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Mathematical Modelling of Human Papillomavirus (HPV) Dynamics with Vaccination Incorporating Optimal Control Analysis

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Abstract

Human Papillomavirus (HPV) is an infectious illness with complex behavior that has had dangerous consequences in the society. In women, HPV is the leading cause of Cervical Cancer (CC). If not treated early, cervical cancer causes abnormal growth of the cervical walls, which leads to death. It is a threat, with half a million documented cases worldwide resulting in over 200 000 recorded deaths every year. In this research, we develop a mathematical model of HPV dynamics with vaccination and perform optimal control to reduce HPV and CC preventive expenses. The invariant region of the model solution was examined, and it was determined that the model was well posed and biologically meaningful. The feasibility of the model solution was examined, and it was discovered that the solution of the model remained positive in the feasible

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limited region Ω. The disease equilibrium points were shown to exist. The basic reproduction number was examined and discovered to be the biggest eigenvalue of the next generation matrix. The local stability of the equilibrium points was investigated, and it was discovered that the disease free equilibrium and the endemic equilibrium points were asymptotically stable. The model was extended into optimal control, and their optimality system was derived analytically using the Pontryagin Maximum Principle. The optimality system was numerically solved using MATLAB software, and the graphs for various interventions were shown against time. Finally, the outcomes of this study suggest that when the three interventions (awareness, screening and treatment of HPV and CC, and vaccination) are combined, the infection begins to decrease considerably and eventually dies out in the community when the interventions are intensified.

Keywords: HPV and CC; transmission dynamics; optimality system; interventions; local stability; equilibrium points; numerical simulation.

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1 Introduction

Human papillomavirus (HPV) is an infectious disease that spreads through sexual contact with infected individuals. There are currently 78 million HPV-positive persons in the United States, and 14 million people contract the virus every year [1]. There are around 200 different forms of HPV, of which about 40 are linked to both men and women genitalia [2, 3, 4]. To combat the risk of HPV-related cancers, vaccines have been developed that target highly prevalent HPV types. These vaccines have been used effectively to prevent most prevalent HPV infections and have been recommended for both males and females to reduce the risk of HPV-related cervical cancers[5].

The abnormal growth of cervical walls is referred to as cervical cancer. It is brought on by the HPV virus. 110 000 incidences are reported each year in Latin America[6, 7]. About 11 000 new infections of CC occur in Mexico with 4 500 documented deaths [2]. In Sub-Saharan Africa 19 out of the top 20 countries were reported having the biggest burden of CC in 2018 [5]. There were 11632 new reported cases and 68 percent of the victims were female [5]. According to current estimates by WHO, 3211 women die from the disease in Kenya each year, while 5236 women are diagnosed with CC [1].

In Kenya, CC occurs frequently among women after breast cancer. It occurs in young women as well, although it is more prevalent in women between the ages of 35 and 55 [8, 9]. Unusual birth canal bleeding and bleeding between periods are the ways in which CC manifests itself in an individual. Chemotherapy, surgery, radiography, and palliative care are available as cervical cancer treatments. HPV eradication in the community is a challenging and expensive task. To solve the issue, several mathematical models were developed. Malia *et al* [10] came up with a model to investigate the outcomes of HPV infection with immunization in Kenya in presence of poor informative media awareness initiatives. According to the model, HPV infections continue to spread throughout the population as long as unsuccessful mass media awareness programs are in place.

A mathematical model of CC caused by HPV dynamics in presence of immunization was studied by D.D. Tokose [11]. The model feasible region, solution set positivity, fundamental reproduction number, equilibrium points, and stability analysis were all examined. The author came to the conclusion that if immunization and the right treatment are carefully combined, the number of infected people will continue to decline.

Zhang *et al* [12] carried out a study on the best course of treatment and sensitivity analysis of the model of HPV transmission dynamics. The investigation came to the conclusion that the sickness disappears when the value of the parameter R_0 is changed to $R_0 < 1$. There will be an epidemic of the infection, which will thereafter turn into an endemic illness when $R_0 > 1$. The outcomes also demonstrated that a sound treatment plan can successfully stop the disease from spreading.

A mathematical model was developed by Saldaña *et al* [2] as an optimal control strategy to study HPV infection dynamics and vaccination techniques. The fundamental reproduction number R_0 was analysed using the next generation matrix. The local stability of Disease Free Equilibrium point (DFE) was examined for $R_0 > 1$; the model shows a singular Endemic Equilibrium point(EE) that is locally asymptotically stable. Additionally, the model incorporated vaccination rates over time. The results therefore indicate that even if males are not given the vaccine, vaccination strategies for girls alone combined with catch-up vaccination for adult females can assist to eradicate HPV-related malignancies as long as high female coverage is maintained for several years. Further, HPV eradication can be accomplished much more quickly if both sexes are involved. The author also reported that the best way to distribute vaccines is to give them out in large quantities at the beginning of an outbreak and then gradually reduce immunization rates until they are nil. Despite all of this research, it is still difficult and expensive to eradicate HPV in the population. An optimal control analysis of a mathematical model of HPV with vaccination that included optimal control analysis was therefore carried out to bridge the gap.

This paper is organized as follows; section 1 is introduction, section 2 the model is formulated and the dynamics HPV with vaccination analysed. The invariant region, positivity and boundedness of the model solutions have also been examined. In section 3 local stability analysis at the Disease-Free Equilibrium and at Endemic Equilibrium point are analysed. In section 4, the model is extended into optimal control. Section 5 Numerical simulation of the optimal control model where graphical representation of simulation results have been described. To conclude, the study has discussed the main results and future directions implicated by findings of this research.

2 Model Formulation

The total population $N(t)$ was subdivided into five compartments; S(t) Susceptible to HPV infection, V(t) Individuals that are vaccinated against HPV , I(t) Individuals infected with HPV without CC, C(t) Individuals that have developed cervical cancer due to HPV infection, R(t) Individuals that are permanently recovered due to vaccination and body immune system.

The total population $N(t) = S(t) + V(t) + I(t) + R(t) + C(t)$.

The model was described by the following system of ODEs;

$$\begin{aligned} \frac{dS}{dt} &= (1-p)\Lambda - (a+\mu+\beta I)S + \sigma I + bV \\ \frac{dV}{dt} &= p\Lambda + aS - (b+\mu+\kappa)V \\ \frac{dI}{dt} &= \beta SI - (\sigma+\mu+\alpha+\gamma)I \\ \frac{dC}{dt} &= I\alpha - (\mu+\delta)C \\ \frac{dR}{dt} &= \gamma I + \kappa V - \mu R \end{aligned} \tag{2.1}$$

Parameters used in the model include: Λ Recruitment rate, $(1-p)\Lambda$ likelihood recruitment into susceptible, $p\Lambda$ likelihood recruitment into vaccinated, a rate of vaccination for those who are at risk, b how quickly those who have had vaccinations are vulnerable, κ rate for vaccine-protected people to fully recover, β rate of HPV infection among those who are susceptible, σ rate at which infected individuals go back to being susceptible, α rate at which CC develops in those who have HPV infection, δ mortality due to CC, μ natural mortality rate, γ rate of recovery for infected people.

The study was based on the following assumptions;

(i) Recruitment into the population is by females becoming sexually active and other factors like immigration

(ii) HPV recoveries acquire permanent immunity and are not susceptible to cervical cancer infection.

2.1 Invariant Region

The Invariant region gives the region of study. The model in equation 2.1 was analysed in a feasible bounded region Ω that was defined as:

$\Omega = \{[S(t), V(t), I(t), C(t), R(t)] \in \mathbb{R}^5_+ : N(t) \leqslant \frac{\Lambda}{\mu}\}$

To show that the region Ω was a bounded set, the time derivatives of N was taken as follows;

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dV}{dt} + \frac{dI}{dt} + \frac{dC}{dt} + \frac{dR}{dt} \tag{2.2}$$

Substituting the right hand side of equation 2.2 with their equivalent from the system of equation 2.1 we get;

$$\frac{dN}{dt} = \Lambda - p\Lambda - aS - \mu S - \beta S + \sigma I + bV + p\Lambda + aS - bV - \mu V - \kappa V + \beta S - \sigma I - \mu I - \alpha I - \gamma I + \alpha I - \mu C - \delta + \gamma I + \kappa V - \mu R. \tag{2.3}$$

Simplifying equation 2.3 we obtain;

$\frac{dN}{dt} = \Lambda - \mu N - \delta C$

For any increasing population $\delta C > 0$ holds. Thus if Cervical cancer deaths were not considered, then;

$\frac{dN}{dt} \leqslant \Lambda - \mu N$

$$\frac{dN}{dt} + \mu N \leqslant \Lambda \tag{2.4}$$

Integrating the equation 2.4 by integrating factor (I.F) method we get;

$$N(t) \leqslant \frac{\Lambda}{\mu} + A\exp^{-\mu t} \tag{2.5}$$

To find the value of A consider the initial condition for $N(t)$, at initial time where $N(t) = N(0)$ and Substituting into equation 2.5 becomes;

$N(0) \leqslant \frac{\Lambda}{\mu} + A\exp^0$

$A = N(0) - \frac{\Lambda}{\mu}$

Substituting back into 2.5, results to;

$N(t) \leqslant \frac{\Lambda}{\mu} + [N(0) - \frac{\Lambda}{\mu}]exp^{-\mu t}$

But $N(t) \leqslant 0$, thus we have;

$0 \leqslant N(t) \leqslant \frac{\Lambda}{\mu} + [N(0) - \frac{\Lambda}{\mu}]exp^{-\mu t}$

As $t \longrightarrow \infty$, we have

$$0 \leqslant N(t) \leqslant \frac{\Lambda}{\mu} \tag{2.6}$$

This implies that the total population was bounded hence the set of solutions was bounded. Therefore the model is well posed and hence biologically meaningful.

Theorem: Given the model represented by the system of equation 2.1 with conditions $S(0) \geqslant 0$, $V(0) > 0$, $I(0) \geqslant 0$, $C(0) \geqslant 0$, $R(0) \geqslant 0$, then the solutions set $\{[S(t), V(t), I(t), C(t), C(t), R(t)]\}$ of the model remain positive for all time $t \geqslant 0$ in the feasible region Ω.

Proof: Given the initial conditions $S(0) \geqslant 0$, $V(0) \geqslant 0$, $I(0) \geqslant 0$, $C(0) \geqslant 0$, $R(t) \geqslant 0$ for $t \geqslant 0$, it can be shown that the solutions of equation 2.1 will remain to be positive.

This was done by showing that each of the trajectories of the system of equation 2.1 was non-negative for all time $t \geqslant 0$. Considering the first equation of the system in equation 2.1,

$\frac{dS}{dt} = (1-p)\Lambda - (a+\mu+\beta)S + \sigma I + bV)$

The resulting differential inequality was given as

$\frac{dS}{dt} \geqslant -(a+\mu+\beta)S$

The differential inequality was solved by the method of separation of variables and finally we get;

$S(t) \geqslant S(0)\exp^{-(a+\mu+\beta)t} > 0$

Repeating the same process of solving the second, third, fourth and fifth equations in the system of equation 2.1 by the method of separation of variables we get;

$V(t) \geqslant V(0)\exp^{-(b+\mu+\kappa)t} > 0$

$I(t) \geqslant I(0)\exp^{-(\sigma+\mu+\alpha+\gamma)t} > 0$

$C(t) \geqslant C(0)\exp^{-(\mu+\delta)t} > 0$

$R(t) \geqslant R(0)\exp^{-\mu t} > 0$

respectively.

Hence all solutions of the model represented by the system of equation 2.1 with positive initial data remained positive in the feasible bounded region Ω

3 Analysis of the Formulated Model

3.1 The basic reproduction Number, R_0

The next generation matrix approach was used to determine the basic reproduction number denoted by R_0. It is defined as the average number of secondary infections caused by a typical infected individual during their entire period of infectiousness when introduced in a purely susceptible population [11]. R_0 is used to measure the ability of an infection reproducing itself. The basic reproduction number was defined as:

R_0 = Spectral radius of the matrix FV^{-1}

F and V were computed by first determining matrices f and v.

$f = \begin{bmatrix} \beta SI \\ 0 \end{bmatrix}$ and $v = \begin{bmatrix} \sigma I + \mu I + \alpha I + \gamma I \\ \mu C + \delta C \end{bmatrix}$

To find F and V, the partial derivatives of f and v were evaluated to obtain;

$F = \begin{bmatrix} \beta S & 0 \\ 0 & 0 \end{bmatrix}$, $V = \begin{bmatrix} \sigma+\mu+\kappa+\gamma & 0 \\ 0 & \mu+\delta \end{bmatrix}$

$detV = \mu + \delta(\sigma+\mu+\alpha+\gamma) - 0$

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

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

Therefore, $R_0 = \frac{\beta S}{\sigma+\mu+\alpha+\gamma}$

where $\frac{\beta S}{\sigma+\mu+\alpha+\gamma}$ is the average secondary infection arising from HPV infected class.

3.2 Disease-Free Equilibrium point (DFE)

The DFE point was denoted as E^0. It is defined as a steady-state solution for which there is no disease or infection in the population [3, 4]. To obtain the DFE point we set equation 2.1 equal to zero and solve for $\{S(t), V(t), I(t), C(t), R(t)\}$. We set $V(t) = I(t) = C(t) = R(t) = 0$ since there were no infections and obtained E^0 of the model represented by the system of equation 2.1 as;

$E^0 = \{S(t), V(t), I(t), C(t), R(t)\} = [\frac{(1-p)\Lambda}{a+\mu}, 0, 0, 0, 0]$

3.3 Local stability at Disease Free Equilibrium point

The Jacobian matrix of the models in mathematics is used to evaluate the local stability of the system at E^0 using the signs of the determined corresponding eigenvalues [13]. The Jacobian matrix of the system of equation 2.1 was given by;

$$J = \begin{bmatrix} -a-\mu-\beta I & b & -\beta S+\sigma & 0 & 0 \\ a & -b-\mu-\kappa & 0 & 0 & 0 \\ \beta I & 0 & \beta S-\sigma-\mu-\alpha-\gamma & 0 & 0 \\ 0 & 0 & \alpha & -\mu-\delta & 0 \\ 0 & \kappa & \gamma & 0 & -\mu \end{bmatrix} \tag{3.1}$$

At E^0, the Jacobian in equation 3.1 becomes

$$J_{E^0} = \begin{bmatrix} -a-\mu & b & -\beta[\frac{(1-p)\Lambda}{a+\mu}]+\sigma & 0 & 0 \\ a & -b-\mu-\kappa & 0 & 0 & 0 \\ 0 & 0 & \beta[\frac{(1-p)\Lambda}{a+\mu}-\sigma-\mu-\alpha-\gamma & 0 & 0 \\ 0 & 0 & \alpha & -\mu-\delta & 0 \\ 0 & \kappa & \gamma & 0 & -\mu \end{bmatrix} \tag{3.2}$$

whose eigenvalues were found to be,
$\lambda_1 = -\mu, \lambda_2 = -\mu-\delta, \lambda_3 = -b-\mu-\kappa, \lambda_4 = -a-\mu$ and $\lambda_5 = \beta S-\sigma-\alpha-\gamma$
which were negative if;

$$\beta S-\sigma-\mu-\alpha-\gamma < 0 \tag{3.3}$$

In light of this, the analysis comes to the conclusion that the disease free equilibrium is locally asymptotically stable whenever $R_0 < 1$. That is, given a small HPV infected population, each infective in the entire time frame of infectiousness, will produce on average less than one infective when $R_0 < 1$. This implies that HPV infection vanishes in the population when $R_0 < 1$. This is because the interventions might have been well implemented hence further minimization of disease transmission.

Therefore, the disease free equilibrium point was asymptotically stable provided the inequality in equation 3.3 holds.

3.4 Endemic Equilibrium point (EE)

The EE point was denoted as E^*. It is defined as a steady-sate solution for which there exists a constant occurrence of diseases within the population [14, 15]. It occurs when the disease persists in the community. To obtain the endemic equilibrium point, the system of equation 2.1 was equated to zero and solved for $\{S(t), V(t), I(t), C(t), R(t))\}$ which were denoted by;

$E^* = \{S^*(t), V^*(t), I^*(t), C^*(t), R^*(t)\}$ where

$S^* = \frac{(-bp\Lambda-(1-p)\Lambda(-b-\kappa-\mu)(-\alpha-\gamma-\mu-\sigma)}{-(-ab+(-b-\kappa-\mu)(-a-\beta-\mu)(-a-\gamma-\mu-\sigma)+\beta(-b-\kappa-\mu)\sigma}$

$V^*(t) = \frac{p\Lambda}{-b-\kappa-\mu} - \frac{a(-bp\Lambda+(1-p)\Lambda(-b-\kappa-\mu)(-a-\gamma-\mu-\sigma}{(-b-\kappa-\mu)(-(-ab+(-b-\kappa-\mu)(-a-\beta-\mu)(-a-\gamma-\mu-\sigma)+\beta(-b-\kappa-\mu)\sigma)}$

$I^*(t) = \frac{\beta(-bp\Lambda+(1-p)\Lambda(-b-\kappa-\mu)}{-(-ab+(-b-\kappa-\mu)(-a-\beta-\mu))(-\alpha-\gamma-\mu-\sigma)+\beta(-b-\kappa-\mu)\sigma}$

$C^*(t) = \frac{\alpha\beta(-bp\Lambda+(1-p)\Lambda(-b-\kappa-\mu)}{(-\delta-\mu)(-ab+(-b-\kappa-\mu)(-a-\beta-\mu))(-\alpha-\gamma-\mu-\sigma)+\beta(-b-\kappa-\mu)\sigma}$

$R^*(t) = \frac{\beta\gamma(-bp\Lambda+(1-p)\Lambda(-b-\kappa-\mu))}{\mu(-(-ab+(-b-\kappa-\mu)(-a-\beta-\mu))(-\alpha-\gamma-\mu-\sigma)+\beta(-b-\kappa-\mu)\sigma)}$

$-\frac{k[\frac{p\Lambda}{-b-\kappa-\mu}+\frac{a(-bp\Lambda+(1-p)\Lambda(-b-\kappa-\mu))(-\alpha-\gamma-\mu-\sigma)}{(-b-\kappa-\mu)(-(-ab+(-b-\kappa-\mu)(-a-\beta-\mu))(-\alpha-\gamma-\mu-\sigma)+\beta(-b-\kappa-\mu)\sigma)}]}{\mu}$

3.5 Local stability at Endemic Equilibrium point

The Jacobian in equation 3.1 at endemic equilibrium , $E^* = \{S^*(t), V^*(t), I^*(t), C^*(t), R^*(t)\}$ was given as;

$$J_{EE} = \begin{bmatrix} -a-\mu-\beta I^* & b & -\beta S^*+\sigma & 0 & 0 \\ a & -b-\mu-\kappa & 0 & 0 & 0 \\ \beta I^* & 0 & \beta S^*-\sigma-\mu-\alpha-\gamma & 0 & 0 \\ 0 & 0 & \alpha & -\mu-\delta & 0 \\ 0 & 0 & \gamma & 0 & -\mu \end{bmatrix} \tag{3.4}$$

From the matrix in the equation 3.4, the Trace, $Tr(J_{EE}) = -a-\mu-\beta I^*-b-\mu-\kappa+\beta S^*-\sigma-\mu-\alpha-\gamma$.

which was negative if;

$$-a-\mu-\beta I^*-b-\mu-\kappa+\beta S^*-\sigma-\mu-\alpha-\gamma \leqslant 0 \tag{3.5}$$

The determinant of matrix in equation 3.4 the determinant, $DetJ_{EE} = (-a-\mu-\beta I^*)(-b-\mu-\kappa)(\beta S^*-\sigma-\mu-\alpha-\gamma) - b(a\beta S^*-a\sigma-a\mu\alpha-a\gamma)+(\beta S^*+\sigma)(-\beta I^*(-b-\mu-\kappa))$.

$DetJ_{EE} > 0$ if

$$(\beta S^*+\sigma) < 0 \tag{3.6}$$

From stability theory [16], for negative real roots the Trace, $TrJ1 < 0$ and determinant, $DetJ1 > 0$ were to hold. Hence, the endemic equilibrium point was asymptotically stable provided the inequalities in equation 3.5 and equation 3.6 hold.

4 Extension of the Model into Optimal Control

The model represented by the system of equation 2.1 was extended into an optimal control problem using the concepts of optimal control theory. The three control disease interventions which had a significant effect in controlling the spread of HPV were incorporated. These interventions were; ϕ_1 : effective awareness, ϕ_2 : treatment of HPV symptoms and Cervical Cancer ϕ_3 :vaccination against HPV. After incorporating the three controls into the system of equation 2.1, the extended model is shown below;

$$\begin{aligned} \frac{dS}{dt} &= (1-p)\Lambda-(\phi_1+a+\mu+\beta I)S+(\sigma+\phi_2)I+(b+\phi_3)V \\ \frac{dV}{dt} &= p\Lambda+(\phi_1+a)S-(\phi_3+b+\mu+\kappa)V \\ \frac{dI}{dt} &= (\phi_2+\beta S)I-(\phi_2+\sigma+\mu+\alpha+\gamma)I \\ \frac{dC}{dt} &= (\phi_2+\alpha)I-(\phi_2+\mu+\delta)C \\ \frac{dR}{dt} &= (\phi_2+\gamma)I+(\phi_3+\kappa)V-(\phi_1+\mu)R \end{aligned} \tag{4.1}$$

The control set ϕ was considered to be Lebesgue measurable and it is defined as follows to determine the best control levels:

$$\phi = \{[\phi_1(t), \phi_2(t), \phi_3(t)] : 0 \leqslant t \leqslant T\} \tag{4.2}$$

where T is the final time.

The goal was to obtain controls ϕ_1, ϕ_2 and ϕ_3 and the set of solutions $\{S(t), V(t), I(t), C(t), R(t)\}$ that minimizes the objective functional J given by;

$$J = \int_{t_0}^{T} (\varphi_1 V+\varphi_2 I+\varphi_3 C+\frac{1}{2}\omega_1\phi_1^2+\frac{1}{2}\omega_2\phi_2^2+\frac{1}{2}\omega_3\phi_3^2)dt \tag{4.3}$$

where φ_1, φ_2,φ_3, ω_1, ω_2, and ω_3 were non-negative balancing coefficients (weights) which regularize the optimal control.

The expressions $\frac{1}{2}\omega_1\phi_1^2$, $\frac{1}{2}\omega_2\phi_2^2$ and $\frac{1}{2}\omega_3\phi_3^2$ represented costs associated with the controls ϕ_1, ϕ_2, ϕ_3. The equation 4.3 was quadratic in nature because it was assumed that costs associated with the treatments were non-linear in nature in that there was no relationship that was linear between the effects of interventions and the related costs. Thus, optimal controls $(\phi_1^*, \phi_2^*, \phi_3^*)$ were obtained such that;

$$J(\phi_1^*, \phi_2^*, \phi_3^*) = min\{J[\phi_1(t), \phi_2(t), \phi_3(t)] : \phi_1, \phi_2, \phi_3 \in \phi\} \tag{4.4}$$

Subject to the dynamical system equation 4.1 and the control set equation 4.2.

The final time was considered to be fixed under optimal control problem because most governments may choose a program that a disease could be eradicated within a set certain time frame than implementing disease interventions indefinitely.

4.1 Existence of the optimal control problem

Consider the control state system in equation 4.1, there exists optimal control such that;
$J(\phi_1^*, \phi_2^*, \phi_3^*) = min\{J[\phi_1(t), \phi_2(t), \phi_3(t)] : \phi_1, \phi_2, \phi_3 \in \phi\}$
if the following conditions are met;

(i) the integrand of the objective functional,J $f^0 : \Re^n \times \phi \longrightarrow \Re$ is convex on ϕ.

(ii) The set of controls and corresponding state variables ϕ is not empty. From the definition of the control variables and non-negativity of the initial conditions, solution of the control state system in equation 4.2 exists. Therefore, ϕ was not empty [16].

(iii) The control set ϕ is compact. Convex and closedness are properties of a compact set. Therefore ϕ is by definition closed.

(iv) there exists positive constants τ_1, τ_2,and τ_3 and $\psi \leqslant 1$ such that the integrand of the objective functional is bounded by $\tau_1 + \tau_2 + \tau_3(|\phi_1|^3 + |\phi_2|^3 + |\phi_3|^3)^{\frac{\psi}{3}}$.
This condition was satisfied when $\psi = 3, \tau > 0$, and $\tau_1 = \tau_2 = \min\{\omega_1, \omega_2, \omega_3\}$

(v) each right hand side of the state system is continuous and bounded above by a linear function in the state and control variables.

Since the conditions were met, there existed optimal controls.

4.2 Characterization of optimal Controls

Consideration was given to the prerequisites for establishing the optimal controls given in equation 4.4 with the constraint model in equation 4.1 that were obtained utilizing the Pontryagin Maximun Principle. The concept of the theorem that relates to optimal control characterization which relates to Lagrangian multipliers was applied.

1 the Hamiltonian function H was defined as

$$H(S, V, I, C, R, \phi_1, \phi_2, \phi_3, \xi_1, \xi_2, \xi_3, \xi_4, \xi_5) = \varphi_1 V + \varphi_2 I + \varphi_2 C + \frac{1}{2}\omega_1\phi_1^2 + \frac{1}{2}\omega_2\phi_2^2 + \frac{1}{2}\omega_3\phi_3^2 + \Sigma_{i=1}^5 \xi_i f_i \tag{4.5}$$

where f_i stands for the right hand side of equation 4.1 for $i = 1, 2, 3, 4, 5$.

2 the Hamiltonian function control system

$$S' = \frac{\partial H}{\partial \xi_1}, V' = \frac{\partial H}{\xi_2}, I' = \frac{\partial H}{\partial \xi_3}, C' = \frac{\partial H}{\partial \xi_4}, R' = \frac{\partial H}{\partial \xi_5}. \tag{4.6}$$

3 the ad-joint system was given by;

$$\xi_1^{'} = -\frac{\partial H}{\partial S}, \xi_2^{'} = -\frac{\partial H}{\partial V}, \xi_3^{'} = -\frac{\partial H}{\partial I}, \xi_4^{'} = -\frac{\partial H}{\partial C}, \xi_5^{'} = -\frac{\partial H}{\partial R}. \tag{4.7}$$

4 and the optimality condition

$$H[S(t), V(t), I(t), C(t), R(t), \phi(t), \xi(t)] = minH[S(t), V(t), I(t), C(t), R(t), \phi(t), \xi(t)]\phi \in \Omega \tag{4.8}$$

holds for all $t \in [0, T]$ Further the transversality requirements $\xi_i(T) = 0, i = 1, ..., 5$ holds.

the system of ad-joints ξ_i where $i = 1, ..., 5$ in equation 4.7 are such that they satisfy the following theorem.

Theorem: For optimal controls $(\phi_1^*, \phi_2^*, \phi_3^*)$ and solution set $\{S(t), V(t), I(t), C(t), R(t)\}$ of the corresponding state system that minimizes the objective function J over ϕ there exist ad-joint variables $\xi_1, ..., \xi_5$ such that:

$$\begin{aligned}
\xi_1^{'} &= (\phi_1 + a + \mu + \beta I)\xi_1 - (\phi_1 + a)\xi_2 - \beta I\xi_3 \\
\xi_2^{'} &= -\varphi_1 - (\phi_3 + b)\xi_1 + (\phi_3 + b + \mu + \kappa)\xi_2 - (\phi_3 + \kappa)\xi_5 \\
\xi_3^{'} &= -\varphi_2 - (\phi_2 + \sigma)\xi_1 - (\phi_2 + \beta S)\xi_3 + (\phi_2 + \sigma + \mu + \alpha + \gamma)\xi_3 - (\phi_2 + \alpha)\xi_4 - (\phi_2 + \gamma)\xi_5 \\
\xi_4^{'} &= -\varphi_3 + (\phi_2 + \mu + \delta)\xi_4 \\
\xi_4^{'} &= (\phi_1 + \mu)\xi_5
\end{aligned} \tag{4.9}$$

with transversality conditions
$\xi_1(T) = \xi_2(T) = \xi_3(T) = \xi_4(T) = \xi_5(T) = 0$
Furthermore, the optimal controls ($\phi_1^*(t)$, $\phi_2^*(t)$ and $\phi_3^*(t)$) were given by

$$\begin{aligned}
\phi_1^*(t) &= max\{0, min(1, \frac{S(\xi_1 - \xi_2)}{\omega_1}\} \\
\phi_2^*(t) &= max\{0, min(1, \frac{I(-\xi_1 - \xi_4 - \xi_5) + C\xi_4)}{\omega_2}\} \\
\phi_3^*(t) &= max\{0, min(1, \frac{V(\xi_3 - \xi_1 - \xi_5)}{\omega_3}\}
\end{aligned} \tag{4.10}$$

Proof: The adjoint system, transversality conditions and optimality conditions are standard results from Pontryagin Maximum Principle. Thus, the differential equations regulating the adjoint variables were derived. Furthermore, using the optimality condition the equation 4.11 below holds.

$$\frac{\partial H}{\partial \phi_i} = 0 \tag{4.11}$$

Consequently, the optimal controls equation 4.2 can be apparently solved from the constraint model in equation 4.1 by considering the boundedness condition given in equation 2.6

5 Numerical Simulations and Analysis

Through the use of numerical simulations, we examined the behaviour of the transmission dynamics of HPV and CC mentioned in the preceding chapters in this section. We paid close attention to each class and check its behaviour when particular parameters increase or decrease. The MATLAB program employed a monthly time step to solve the optimality system. To carry out the simulations, a set of meaningful values were either estimated or assumed for the model parameters and intervention parameters, with the estimations being carried out using the years 2018 to 2022 as an average of table 1. We took assumption for the parameters; Λ, a, b, κ,

σ, β, α, γ, δ, and μ whose values are tabulated in table 1 below without the interventions. These parameter values were varied, and their impact on the model explored. The mortality rate μ was calculated by taking the inverse of life expectancy at birth, $\mu(t) = \frac{1}{\tau}$. According to the most recent WHO data published in 2021, the life expectancy of females in Kenya is 64.09. Therefore $\mu(t) = \frac{1}{64.09} = 0.01560$

$b = \frac{Number\ of\ vaccinated}{Number\ of\ susceptible} = \frac{4824}{40458} = 0.1192$

$a = \frac{Number\ of\ Susceptible}{Number\ of\ Vaccinated} = \frac{4924}{40458} = 0.1217$

$\kappa = \frac{Number\ of\ Recoveries}{Numberof Vaccinated} = \frac{183}{4824} = .0379$

$\gamma = \frac{Number\ of\ Recoveries}{Number\ of\ infected\ with\ CC} = \frac{183}{5236} = 0.0350.$

Table 1. Parameters and their estimated values without interventions

Parameter	Description	Value
Λ	Recruitment	50
p	Probability of recruitment	0.04
a	Vaccination rate	0.0.1192
b	rate of vaccinated going back to being susceptible	0.1217
κ	Recovery rate due to vaccination	0.0379
β	Rate of susceptible become infected with HPV	0.008
σ	Rate of infected going back to being susceptible	0.2
α	Rate of infected with HPV contact CC	0.1
δ	CC induced death	0.01
μ	Natural mortality rate	0.07
γ	Recovery rate due to CC screening and treatment	0.0350

We took assumption for the parameters; Λ, a, b, κ, σ, β, α, γ, δ, μ ϕ_1, ϕ_2 and ϕ_3 whose values are tabulated in table 2 below with the interventions included. The values of these parameters were varied and their impact on the model investigated.

Table 2. Parameters and their estimated values with interventions

Parameter	Description	Value
Λ	Recruitment	1000
p	Probability of recruitment	0.9
a	Vaccination rate	0.003
b	rate of vaccinated going back to being susceptible	0.05
κ	Recovery rate due to vaccination	0.2
β	Rate of susceptible become infected with HPV	0.0001
σ	Rate of infected going back to being susceptible	0.2
α	Rate of infected with HPV contact CC	0.01
δ	Death rate due to CC	0.4
μ	Natural mortality rate	0.07
γ	Recovery rate due to CC screening and treatment	0.2
ϕ_1	Effective awareness intervention	0.2
ϕ_2	Screening and treatment intervention	0.3
ϕ_2	Vaccination as an intervention	0.03

Along with the initial conditions S(0) = 500, V(0) = 300, I(0) = 200, C(0) = 100, R(0) = 80. we employed the parameter values shown in Table 1, our simulation was run in the interval of five months.
The data were used to run numerical simulations on our model of HPV infection. The parameters values from Tables 1 and 2 were entered into the MATLAB program. When the values of each of the model compartments were changed, the impacts and changes manifested in the model.

We included interventions ϕ_1 (effective awareness), ϕ_2 (Screening and treatment of HPV and CC) and ϕ_3 (Vaccination) as parameters. We compared the simulations without interventions first, and then with the interventions included. Time was measured in months for a period of 50 months. The simulation gave the comparison graphs shown in Fig. 1 and Fig. 2 below.

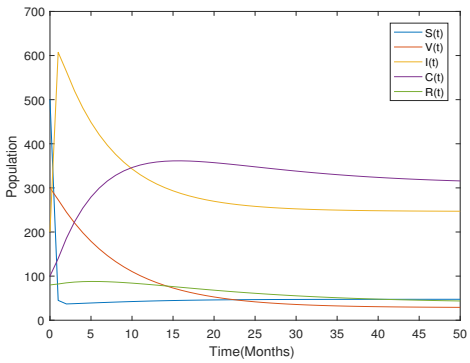

Fig. 1. ***Profiles of population without interventions***

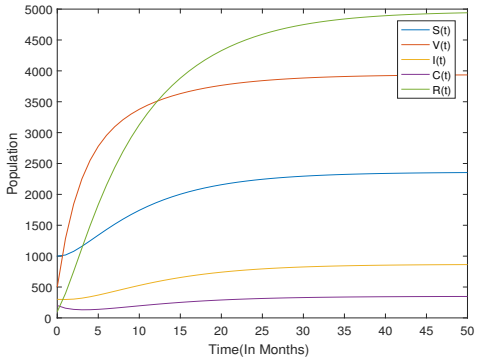

Fig. 2. ***Profiles of population with interventions applied at a lower rate***

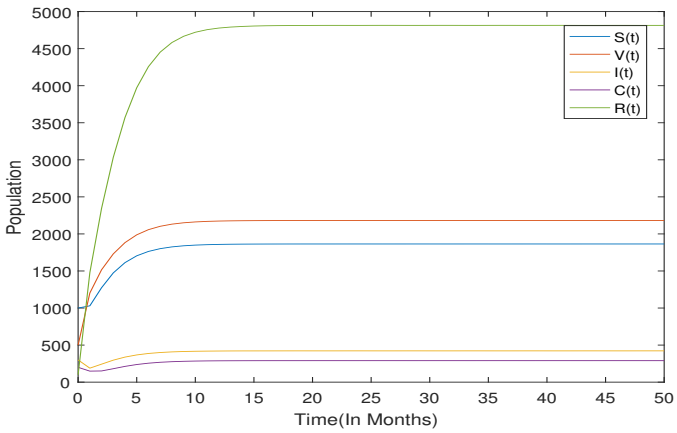

Fig. 3 ***Profiles of population with Interventions applied at higher rates***

In Fig. 1, it can be observed that, without the interventions, HPV increases rapidly in the population and stabilizes. At the same time, CC increases in the population and then stabilizes in the final time at higher values. The immunity in the population is natural and hence decreases as the disease breaks out. The number of susceptible also decreases drastically as the disease breaks out.

In Fig. 2, when the interventions; ϕ_1, ϕ_2 and ϕ_3 are applied simultaneously at low rates, its observed that the disease reduces significantly and stabilizes in the final time. At the same time as the susceptible and vaccinated increase, the population recover significantly and stabilizes in the final time.

In Fig. 3, the interventions; ϕ_1, ϕ_2 and ϕ_3 are applied at higher rates in the population. There is a huge decrease of HPV in the population. The susceptible shoot up as vaccination is intensified leading to huge number of recovery population.

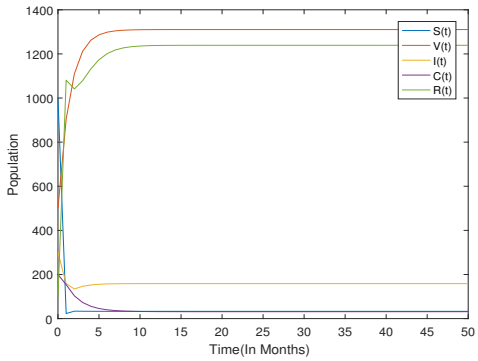

Fig. 4 ***Profiles of population effective awareness intervention applied at lower rates***

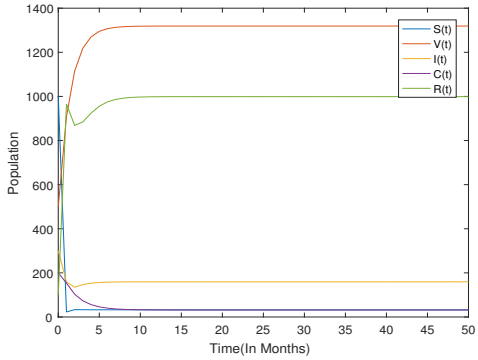

Fig. 5 ***: Profiles of population with effective awareness intervention applied at higher rates***

Fig. 4 shows intervention ϕ_1 (effective awareness) applied at a lower rate. One can observe that, the vaccinated population increases significantly and stabilizes leading to a minute increase of HPV but not enough to cause cervical. In this case HPV stabilizes in the final time and hence recovery population increases significantly.

Fig. 5 shows intervention ϕ_1 (effective awareness) applied at a higher rate. Its observed that the number of recoveries increases within a short time and stabilizes .

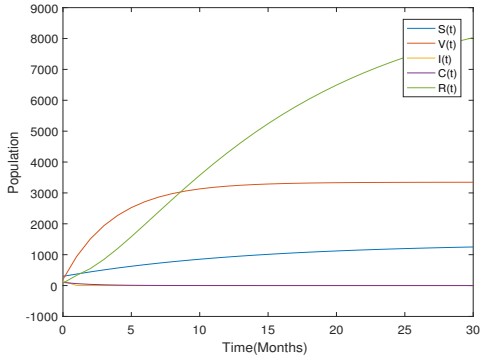

Fig. 6 ***Profiles of population with ϕ_2 applied at a lower rate***

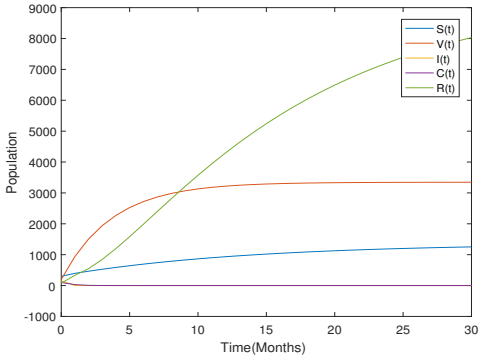

Fig. 7 ***Profiles of population with ϕ_2 applied at a higher rate***

In Fig. 6, the intervention ϕ_2 (Screening and treatment of HPV and CC) was applied at a lower rate. It is observed that HPV and CC population reduce significantly at a very short time and stabilizes. At the same time the susceptible increase slightly and acquire immunity hence more recoveries are obtained within a short time and stabilizes in the final time.

In Fig. 7, the intervention ϕ_2 (Screening and treatment of HPV and CC) was intensified by applying at a higher rate. It can be observed that HPV and CC reduce significantly within a short period of time. As susceptible increase they acquire immunity hence recovery achieved within a short time and hence stabilizes in the final time.

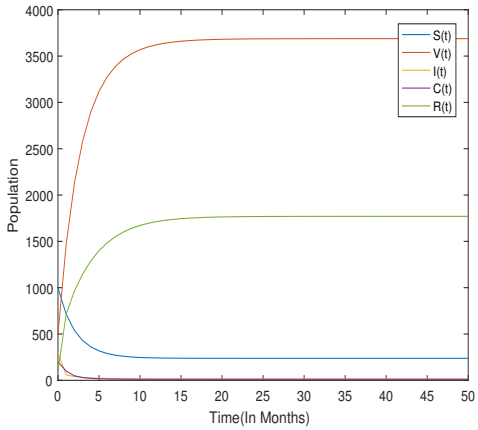

Fig. 8. ***Profiles of the population with*** ϕ_1 ***and*** ϕ_2 ***at lower rates***

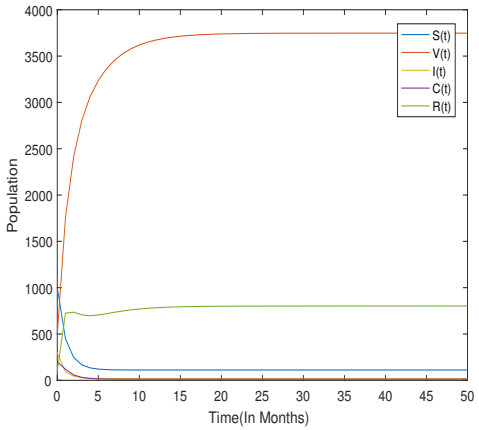

Fig. 9 ***Profiles of the population with*** ϕ_1 ***and*** ϕ_2 ***applied at higher rates***

In Fig. 8 and Fig. 9, the interventions ϕ_1 (effective awareness) and ϕ_2 (screening and treatment of HPV and CC) are applied at a lower and higher rates in the population respectively. It is apparent that whether these interventions are applied minimumly or maximumly, the recovery population increases significantly and HPV and CC reduces to zero and stabilizes as long as the interventions are present.

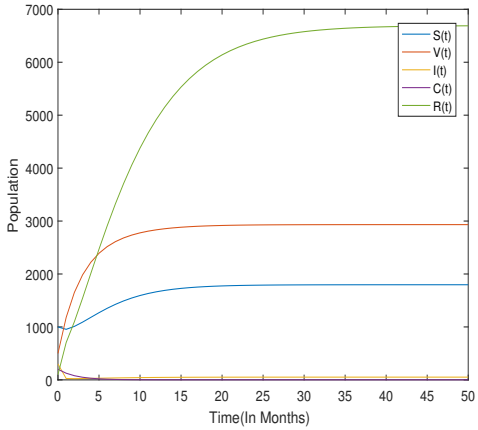

Fig. 10 ***: Profiles of the population when*** ϕ_1 ***and*** ϕ_3 ***are applied at lower rates***

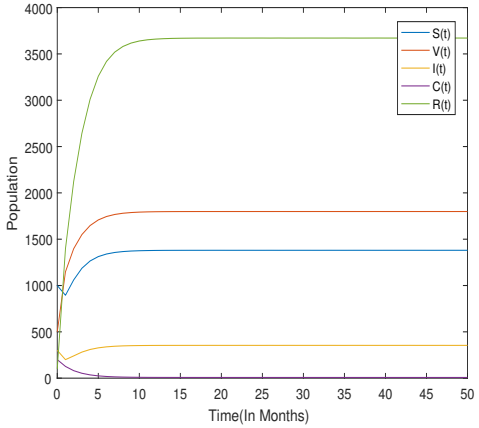

Fig. 11. ***Profiles of the population when*** ϕ_1 ***and*** ϕ_3 ***are applied at higher rates***

In Fig. 10 and Fig. 11, interventions ϕ_1 (effective awareness) and ϕ_3 (vaccination) are applied in the population at lower and higher rates respectively. Therefore it can be observed that, with minimum intervention in Fig. 10, it takes some time for the infected population to recover before attaining stability in the final time. When the interventions are intensified in Fig. 11, it takes a shorter time for the population to recover before attaining stability in the final time. Also HPV and CC infections decrease significantly in the population and hence dies out in the final time.

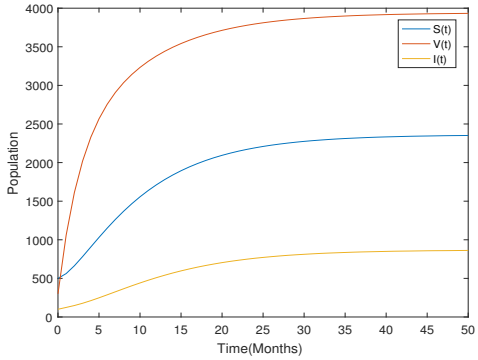

Fig. 12 ***Profiles of Susceptible, Vaccinated and Infected with*** ϕ_1, ϕ_2 ***and*** ϕ_3 ***applied at lower rates***

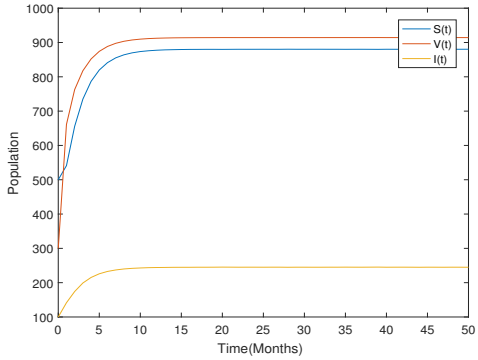

Fig. 13 ***:Profiles of Susceptible, Vaccinated and Infected with*** ϕ_1, ϕ_2 ***and*** ϕ_3 ***applied at higher rates***

In Fig. 12 and Fig. 13, only three classes (susceptible, vaccinated and infected with HPV), were considered. Interventions at lower rates are applied in Fig. 12 and interventions at higher rates are applied in Fig. 13. It can be observed that with lower rate application, it takes some time for the population to attain immunity before stabilizing. Susceptible increase slowly and then attain stability. The HPV infected population reduce significantly and then stabilizes in the final time. When interventions are applied at higher rates, it takes a very short time for the population to gain immunity and thereafter attain stability. And also the infected population decrease significantly within a short time before attaining stability in the final time. The susceptible population increase significantly before attaining stability, indicating that HPV dies out in the community.

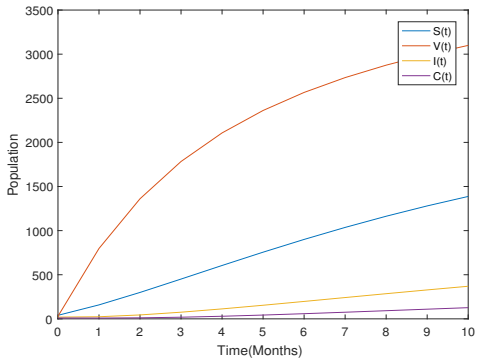

Fig. 14 ***: Profiles of Susceptible, Vaccinated, Infected with HPV and infected with CC with*** ϕ_1, ϕ_2 ***and*** ϕ_3 ***applied at low rates***

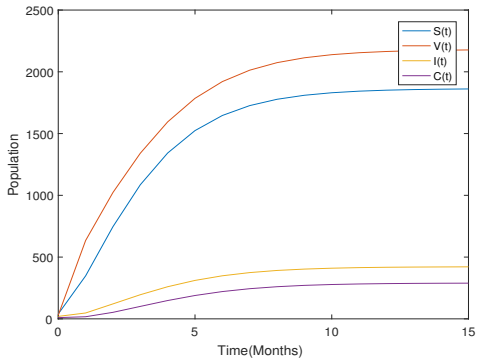

Fig. 15 ***: Profiles of Susceptible, Vaccinated, Infected with HPV and infected with CC with*** ϕ_1, ϕ_2 ***and*** ϕ_3 ***applied at higher rates***

In Fig. 14, four classes without recovery class were plotted in presence of ϕ_1, ϕ_2 and ϕ_3 to check the behaviour of their graphs. It is apparent that vaccinated population and the susceptible increase before stabilizing in the final time. The population infected with HPV and CC reduce significantly and stabilizes in the final time. In Fig. 15, ϕ_1, ϕ_2 and ϕ_3 are applied at higher rates. Apparently the vaccinated and the susceptible populations increase significantly in a short while implying that infection decreases drastically in the population and then stabilizes in the final time.

6 Conclusion

In this paper a mathematical model of HPV vaccination that included optimal control analysis was developed. It was determined from an analysis of the model invariant region that the model was well posed and biologically meaningful. The model solution feasibility was examined, and it was discovered that the model solution remained positive in the feasible bounded region Ω.

Both endemic equilibrium point and disease free equilibrium point of the model were performed and discovered. Their local stability were also performed and revealed that the disease free equilibrium points were asymptotically stable. The analysis also established that, the endemic equilibrium points were asymptotically stable. The fundamental reproduction number was analysed around the equilibrium points and found to be less than one. The optimal control component of the model was added. The modifications were incorporated into the model and then examined using the Pontryagin Maximum Principle. Using MATLAB software, the optimality system was mathematically solved before being plotted against time for several interventions and their graphs described.

From the numerical results, we realized that when interventions are not present, the disease breaks out in the community. But when the interventions (awareness, treatment and vaccination) are gradually introduced into the population HPV and cervical cancer keep on decreasing.

If the interventions are intensified, then the number of infected people reduce drastically as permanent recovery is achieved within a short time in the community. We therefore conclude that, the best strategy is to gradually increase the application of the three interventions in the population.

7 Recommendations

1. The study recommends that the authorities should encourage effective awareness, treatment of HPV and CC, and vaccination in order to prevent the disease from spreading.
2. The Health care providers to consider Setting up vaccination centres for HPV and effect mass media awareness on Kenyan.
3. The study suggests that future work to focus on other effective prevention measures that are affordable to low income individuals.
4. Future research to be done on other HPV types to determine the transmission dynamics of head, neck and breast cancers.

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Competing interests

Authors declared that no competing interests exists.

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