\frac{MQ}{F+M}+\beta+\delta_1+\eta_1\right)(\delta_1+\eta_3)\left(\frac{L\epsilon}{L+K_4}+\delta_2+S\tau_1\right)}$$
$$-\frac{S^2r_1^2r_2}{K_1^2\left(\frac{MQ}{F+M}+\beta+\delta_1+\eta_1\right)(\delta_1+\eta_3)\left(\frac{L\epsilon}{L+K_4}+\delta_2+S\tau_1\right)}+\frac{2Sr_1^2r_2}{K_1\left(\frac{MQ}{F+M}+\beta+\delta_1+\eta_1\right)(\delta_1+\eta_3)\left(\frac{L\epsilon}{L+K_4}+\delta_2+S\tau_1\right)}$$
$$-\frac{r_1^2r_2}{(\delta_1+\eta_2)(\delta_1+\eta_3)\left(\frac{L\epsilon}{L+K_4}+\delta_2+S\tau_1\right)}-\frac{S^2r_1^2r_2}{K_1^2(\delta_1+\eta_2)(\delta_1+\eta_3)\left(\frac{L\epsilon}{L+K_4}+\delta_2+S\tau_1\right)}+\frac{2Sr_1^2r_2}{K_1(\delta_1+\eta_2)(\delta_1+\eta_3)\left(\frac{L\epsilon}{L+K_4}+\delta_2+S\tau_1\right)}.$$

$$b_0 = \frac{(F+M)\left(S^0-K_1\right)^3\left(L^0+K_4\right)r_1^3r_2}{K_1^3(F\beta+M(Q+\beta)+(F+M)(\delta_1+\eta_1))(\delta_1+\eta_2)(\delta_1+\eta_3)\left(L^0\epsilon+\left(L^0+K_4\right)(\delta_2+S\tau_1)\right)}$$

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