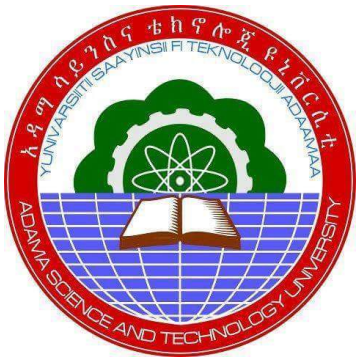
MATHEMATICAL MODEL OF HUMAN PAPILLOMA VIRUS (HPV) WITH OPTIMAL CONTROL



By

Getachew Beyecha Batu

A Thesis Submitted to Department of Applied Mathematics

School of Applied Natural Science

Office of Graduate Studies

Adama Science and Technology University

August 4, 2020

Adama, Ethiopia

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Declaration

Here, I submit the thesis entitled " Mathematical Model of Human Papilloma Virus (HPV) with Optimal Control" for the award of degree of Master of Science in Applied Mathematics. I, the undersigned declare that, this study is original and it has not been submitted to any institution elsewhere for the award of any academic degree or the like, where other sources of information have been used, they have been duly acknowledged.

Name of students:_____ Signiture_____ Date_____

I here by confirm that the work has been done under my supervision and approval.

Advisor:_____ Signiture_____ Date_____

Approval Sheet

We, the undersigned, members of the Board of Examiners of the final open defened by Getachew Beyecha Batu have read and evaluated his thesis entitled ”Mathematical Model of Human Papilloma Virus (HPV) with Optimal Control ” and examined the candidate. This is therefore to certify that the thesis has been accepted in partial fulfillment for the requirement of the degree of Master of Science in Applied Mathematics.

Name	Signiture	Date
Name of Student		
Advisor		
Internal Examiner		
External Examiner		
HOD		
School Dean		
Post graduate Dean		

LIST OF ABBREVIATIONS

HPV	Human Papilloma Virus.
DFE	Disease Free Equilibrium .
EE	Endemic Equilibrium .
PMP	Pontryagin's Maximum Principle.
OC	Optimal Control.
SEAIR	Susceptible, Exposed, Asymptomatic, Infected, Recovered.
ODEs	Ordinary Differential Equations
SITR	Susceptible, Infected, Treated, Recovered

LIST OF NOTATIONS

R_0	Reproduction Number
E_0	Disease Free Equilibrium Points
E_1	Endemic Equilibrium Points
J	Jacobian Matrix

Abstract

In this thesis work, a deterministic mathematical model has been formulated to describe the transmission dynamic of human papilloma virus (HPV) using a system of non-linear ordinary differential equations with optimal control. The system has two equilibrium points, namely the disease free equilibrium point and the endemic equilibrium point which exists conditionally. The basic reproduction number R_0 was calculated using the next-generation matrix and the stability of the equilibrium points were analyzed. From the qualitative analysis the disease free equilibrium point is both locally and globally stable if $R_0 < 1$, and the endemic equilibrium point is also both locally and globally stable under some conditions on the system parameters. Furthermore, sensitivity analysis of the model equation was performed on the key parameters to find out their relative significance and potential impact on the transmission dynamic of HPV. Finally numerical simulations of the model equations were carried out using MATLAB $R2015b$ with $ode45$ solver. The simulations result illustrated that applying control strategy can successfully reduces the transmission dynamic of HPV disease.

Keyordsw: *HPV infection, Basic Reproduction Number, Stability, Optimal Control.*

ACKNOWLEDGMENT

First of all, I would like to thank the almighty God for caring my life, blessing all my activities and for giving me strength and perseverance to complete this study. My special and heart full gratitude goes to my advisor Dr. Shiferaw Feyissa for his immense and invaluable advice that contribute a lot to the success of this thesis work. And also I am thankful for his support. I greatly appreciate him not only with his keen and unlimited constructive advises in every aspect of my thesis work, but also for his professional and personal ethics. I would also like to thank my teacher Dr.Legessa Lemecha for his critical support and guidance during my work. I am thankful to him so much. And also I would like to say thank you to all my classmates for their cooperative work through our study time and doing the thesis. Also I would like to thank my friend Eshetu Dadi(Phd candidate) for his immense and invaluable help. Finally, my great appreciation goes to my friend Firaol Shambel, my parents, sisters, brothers and relatives for their support and encouragement during my study. May the almighty God bless all I acknowledged above abundantly.

Chapter 1

Introduction

1.1 Background of the study

Human papilloma virus (HPV) is the name of a family of viruses that includes more than 100 different types, and more than 30 of these virus are sexually transmitted [7, 8, 9]. Most of the HPV infections are asymptomatic and can fed away without treatment over the course of a few years. For instance, about 70% of HPV infections fed away within a year and 90% with in two years. However, in some people infection can persist for many years and can cause warts (low risk genotype of HPV), while other types lead to different kinds of cancers (high risk genotype of HPV) including cervical cancer [14, 15].

Although HPV itself cannot be treated, the cellular changes that come from any HPV infection can be treated. For examples, genital warts, cervical, anal and genital cancers can be treated if the infection is diagnosed during the early stage of development[17]. Pre-cancerous cell changes caused by HPV can be detected by Pap tests and treat individuals who are found already infected [8]. With proper treatment, pre-cancerous cells may be prevented from progressing to the cancerous stage[9]. The targets of initial infections are the basal epithelial cells in the cervix[8]. Subsequent binding and entry, viral material migrates to the nucleus and establishes the HPV genomes as multiple-copy extra chromosomal plasmids, which are maintained at approximately 20 to 100 copies per infected cells[12]. Infected cells express viral proteins (E6 and E7), which interfere with the normal cell cycle, promoting proliferation and deactivating the tumor suppressor proteins p53 and pRb[1]. Subsequent viral genome replication and cell division, one of the daughter cells migrates away from the basal layer and starts a program of differentiation[1, 18]. Unlike normal cells, HPV-infected cells undergo differentiations but remain active in the cell cycle.

Some HPV infections of healthy hosts can be cleared by the immune system[9, 19]. However, many infections, especially by high risk strains such as HPV 16 and 18, become chronic. These persistent infections constantly shed HPV virions. Ultimately, the persistence of actively proliferating cells leads to the development of precancerous cells, which are at risk, in turn of becoming cancer cells[9]. HPV infection is now a well-established cause of cervical cancer and there is growing evidence of HPV being a relevant factor in other anogenital cancers (anus, vulva, vagina and penis) as well as head and neck cancers [16]. HPV types 16 and 18 are responsible for about 70% of all cervical cancer cases worldwide and it ranks as the 3^{rd} most frequent cancer among women in the world [16].
Various methods are used to cure or inhibit the growth of cancer. Now-a-days various types of treatments are available[17] such as surgery, radiation therapy, chemotherapy, target therapy, immunotherapy, hormonal therapy and the latest is a gene therapy. However, each treatment has side effects attributed to it, for example, vomiting, pressing the blood production, fatigue, hair loss and mouth sores .

The World has a population of $2,784$ million female aged 15 years and older who are at risk of developing cervical cancer. Current estimates indicate that every year $569,847$ female are diagnosed with cervical cancer and $311,365$ die from the disease in 2018. The majority of cases are squamous cell carcinoma followed by adenocarcinomas[16].

Africa has an estimated population of 372.2 million female aged 15 years and older who are at risk of developing cervical cancer. Current estimates indicate that every year $119,284$ female are diagnosed with cervical cancer and 81,687 die from the disease. Cervical cancer ranks as the 2^{nd} most frequent cancer among female and it is the most common female cancer in female aged 15 to 44 years in Africa[16]. Almost 80% of cervical cancer cases and deaths occur in poor countries. In Sub-Saharan Africa, cervical cancer accounts for 22.5% of all cancer cases in female, and the majority of female who develop cervical cancer live in rural areas [3]. Eastern Africa is one of the most heavily affected areas with an incidence of more than 30 cases per $100,000$ women per year [16].

In Ethiopia [1], cancer accounts for about 5.8% of total national mortality. Although population-based data does not exist in the country except for Addis Ababa, it is estimated that about $6,294$ new cervical cancer cases are diagnosed and $4,884$ death occurs annually in Ethiopia[16]. The most prevalent cancers in Ethiopia among the entire adult population are breast cancer (30.2%), cancer of the cervix (13.4%) and colorectal cancer (5.7%) [1].

1.2 Statement of the problem

HPV infection is one of the major health challenges mostly in the developing countries where there is low awareness and health facilities. For example, genital HPV infection represents the most common viral sexually transmitted infection and a major public health problem leading to significant morbidity and mortality worldwide[16]. More than 80% of cervical cancer cases and deaths occur in poor countries. In Sub-Saharan Africa, cervical cancer accounts for 22.5% of all cancer cases in women, and the majority of women who develop cervical cancer live in rural areas [3].

Many mathematical models have been developed to analyse the transmission dynamics of HPV infection and its associated health problems, and a lot has been done to study the impact of some control strategies against the virus. It is an essential and effective way to totally understand the problems by establishing mathematical models and analysing their dynamical behaviours[6]. Authors in [1] formulated a mathematical model on the transmission dynamic of HPV infection by incorporating the combined effects of screening and treatment as control strategies. Their aim is to investigate the role of screening as a control strategy in reducing the transmission dynamic of the disease. From the result of their study they conclude that HPV infection is reduced by using both screening and treatment strategies. Due to the presence of interventions, the number of susceptible cells decreases implying that, most of the susceptible cells are screened. Similarly, the number of unaware infected cells decreases. The screened infected cells initially increase and then start to diminish after getting a treatment . This is because many people from screened class recovered through treatment. Thus, in this thesis we are going to develop a mathematical model to address the highlighted issues and formulate a better model with more realistic assumptions in order to achieve better results on the transmission dynamic of HPV infection by introducing exposed class of HPV, asymptomatic class of HPV and optimal control for fulfilling the entire gap of the earlier model [17]. Therefore, this study is intended to answer the following basic questions;

- How can we modify a mathematical model of HPV infection with optimal control?
- What are the basic assumptions to develop a mathematical model that describe the transmission dynamics of HPV infection?
- How can we analyse the modified model?
- How we can interprate the solution of the model?

1.3 Objectives of the study

1.3.1 General objective

The general objective of this study is to investigate the transmission dynamic of Human Papilloma Virus with optimal control.

1.3.2 Specific objectives

The specific objectives of this study are to:

- develop mathematical model which describes the transmission dynamic of HPV with optimal control,
- perform stability analysis of the model,
- perform numerical simulation of the model to supplement the analytical solution,
- investigate the impact of optimal control on the transmission dynamic of HPV

1.4 Significance of the study

The impact on health as well as the socio-economic issues due to emerging and re-emerging infectious diseases like HPV are significant. This study is will help:

- health care sectors to optimize controls and minimizing the cost of control strategies in order to reduce the transmission dynamic of HPV infection in the society.
- to guide the national health authorities about the burden of HPV that help them to develop national policy and to understand effective control strategies of the transmission dynamic of HPV.
- the educationalists to develop educational seminars, workshops or training programmers to educate people about the transmission dynamic of HPV.
- to act as a platform for further research on the control of HPV, and form a base for further studies of related problem.

1.5 Mathematical Preliminary

1.5.1 Basics Ordinary Differential Equations

Consider the general differential equation of the form:

$$\frac{dx}{dt} = f(x,t), x(t_0) = x_0 \tag{1.1}$$

with $x \in \mathbb{R}^n$ and $t \geq 0$. The system defined by (1.1) is said to be autonomous or time-invariant if f does not depend explicitly on t. It is said to be linear if $f(x,t) = A(t)x$ for some $A(.) : \mathbb{R}_+ \mapsto \mathbb{R}^{n\times n}$, and nonlinear otherwise[49].

Lipschitz Continuity: The function f is said to be locally Lipschitz continuous in x if there exists $l \geq 0$ such that

$$|f(x_1,t) - f(x_2,t)| \leq l|x_1 - x_2|$$

for all x_1, x_2 and $t \geq 0$. The constant l is called the Lipschitz constant [32].

1.5.2 Equilibria of the system

Definition 1.5.1 *A point $x^* \in \mathbb{R}^n$ is called an equilibrium point (also critical point, steady state solution, etc.) of (1.1) , if $f(x^*,t) = 0$ for all $t \geq 0$ [41].*

If $f(x,t)$ is Lipschitz continuous in x, then the solution $x(t) = x^*$ for all t is called an equilibrium solution. One of the most important consequences of the Lipschitz continuity hypothesis is that it gives bounds on the rate of convergence or divergence of solutions from the origin[49]:

1.5.3 Linearizion and the Jacobian

In most of the systems of real word problem, it becomes apparent that nearly all systems are non-linear, including the model we are examining. However, most of the theory that has been developed by mathematicians governing the behavior of systems of differential equations, especially stability, is centered upon linear systems[30]. Thus, in order to further understand the behavior of a non-linear system it is first crucial to linearize the system. Essentially, this process approximates a non-linear system in a linear manner near the values around which a linear approximation occurs. In a neighborhood of the equilibria we can make a linear approximation to determine the local character of the paths[49]. This technique allows the stability of the system at the equilibria to be determined and provides a starting point for global investigations of solutions. The goal of this stability analysis is to perturb the system from equilibrium and study the behavior of the system. Thus, we will look to see if the

solutions move towards or away from equilibrium. In order to linearize the system, we must compute the Jacobian matrix of the system. The Jacobian is the matrix of the partial derivatives of each function with respect to each variable. Essentially, the Jacobian provides a linear approximation of a system at any given value[49].

1.5.4 Stability of Equilibria

The notion of stability of an equilibrium point is considerable theoretical and practical importance. An equilibrium point x^* is said to be stable if all solutions sufficiently close to x^* stay nearby for all $t \geq 0$. It is asymptotically stable if nearby solutions actually converge to x^* as $t \to \infty$[49].

Definition 1.5.2 *An equilibrium point x^* is said to be unstable if it is not stable.*

Definition 1.5.3 *(Asymptotic Stability). An equilibrium point x^* of (1.1) is said to be asymptotically stable if it is stable and, in addition, there exists a constant $c > 0$ such that if $|x^* - x_0| < c$ then $|y(t, x_0) - x^*| \to 0$ as $t \to \infty$.*

Suppose all the eigenvalues of $Df(x^*)$ have negative real parts. Then the equilibrium point x^* of the system [1.1] is locally asymptotically stable, and unstable if at least one of the eigenvalues has positive real part.
Poincare-Perron Theorem. Let A be a constant matrix in the system $\frac{dx}{dt} = Ax$ with eigenvalues λ_i, for $i = 1, 2, \cdots, n$
i. If the system is stable, then $Re(\lambda_i) \leq 0$ for $i = 1, 2, \cdots n$.
ii. If either $Re(\lambda_i) < 0$; or if $Re(\lambda i) \leq 0$ for $i = 1, 2, \cdots n$ and there is no zero repeated eigenvalue; then the system is uniformly stable.
iii. The system is asymptotically stable if and only if $Re(\lambda_i) < 0, i = 1, 2, \cdots, n$; note that it is also uniformly stable by (ii).
iv. If $Re(\lambda_i) > 0$, for any $i = 1, 2, \cdots n$ the solution is unstable[49].

Definition 1.5.4 *A matrix $A \in \mathbb{R}^{n \times n}$ is called Hurwitz or asymptotically stable, if and only if $Re(\lambda_i) < 0; \forall i = 1; 2...n$. where $\lambda_i's$ are the eigenvalues of the matrix A[45, 47].*

Given the polynomial;

$$P(\lambda) = \lambda^n + a_1\lambda^{n-1} + \cdots + a_{n-1}\lambda + a_n;$$

where the coefficients a_i are real constants, $\{i = 1, \cdots, n\}$.

Define the n Hurwitz matrices using the coefficients a_i of the characteristic polynomial such that:

$$H_n = \begin{pmatrix} a_1 & 1 & 0 & 0 & \cdots & 0 \\ a_3 & a_2 & a_1 & 1 & \cdots & 0 \\ a_5 & a_4 & a_3 & a_2 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \cdots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & a_n \end{pmatrix}$$

where $a_j = 0$ if $j > n$.

$$H_1 = a_1, H_2 = \begin{pmatrix} a_1 & 1 \\ 0 & a_2 \end{pmatrix}, H_3 = \begin{pmatrix} a_1 & 1 \\ a_3 & a_2 \end{pmatrix}.$$

All the roots of the polynomial $p(\lambda)$ are negative or have negative real part if the determinants of all Hurwitz matrices are positive, $det(H_j) > 0, j = 1, 2, .., n$. When $n = 2$ the Routh-Hurwitz Criteria simplify to det $H_1 = a_1 > 0$ and

$$detH_2 = \text{det} \begin{pmatrix} a_1 & 1 \\ 0 & a_2 \end{pmatrix}.$$

For a polynomial of degree n=2, 3, 4 and 5, the Routh-Hurwitz Criteria are summarized as follows:

(i) Quadratic equation:$\lambda^2 + a_1\lambda + a_2 = 0$,

Stability Criteria: $a_1 > 0, a_2 > 0$.

(ii) Cubic equation: $\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0$,

Stability criteria: $a_1 > 0, a_2 > 0, a_3 > 0, a_1a_2 > a_3 > 0$.

(iii) Fourth order equation:$\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 = 0$,

Stability criteria: $a_i > 0(i = 1, 2, 3, 4), a_1a_2 - a_3 > 0, a_1a_2a_3 - a_3^2 - a_1^2a_4 > 0$.

iv) Fifth order equation: $\lambda^5 + a_1\lambda^4 + a_2\lambda^3 + a_3\lambda^2 + a_4\lambda + a_5 = 0$,

Stability criteria:$a_i > 0(i = 1, 2, 3, 4, 5)$ and

$a_1a_2 - a_3 > 0, a_1a_2a_3 - a_3^2 - a_1^2a_4 > 0$,

$a_1a_2a_3a_4 + 2a_1a_4a_5 + a_2a_3a_5 - a_1a_2^2a_5 - a_1^2a_4^2 - a_3^2a_4 - a_5^2 > 0$.

Chapter 2

Literature Review

Mathematical models are of great importance in the natural sciences and engineering, including biology and epidemiology. They help us to gain new understanding about a system, organize and make sense of biological data, obtain the response behavior of the system, seek optimal performance and intervention strategies, and make predictions about the system. Mathematical modeling of infectious diseases began in 1760s with Daniel Bernoulli's modeling of smallpox. Since then, mathematical models have been developed to simulate the spread of a wide range of infectious diseases, such as HIV, HPV, Tuberculosis(TB), Chlamydia, Cholera, COVID-19 and Influenza to name a few. These mathematical models have been developed to address a range of questions that cannot be answered through the use of traditional epidemiological methods.

Many mathematical models have been developed to analyze the transmission dynamics of HPV infection and its associated health problems, and as well study the impact of some control strategies against the virus. For instance:
Shaban and Mofi [8] developed modelling the impact of vaccination and screening on the transimission dynamics of HPV infection. While HPV has been a recognized disease for a long time, the control of outbreaks remains a challenge. The aim of their study is to investigate the role of screening and vaccination as control strategies in curtailing the spread of the disease. They use the next generation matrix and determine that the disease free equilibrium has been shown to be asymptotically stable. Furthermore, they performed sensitivity analysis on the key parameters in order to detrmine their relative importance and potential impact in HPV dynamics and determine the impacts of vaccination and screening in the spread of HPV. Thus from the results of their study they conlcude that HPV infection can be reduced when both interventions, that is screenig and vaccination are implemented in order to reduce the burden of the disease.

Usman . et al [25] developed a mathematical model on the impact of natural immunity, vaccination, screening and treatment on the dynamics of the HPV infection and cervical cancer to investigate the combined impact of vaccination, screening program and treatment strategies on the transmission dynamics of the HPV infection and cervical cancer in a completely susceptible population. They were computed two distinct equilibria for the frequency-dependent model recharged by constant birth, namely; disease-free and endemic, with both local and global stability on the disease-free equilibrium point using both next-generation matrix and linearization approach. Exposure before infection was considered in their model and possibility for the development of cervical cancer in the screened infected individuals was also considered due to the fact that HPV infection has no specific treatment. The basic reproduction number for the model was established and evaluated using the sourced parameter values to be $R_0 = 0.026180$ which served as a threshold for measuring new infections in the population. The disease-free equilibrium was therefore found to be both locally and globally asymptotically stable meaning that, the disease will be wiped out of the population in due time. Furthermore, they carried out qualitative analysis on the model using MATLAB $R2012b$ encoded with $ODE45$ revealed that the HPV infection and cervical cancer can be eradicated out of the population with the intervention of combining both vaccination and screening program on the susceptible individuals and using any available means of treating infected individuals with HPV to help boost their natural immunity to fight the virus.

Hughes. et al [21] developed a simple ODE dynamical systems model on the SIR framework of susceptible, infectious, and recovered/immune by adding compartments for vaccinated and vaccinated-but-infected persons (to account for the possibility of only reduced susceptibility and loss of immunity). This model considered three sexual activity levels and distinguished between female-to-male and male-to-female transmission. Under the assumptions of 90% vaccination coverage, 75% vaccination efficacy, and a ten year mean immunity; they found that vaccinating both sexes would lead to a 44% reduction in prevalence while vaccinating women alone would only result in a 30% reduction. Further, they coupled their dynamical transmission model to an ODE model of cancer that took into account age-specific risk of disease development. The models together allowed the authors to estimate the effect of different vaccination strategies on cervical cancer incidence. In addition to the result of their transmission model described above, the authors determined that reducing HPV prevalence would result in a smaller reduction in cancer incidence and that targeting core groups only would not be an effective vaccination strategy.

Sanders and Taira [20] developed a transmission model for HPV 16 and 18 that used four sexual activity groups, nine age divisions, and age based mixing patterns. Basic economic

considerations were taken into account to assess cost per quality-adjusted life-year. The authors recommended achieving at least 70% vaccination coverage to achieve significantly reduce cohort life time cervical cancer cases. The cost-effectiveness of vaccinating men and boys was questioned but depended upon vaccination coverage among women.

Barnabas. et al [9] created a compartment deterministic transmission model for HPV 16 and progression to cervical cancer and calibrated it to period data of finnish seroprevalence. Groups were stratified by age, and regression/progression rates were combined into estimated transmission probabilities. The authors found that reported data about sexual activity and number of partner changes did not account for the seroprevalence of HPV 16 even with a theoretical maximum of 100% transmission probability. Assuming an under-reporting rate, they derived a transmission probability of 0.6 per partnership. The results for vaccination impact were similar to other modeling reports in that high vaccination coverage was necessary and that vaccinating men as well as women had only a small additional impact.
Günther. et al[22] developed a deterministic compartmental model of HPV transmission and progression to cervical cancer including progression subcompartments for loss of immunity, treatment, and progression to cervical cancer. An important addition of this model was the complex model of sexual behavior and mixing underlying the transmission process. The authors focused on the optimal age to vaccinate girls as a function of duration of immunity.
Garnett. et al [11] developed the impact of HPV vaccines on cervical cancer and screening programmes. They analyze their model using cost-effectiveness approach and established that, there are limited benefits from vaccinating boys in addition to girls and that even a vaccine with moderate(10 years) duration of protection can be effective. Using within-host approach, [13] modeled the effect of vaccines on HPV and found that combination of successful vaccines and vaccination strategies seems to be the best approach towards preventing cervical cancer.

Malik. et al [23] formulate optimal control with multiple HPV vaccines.They consruct a two-sex, deterministic ordinary differential equations model for HPV and analyzed for optimal control strategies in a vaccination program administering three types of vaccines in the female population: a bivalent vaccine that targets two HPV types and provides longer duration of protection and cross-protection against some non-target types, a quadrivalent vaccine which targets an additional two HPV types, and a nonavalent vaccine which targets nine HPV types (including those covered by the quadrivalent vaccine), but with lesser type-specific efficacy. Considering constant vaccination controls, the disease-free equilibrium and the effective reproduction number for the autonomous model are computed in terms of the model parameters. Local-asymptotic stability of the disease-free equilibrium is established in terms

of reprouction number. Assuming the HPV infection prevalence in the population under the constant control, optimal control theory is used to devise optimal vaccination strategies for the associated non-autonomous model when the vaccination rates are functions of time. The impact of these strategies on the number of infected individuals and the accumulated cost is assessed and compared with the constant control case. Switch times from one vaccine combination to a different combination including the nonavalent vaccine are assessed during an optimally designed HPV immunization program.

Bakare. et al [24] developed optimal control analysis of an SIR epidemic model with constant recruitment. In their study mathematical model of an SIR epidemic model with constant recruitment and two control variables using control terms and a deterministic system of differential equation is presented and analyzed mathematically and numerically. They intend to control the susceptible and infected individuals with educational campaign and treatment strategies. They analyzed the model by non-dimensionalizing the system of equations of their SIR epidemic model and derived their basic reproduction number. Their aim are to minimize the total number of infective individuals and the cost associated with the use of educational campaign and treatment on $[0, T]$. They used Pontryagin's maximum principle to characterize the optimal levels of the two controls. They solved the resulting optimality system numerically and the results show that the optimal combination of treatment and educational campaign strategy required to achieve the set of their objective which depend on the relative cost of each of the control measures.

Gurmu and Koya [17] formulated and analyzed mathematical model of HPV with chemotherapy as treatment. In their model the cancer cells have been divided into four compartments SITR. The well possedness of the formulated model equations was proved and the equilibrium points of the model have been identified. In addition, they derived the basic reproduction number using next generation matrix method and analyzed the stability of the equilibrium points using Routh Hurwitz criterion. From the analytic and numerical simulation they observed that if the basic reproduction is less than one then disease will wipe out and thus the treatment is said to be successful. On the other hand, if the basic reproduction number is greater than one then the solution converges to endemic equilibrium point and thus the infectious cells continue to replicate i.e., disease will persist and thus the treatment is said to be unsuccessful. They analyzed sensitivity analysis of the model and finally, they conclude that the model formulated in their study effectively addresses the treatment of HPV.

All the above studies were developed mathematical model of HPV transmission dynamic by viewing in different aspects. Some of them considered deterministic model and other stochastic model and subdivided the total population into different compartments and they recommend vaccination as control strategies in curtailling the spread of HPV. Since HPV infection is an asymptomatic in nature then the cell which shows a symptoms moves from exposed class to infection class and those which do not shows symptoms moves to the asymptomatic class. Thus in the present thesis work we are motivated to modify mathematical model proposed in [17] by introducing exposed class of HPV, asymptomatic class of HPV and optimal control for fulfilling the entire gap of the study. Hence, our model is set out to address the highlighted issues and formulate a better model with more realistic assumptions in order to achieve better results for the sake of contributing more understanding on the behavior of the real situation of the transmission dynamic HPV.

Chapter 3

Research Methodology

Mathematical modelling of epidemiological process requires the translation of an epidemiological scenario into a mathematical formulation. It begins with a clear description of the processes based on the modeler understanding of the system. The translation into mathematical equations should be made with a specific goal or biological question in mind. Then the verbal description of the system is encoded in mathematical equations. Mathematical models under normal condition consist of parameters and variables that are connected by relationships. Variables are abstractions of the system properties that can be quantified and parameters describe the rate of variables[1].

We modify a mathematical model which describes the transmission dynamic of HPV with optimal control using a system of nonlinear ODEs. We performed the qualitative analysis of the model. Both local and global stability analysis of the equilibrium points of the model equations have been done using linearization and Lyapunov functions respectively. Sensitivity analysis of the system have been studied to determine which parameter plays greater role in the transmission dynamic of HPV infection. The optimal control have been derived by using the Pontryagin's maximum principle (PMP). To supplement the analytical solution of the model equation we performed a numerical simulation of the model using the software MATLAB $R2015b$ with $ODE45$ solver.

Chapter 4

Model Formulation and Analysis

4.1 Model Formulation

In this section we are going to develop a mathematical model which describes the transmission dynamics of HPV using a system of non-linear ordinary differential equations with optimal control. We categorize the total population under consideration into five non overlapping compartments. We consider vaccination, screening and treatment as a control strategy to develop the mathematical model.

4.1.1 Model Description

The model we are going to formulate is based on the following assumptions; The individuals that make up the population can be grouped into different compartments . The population function in a compartment is differentiable with respect to time (t) and that the epidemic process is deterministic. In other words, the output of the model is fully determined by the parameter values and the initial conditions. The HPV model sub-divided the total population at any time t, denoted by $N(t)$ into five compartments, namely,

- Susceptible individuals (individuals those who are vulnerable to the disease) $S(t)$.
- Exposed individuals (individuals who are already infected but are not yet infectious) $E(t)$.
- Asymptomatic individuals (individuals those who are both infected and infectious but do not show any symptoms of the disease) $A(t)$.
- Infected individuals (individual those who are infectious and shows a symptoms of the disease) $I(t)$ and

- Recovered individuals (individuals those who are recovered from the disease at a time t) $R(t)$.

Then the total population at time t, denoted by $N(t)$, is given by

$$N(t) = S(t) + E(t) + A(t) + I(t) + R(t).$$

Thus, the population is compartmentalized into the proportions of susceptible, exposed, asymptomatic, infected and recovered individuals and the model assumed that; susceptible individuals are recruited (by birth or immigration) into the population at a constant rate π. A proportion of the susceptible individuals become exposed to the HPV infection at a rate λ when they come into effective contact with an infectious individuals at a rate β and move to $E(t)$ class that may lead to infectious class or recovery class due to natural immunity at a rate φ. The force of infection(or rate of infection) of the model is given as $\lambda = \frac{\beta(I+qA)}{N}$, where β is an effective contact rate and q is the transmission coefficient for the asymptomatic individuals. If $q > 1$ then the asymptomatic individuals infect the susceptible indiviuals more likely than the infective individuals. If $q < 1$, then the infected individuals have a good chance to infect the susceptible individuals than asymptomatic individuals and if $q = 1$, then both asymptomatic and infected individuals have equal chance to infect the susceptible individuals. After the disease incubation priod $\frac{1}{\eta}$, where η is a per capita rate of becoming infections a proportion of p of the individuals in $E(t)$ may develop a symptoms of the HPV infection and move to the infected compartment $I(t)$ at a rate $p\eta$ and the rest become asymptomatic individuals with HPV infection with probability $(1-p)$ and move to the $A(t)$ at a rate $(1-p)\eta$. Furthermore, an individual in asymptomatic $A(t)$ compartment is recovered due to natural immunity and move to recovered class $R(t)$ at a rate γ. The infected individuals $I(t)$ recovered after receiving a treatement at a rate α and move to the recovered class $R(t)$. A recovered individuals may revert to the susceptible class $S(t)$ after lossing their immunity at a rate θ. Both infectious individuals in $N(t)$ have induced death at a rate ζ. All individuals in $N(t)$ suffers natural mortality at a rate μ and all the parameter in the model are non-negative.

The above model variables and parameters description can be represented respectively in the table below.

Table 4.1: Notations and description of the model variables

Variable	**Description**
S(t)	Population size of susceptible cells which are vulnerable to the disease.
$E(t)$	The number of individuals who are infected but are not yet infectious.
$A(t)$	Infectious individuals who are not show symptoms of the disease .
$I(t)$	Infectious individuals who show symptoms of the disease .
$R(t)$	Individuals who have been recovered from the infection at time t.

Table 4.2: Notations and description of model parameters

Parameter	**Description**
π	Recruited rate of susceptible individual.
β	Effective contact rate of infection.
λ	Force of infection(or Infection) rate
η	Percapita rate of becoming infectious.
α	Treatment rate; With this rate cells transfer from compartment $I(t)$ to R
φ	Recovery rate; With this rate cells transfer from compartment E to R
θ	Rate at which recovered individuals reverts to susceptible class.
γ	Rate at which asymptomatic individuals moves to the recovered class.
q	Transmission rate for asymptomatic individuals
p	Probability of exposed individuals joining infectious class
μ	Natural death rate; With this rate cells of all the compartments die naturally.
ζ	Induced death rate(death rate due to the disease).

Upon including the basic assumptions together with the description of both model variables and parameters the schematic diagram of the flow between the five compartments of the modified model can be given as in figure below.

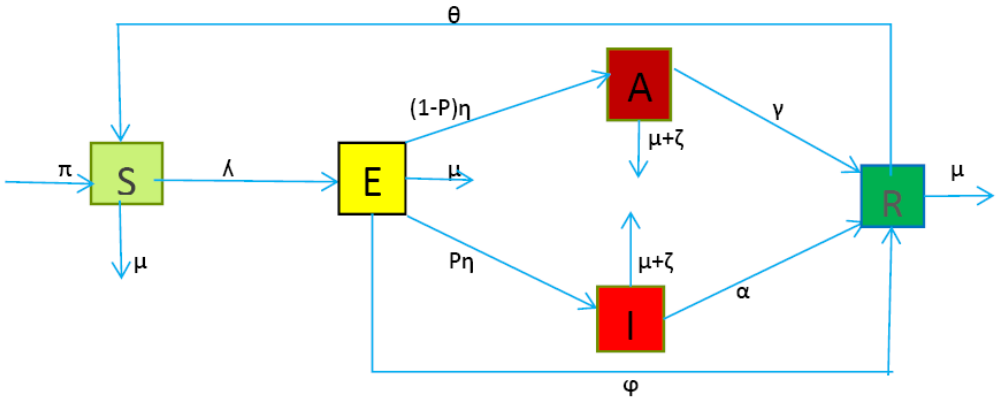

Figure 4.1: Schematic diagram of the transmission dynamic of HPV model

Based on the model formulation, assumptions, notations of the variables and parameters the model equations are formulated into a system of five nonlinear ODEs as follows:

$$\begin{cases} \frac{dS}{dt} = \pi + \theta R - (\lambda + \mu)S, \\ \frac{dE}{dt} = \lambda S - (\mu + \eta + \varphi)E, \\ \frac{dA}{dt} = (1-p)\eta E - (\mu + \gamma + \zeta)A, \\ \frac{dI}{dt} = p\eta E - (\mu + \alpha + \zeta)I, \\ \frac{dR}{dt} = \alpha I + \gamma A + \varphi E - (\theta + \mu)R. \end{cases} \tag{4.1}$$

The non-negative initial conditions of the system of model equations (4.1) are denoted by $S(0) = S_0 > 0, E(0) = E_0 \geq 0, A(0) = A_0 \geq 0, I(0) = I_0 \geq 0, R(0) = R_0 \geq 0.$

4.2 Model Analysis

4.2.1 Invariant Region

In this subsection, we discuss about the invariant region, in which the model solution is bounded. The model system (4.1) governs human population, hence all the variables and parameters used in the model formulation are non-negative. We consider a biologically-feaseble region $\{\Omega = (S, E, A, I, R) \in \mathbb{R}^5_+\}$. We adhere to the following steps to show the positive invariance of Ω, that is all the solution of (4.1) in Ω remains in the region Ω. To do this, first we considered the total human population. The total human population of the model at any time t is given by:

$$N(t) = S(t) + E(t) + A(t) + I(t) + R(t).$$

The rate of change of the total population by adding all the equations considered in (4.1) is:

$$\frac{dN}{dt} = \pi - \mu N - \zeta(A + I).$$

In the absence of induced death rate ζ due to HPV equation, it becomes

$$\frac{dN}{dt} \leq \pi - \mu N.$$

Clearly, whenever $N > \frac{\pi}{\mu}, \frac{dN}{dt} < 0$; Notice that $\frac{dN}{dt}$ is bounded above by $\pi - \mu N$.
By using standard comparison theorem [41] it can be shown that,

$$0 \leq N(t) \leq \frac{\pi}{\mu} + (N_0 - \frac{\pi}{\mu})e^{-\mu t}. \tag{4.2}$$

As $t \longrightarrow \infty$ in equation (4.2) , the population size $N \longrightarrow \frac{\pi}{\mu}$ which implies that $0 \leq N \leq \frac{\pi}{\mu}$.
Thus the feasible solution set of the equation of the model enter and remain in the region

$$\Omega = \{(S, E, A, I, R) \in \mathbb{R}^5_+ : N \leq \tfrac{\pi}{\mu}\}.$$

Therefore, the basic model is wellposed epidemiologically and mathematically.
Hence , it is sufficient to study the dynamic of the basic model in Ω.

4.2.2 Existence and Uniqueness of the Solutions of the Model

The validity and authenticity of any mathematical model depends on whether the given system of equations has a solution, and if the solution exists then it is unique. We shall use the Lipschitz condition to verify the existence and uniqueness of solution for the system of equation (4.1).

Theorem 1 *Let Ω denote the region $0 < \alpha \leq \mathbb{R}$. Then the model equations (4.1) together with the initial conditions $S(0) > 0$, $E(0) \geq 0$, $A(0) \geq 0$, $I(0) \geq 0$, $R(0) \geq 0$ exist in $\mathbb{R}^5_+$ and has a unique solution.*

Proof: Let the right hand side of the system of equation (4.1) can be expressed as follows:

$$\begin{cases} f_1(S,E,A,I,R) = \pi + \theta R - (\lambda+\mu)S \\ f_2(S,E,A,I,R) = \lambda S - (\mu+\eta+\varphi)E \\ f_3(S,E,A,I,R) = (1-p)\eta E - (\mu+\gamma+\zeta)A \\ f_4(S,E,A,I,R) = p\eta E - (\mu+\alpha+\zeta)I \\ f_5(S,E,A,I,R) = \alpha I + \gamma A + \varphi E - (\theta+\mu)R. \end{cases} \tag{4.3}$$

We have to show that $\frac{\partial f_i}{\partial x_j}, i,j = 1,2,3,4,5$ are continues and bounded in Ω.
According to [1], let Ω denote the region

$$\Omega = (S,E,A,I,R) \in \mathbb{R}^5_+; N \leq \tfrac{\pi}{\mu}.$$

Then equations (4.1) have a unique solution if

$$\tfrac{\partial f_i}{\partial x_j}, i,j = 1,2,3,4,5$$

are continuous and bounded in Ω. Here, $x_1 = S, x_2 = E, x_3 = A, x_4 = I, x_5 = R$.
The continuity and the boundedness are verified here under:

For f_1:
$|\frac{\partial f_1}{\partial S}| = |-(\lambda+\mu)| < \infty,$
$|\frac{\partial f_1}{\partial E}| = 0 < \infty,$
$|\frac{\partial f_1}{\partial A}| = |-\frac{\beta q}{N}| < \infty,$
$|\frac{\partial f_1}{\partial I}| = |\frac{-\beta}{N}| < \infty,$
$|\frac{\partial f_1}{\partial R}| = |\theta| < \infty.$

For f_2:
$|\frac{\partial f_2}{\partial S}| = |\lambda| < \infty,$
$|\frac{\partial f_2}{\partial E}| = |-(\eta+\varphi+\mu)| < \infty,$
$|\frac{\partial f_2}{\partial A}| = |\frac{\beta\, q}{N}| < \infty,$
$|\frac{\partial f_2}{\partial I}| = |\frac{\beta}{N}| < \infty,$
$|\frac{\partial f_2}{\partial R}| = 0 < \infty.$

For f_3:
$|\frac{\partial f_3}{\partial S}| = 0 < \infty,$
$|\frac{\partial f_3}{\partial E}| = |(1-p)\eta| < \infty,$
$|\frac{\partial f_3}{\partial A}| = |-(\gamma+\mu+\zeta)| < \infty,$
$|\frac{\partial f_3}{\partial I}| = 0 < \infty,$
$|\frac{\partial f_3}{\partial R}| = 0 < \infty.$

For f_4:
$|\frac{\partial f_4}{\partial S}| = 0 < \infty,$

$|\frac{\partial f_4}{\partial E}| = |p\eta| < \infty,$
$|\frac{\partial f_4}{\partial A}| = |\phi| < \infty,$
$|\frac{\partial f_4}{\partial I}| = |-(\alpha+\mu+\zeta)| < \infty,$
$|\frac{\partial f_4}{\partial R}| = 0 < \infty.$

For f_5:

$|\frac{\partial f_5}{\partial S}| = 0 < \infty,$
$|\frac{\partial f_5}{\partial E}| = |\varphi| < \infty,$
$|\frac{\partial f_5}{\partial A}| = |\gamma| < \infty,$
$|\frac{\partial f_5}{\partial I}| = |\alpha| < \infty,$
$|\frac{\partial f_5}{\partial R}| = |-(\theta+\mu)| < \infty.$

Thus, all the partial derivatives $\frac{\partial f_i}{\partial x_j}, i, j = 1, 2, 3, 4, 5$ exist, continuous and bounded in Ω. Hence, by [1], a solution for the model (4.1) exists and it is unique.

4.2.3 Positivity of the Solution of the Model

It is also necessary to prove that all the variables of the model (4.1) are non-negative; so that the solution of the system with non-negative initial conditions remains non-negative for all $t > 0$. The following lemma describe this fact.

Lemma 1 *If $S(0) > 0, E(0) \geq 0, A(0) \geq 0, I(0) \geq 0, R(0) \geq 0$ the solution $S(t), E(t), A(t), I(t), R(t)$ of the system (4.1) are non-negative for all $t > 0$.*

Proof: *We shall prove this lemma using a contradiction by assuming that the total population $N(t) \neq 0$ for all $t \geq 0$.*

We assume that there exists the first time t_1, t_2, t_3, t_4, t_5 such that:

$$S(t_1) = 0, \frac{dS(t_1)}{dt_1} < 0, E(t) \geq 0, A(t) \geq 0, I(t) \geq 0, R(t) \geq 0, 0 \leq t \leq t_1, \tag{4.4}$$

$$E(t_2) = 0, \frac{dE(t_2)}{dt_2} < 0, S(t) > 0, A(t) \geq 0, I(t) \geq 0, R(t) \geq 0, 0 \leq t \leq t_2, \tag{4.5}$$

$$A(t_3) = 0, \frac{dA(t_3)}{dt_3} < 0, S(t) > 0, E(t) \geq 0, I(t) \geq 0, R(t) \geq 0, 0 \leq t \leq t_3, \tag{4.6}$$

$$I(t_4) = 0, \frac{dI(t_4)}{dt_4} < 0, S(t) > 0, E(t) \geq 0, A(t) \geq 0, R(t) \geq 0, 0 \leq t \leq t_4, \tag{4.7}$$

$$R(t_5) = 0, \frac{dR(t_5)}{dt_5} < 0, S(t) > 0, E(t) \geq 0, A(t) \geq 0, I(t) \geq 0, 0 \leq t \leq t_5. \tag{4.8}$$

From (4.4) $\frac{dS(t_1)}{dt_1} < 0$ implies that,

$$\frac{dS(t_1)}{dt_1}|_{t=t_1} = \pi + \theta R(t_1) - (\lambda + \mu)S(t_1) = \pi + \theta R(t_1) < 0,$$

which is a contradiction, as $\pi + \theta R(t_1) > 0$.

Meaning that $S(t) > 0, \forall t \geq 0$.

From (4.5) $\frac{dE(t_2)}{dt_2} < 0$ implies that,

$$\frac{dE(t_2)}{dt_2}|_{t=t_2} = \lambda S(t_2) - (\mu + \eta + \varphi)E(t_2) = \lambda S(t_2) < 0,$$

Which is a contradiction, as $\lambda S(t_1) \geq 0$,

Meaning that $E(t) \geq 0, \forall t \geq 0$.

From (4.6) $\frac{dA(t_3)}{dt_3} < 0$ implies that,

$$\frac{dA(t_3)}{dt_3}|_{t=t_3} = (1-p)\eta E(t_3) - (\mu + \gamma + \zeta)A(t_3) = (1-p)\eta E(t_3) < 0,$$

which is a contradiction as $(1-p)\eta E(t_3) \geq 0$,

Meaning that $A(t) \geq 0, \forall t \geq 0$.

From (4.7) $\frac{dI(t_4)}{dt_4} < 0$ implies that,

$$\frac{dI(t_4)}{dt_4}|_{t=t_4} = p\eta E(t_4) - (\mu + \alpha + \zeta)I(t_4) = P\eta E(t_4) < 0,$$

which is a contradiction as $p\eta E(t_4) \geq 0$,

Meaning that $I(t) \geq 0, \forall t \geq 0$.

From (4.8) $\frac{dR(t_5)}{dt_5} < 0$ implies that,

$$\frac{dR(t_5)}{dt_5}|_{t=t_5} = \alpha I(_5) + \gamma A(t_5) + \varphi E(t_5) - (\theta + \mu)R(t_5) = \alpha I(t_5) + \gamma A(t_5) + \varphi E(t_5) < 0,$$

which is a contradiction as $(\alpha I(t_5) + \gamma A(t_5) + \varphi E(t_5)) \geq 0$,

Meaning that $R(t) \geq 0, \forall t \geq 0$.

Hence we conclude that, $S(t) \geq 0, E(t) \geq 0, A(t) \geq 0, I(t) \geq 0, R(t) \geq 0, \forall t \geq 0$.

Thus the solutions $S(t), E(t), A(t), I(t), R(t)$ of system (4.1) remain positive for all $t > 0$.

4.3 Steady State

In order to understand the dynamic of the model, it is necessary to determine equilibrium points of the solution region[26]. An equilibrium solution is a steady state solution of the model equations (4.1) in the sense that if the system begins at such a state, it will remain there for all times. In other words, the population sizes remain unchanged and thus the rate of change for each population vanishes. In this section equilibrium points of the model are found, categorized, stability analysis is conducted and the results have been presented in the following sub-sections. The equilibrium points of the system of equation (4.1) is the solution of the system of equation,

$$\begin{cases} \pi + \theta R - (\lambda + \mu)S = 0, \\ \lambda S - (\mu + \eta + \varphi)E = 0, \\ (1-p)\eta E - (\mu + \gamma + \zeta)A = 0, \\ p\eta E - (\mu + \alpha + \zeta)I = 0, \\ \alpha I + \gamma A + \varphi E - (\theta + \mu)R = 0. \end{cases} \tag{4.9}$$

4.3.1 Disease Free Equilibrium Points (DFE)

Disease free equilibrium points are steady state solutions where there is no disease in the population[12]. We denote disease-free equilibrium point by E_0. The disease free equilibrium point, E_0 is obtained in the absence of the HPV in the population.
Then solving the system of differential equation (4.9) at $E(t) = 0, I(t) = 0, A(t) = 0$ and $R(t) = 0$, we obtain the disease free equilibrium point as:

$$E_0 = \{S^0, E^0, A^0, I^0, R^0\} = \{\tfrac{\pi}{\mu}, 0, 0, 0, 0\}$$

4.3.2 The Basic Reproduction Number(R_0)

The basic reproduction number denoted by R_0 is the average number of secondary infections caused by an infectious individual during his or her entire period of infectiousness [37]. The basic reproduction number is an important non-dimensional quantity in epidemiology as it sets the threshold in the study of a disease both for predicting its outbreak and for evaluating its control strategies [37]. Thus, whether a disease becomes persistent or dies out in a community depends on the value of the reproduction number, R_0. Furthermore, the stability of the equilibrium point can be analyzed using R_0 [2]. If $R_0 < 1$ it means that every infectious individual will cause less than one secondary infection which is impossible and hence the disease will die out and when $R_0 > 1$ every infectious individual will cause more than one secondary infection and hence the disease will invade the population. It is obtained by taking the largest (dominant) eigenvalue (spectral radius)

$$R_0 = [\frac{\partial F_i(x_0)}{\partial x_j}][\frac{\partial V_i(x_0)}{\partial x_j}]^{-1}$$

where F_i be the rate of appearance of new criminal in compartments, V_i is the transfer of individuals out of the compartment by another means, x_0 is the disease free equilibrium point. We compute the basic reproduction number using the next generation matrix approch. Thus the associated matrices F and V for the new infectious terms and the remaining transition terms are respectively given by:

$$F_i = \begin{bmatrix} \frac{\beta(\ I+qA)S}{N} \\ 0 \\ 0 \end{bmatrix}, V_i = \begin{bmatrix} (\eta+\varphi+\mu)E \\ -(1-p)\eta E + (\mu+\gamma+\zeta)A \\ -p\eta E + (\alpha+\mu+\zeta)I \end{bmatrix}$$

The Jacobian of F_i and V_i at the disease free equilibrium point E_0 takes the form respectively as:

$$F(E_0) = \begin{bmatrix} 0 & \beta q & \beta \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \text{ and } V(E_0) = \begin{bmatrix} b & 0 & 0 \\ -(1-p)\eta & c & 0 \\ -p\eta & 0 & d \end{bmatrix}$$

where, $b = \eta + \varphi + \mu, c = \mu + \gamma + \zeta, d = \alpha + \mu + \zeta$.

It can be verified that the matrix $V(E_0)$ is non-singular as its determinant is non-zero. That is

$$\det(V(E_0)) = \begin{vmatrix} b & 0 & 0 \\ -(1-p)\eta & c & 0 \\ -p\eta & 0 & d \end{vmatrix} = bcd \neq 0$$

Since $\det(V(E_0)) \neq 0$ then $V(E_0)$ is invertable and the inverse is given by .

$$(V(E_0))^{-1} = \frac{Adj(V)}{det(V)} \tag{4.10}$$

Then after some algebraic computations the inverse matrix is constructed as follows:

$$[V(E_0)]^{-1} = \begin{bmatrix} \frac{1}{b} & 0 & 0 \\ \frac{(1-p)\eta}{bc} & \frac{1}{c} & 0 \\ \frac{p\eta}{bd} & 0 & \frac{1}{d} \end{bmatrix} \tag{4.11}$$

Now,

$$[F(E_0)][V(E_0)]^{-1} = \begin{bmatrix} \frac{\beta\eta q(1-p)}{bc} + \frac{\beta\eta p}{bd} & \frac{\beta q}{c} & \frac{\beta}{d} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \tag{4.12}$$

Thus the eigenvalues of the matrix (4.12) are: $\lambda_1 = 0, \lambda_2 = 0, \lambda_3 = \frac{\beta\eta(pc+qd(1-p))}{bcd}$
where, $b = \eta + \mu + \varphi, c = \mu + \gamma + \zeta, d = \alpha + \mu + \zeta$

Now, $[F(E_0)][V(E_0)]^{-1}$ is the next-generation matrix of system (4.1). It follows that the spectral radius of the matrix $[F(E_0)][V(E_0)]^{-1}$ denoted and defined by [44]:

Then from $\lambda_1, \lambda_2, \lambda_3$ the dominant eigenvalue is $\lambda_3 = \frac{\beta\eta(pc+qd(1-p))}{bcd}$.
Therefore the basic reproduction number is given by

$$R_0 = \frac{\beta\eta(p(\mu+\gamma+\zeta)+q(\alpha+\mu+\zeta)(1-p))}{(\eta+\mu+\varphi)(\mu+\gamma+\zeta)(\alpha+\mu+\zeta)}.$$

4.3.3 Endemic Equilibrium Points (EE)

The endemic equilibrium point denoted by $E_1 = \{S^*, E^*, A^*, I^*, R^*\}$ is a steady state solution where the disease persists in the population. The endemic equilibrium point of a model is a solution of the system of equation. Then solving the system of differential equation (4.9) by substitution and after some algebraic simplificaton we obtain: $E_1 = \{S^*, E^*, A^*, I^*, R^*\}$ as:

$S^* = \frac{N^*}{R_0}$,
$E^* = \frac{\pi cde}{bcde-[pc\alpha\eta\theta+(1-p)\gamma\eta\theta d+\varphi\theta dc]}(1-\frac{1}{R_0})$,
$A^* = \frac{(1-p)\pi\eta de}{bcde-[pc\alpha\eta\theta+(1-p)\gamma\eta\theta d+\varphi\theta dc]}(1-\frac{1}{R_0})$,
$I^* = \frac{\pi\eta pce}{bcde-[pc\alpha\eta\theta+(1-p)\gamma\eta\theta d+\varphi\theta dc]}(1-\frac{1}{R_0})$,
$R^* = \frac{\pi}{\theta}[\frac{bcde}{bcde-[pc\alpha\eta\theta+(1-p)\gamma\eta\theta d+\varphi\theta dc]}+1](1-\frac{1}{R_0})$,
where, $b = \eta+\mu+\varphi, c = \mu+\gamma+\zeta, d = \alpha+\mu+\zeta, e = \theta+\mu$.

Clearly, from the above we conclude that a positive unique endemic quilibrium point exists whenever $R_0 > 1$.

4.4 Stability Analysis

In the absence of infectious disease, the model populations have a unique disease free steady state E_0. To find the local stability of E_0, the Jacobian of the model equations evaluated at E_0 is used. Also to determine the global stability at E_0 Lyapunov function is used. It is already shown that the E_0 of model equation (4.1) is given by $E_0 = \{\frac{\pi}{\mu}, 0, 0, 0, 0\}$. Now, the stability analysis of E_0 is conducted and the results are presented in the form of theorem as follows:

4.4.1 Local Stability of Disease Free Equilibrium Point

Theorem 2 *The DFE, E_0 of the system (4.1) is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.*

Proof: *Consider the right hand side expressions of the equations (4.1) as functions so as to find the Jacobian matrix at the DFE as:*

$$J(E_0) = \begin{bmatrix} -\mu & 0 & -\beta q & -\beta & \theta \\ 0 & -b & \beta q & \beta & 0 \\ 0 & (1-p)\eta & -c & 0 & 0 \\ 0 & p\eta & 0 & -d & 0 \\ 0 & \varphi & \gamma & \alpha & -e \end{bmatrix} \tag{4.13}$$

Where $b = \mu + \eta + \varphi, c = \mu + \gamma + \zeta, d = \mu + \alpha + \zeta, e = \theta + \mu$

The characteristic equation of the Jacobian matrix at the disease free equilibrium point is given by

$(\mu + \lambda)(e + \lambda)(\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3) = 0,$

where

$a_1 = b + c + d = 3\mu + 2\zeta + \eta + \varphi + \alpha + \gamma,$

$a_2 = bc + bd + cd - \beta\eta[p(1-q) + q]$

$= 3\mu^2 + \mu(2\eta + 2\varphi + 2\gamma + 2\alpha + 3\zeta) + \zeta^2 2 + \zeta(2\gamma + 2\eta + 2\varphi + \alpha) + \gamma(\eta + \varphi + \alpha) + \alpha(\eta + \varphi) - \beta\eta[p(1-q) + q],$

$a_3 = bcd(1 - R_0) = (\mu + \eta + \varphi)(\mu + \gamma + \zeta)(\mu + \alpha + \zeta)(1 - R_0),$

$e = \mu + \theta,$

Then, $(\mu + \lambda)(e + \lambda) = 0$ or $(\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3) = 0$

From this the first two eigenvalues $\lambda_1 = -\mu, \lambda_2 = -e$, are real, distinct and negative.

To determine the sign of the three left eigenvalues we use the Routh-Hurwitz criteria for the cubic equation; $\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0$.

According to the Routh-Hurwitz criteria the three roots of a polynomial of order three of type $p(\lambda) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3$, are real distinct and negative if the coefficients satisfy the conditions $a_1 > 0, a_2 > 0, a_3 > 0$ and $a_1a_2 > a_3$

It is straight forward to verify that this conditions are satisfied and hence the last three eigenvalues are real distinct and negative.i.e

$a_1 > 0 \Rightarrow b + c + d > 0$

$a_2 > 0 \Rightarrow bc + bd + cd > \beta\eta[p(1-q) + q]$

$a_3 > 0 \Rightarrow bcd(1 - R_0) > 0 \Rightarrow R_0 < 1$ and

$a_1a_2 > a_3 \Rightarrow (b + c + d)(bc + bd + cd + \beta q\eta(p-1) - \beta p\eta) > bcd(1 - R_0)$.

$= b^2(c + d) + c^2(b + d) + d^2(b + c) + 3bcd - \beta\eta(b + c + d)(p + q(1-p)) > bcd(1 - R_0)$

Therefore the disease free equilibrium point of the system of ordinary differential equation (4.1) is locally asymptotically stable if $R_0 < 1$.

4.4.2 Global Stability of the Disease Free Equilibrium Point

Theorem 3 *The disease free equilibrium point E_0 of the model equation (4.1 is globally asymptotically stable if $R_0 < 1$.*

***Proof**: To establish the global stability of the disease-free equilibrium point, we construct a Lyapunov function.*

Let $\Omega \subseteq \mathbb{R}^5_+$ be an open neighborhood of the disease free equilibrium point E_0 of the function $L : \Omega \longrightarrow \mathbb{R}$ $(L(E_0) = 0)$. Then the function L, defined by:

$$L(S, E, A, I, R) = \frac{B_1}{2}(E(t))^2 + \frac{B_2}{2}(A(t))^2 + \frac{B_3}{2}(I(t))^2 \tag{4.14}$$

where B_i , for $i = 1, 2, 3$ are some positive constants to be chosen later.

Then $L(S, E, A, I, R)$ should satisfies the following properties to be a lyapunov function:

$i)L$ is continuously differentiable.

$ii)L > 0, \forall x \in \Omega \setminus E_0$ and $L(E_0) = 0$, as $(E(t))^2 \geq 0, (A(t))^2 \geq 0, (I(t))^2 \geq 0$.

$iii)\frac{dL}{dt} \leq 0$ in Ω, then E_0 is stable.

The first two condition holds, as L it is continuously differentiable and $L > 0, \forall x \in \Omega \setminus E_0$ and $L(E_0) = 0$. Now let we check the third condition $\frac{dL}{dt} \leq 0$ in Ω.

$\frac{dL}{dt} = B_1\frac{dE}{dt} + B_2\frac{dA}{dt} + B_3\frac{dI}{dt}$

$= B_1(\lambda S - (\mu + \eta + \varphi)E) + B_2((1-p)\eta E - (\mu + \gamma + \zeta)A) + B_3(p\eta E - (\mu + \alpha + \zeta)I)$

$= B_1(\lambda S - \underbrace{(\mu + \eta + \varphi)}_{b} E) + B_2((1-p)\eta E - \underbrace{(\mu + \gamma + \zeta)}_{c} A) + B_3(p\eta E - \underbrace{(\mu + \alpha + \zeta)}_{d} I)$

$= B_1(\lambda S - bE) + B_2((1-p)\eta E - cA) + B_3(p\eta E - dI)$

$= B_1(\frac{\beta(I+qA)}{N} S - bE) + B_2((1-p)\eta E - cA) + B_3(p\eta E - dI), S \leq N$ at E_0.

$= B_1(\beta(I + qA) - bE) + B_2((1-p)\eta E - cA) + B_3(p\eta E - dI)$

$= B_1\beta I + B_1\beta qA - B_1 bE + B_2(1-p)\eta E - B_2 cA + B_3 p\eta E - B_3 dI$

$= (B_3 p\eta + B_2(1-p)\eta - B_1 b)E + (B_1\beta - B_3 d)I + (B_1\beta q - B_2 c)A$

$= B_1 b(\frac{(B_3 p\eta + B_2(1-p)\eta}{B_1 b} - 1)E + (B_1\beta - B_3 d)I + (B_1\beta q - B_2 c)A.$

Now choosing $B_3 = \beta c$, $B_2 = \beta dq$,$B_1 = cd$. Then,

$\frac{dL}{dt} = bcd(\frac{\beta cp\eta + \beta qd(1-P)\eta}{bcd} - 1)E + (cd\beta - \beta cd)I + (cd\beta q - \beta dqc)A$

$= bcd(\frac{\beta cp\eta + \beta qd(1-p)\eta}{bcd} - 1)E + 0$

$= bcd\,\underbrace{(\frac{(pc + qd(1-p))\beta\eta}{bcd}}_{R_0} - 1)E$

$= bcd(R_0 - 1)E$

Therefore $\frac{dL}{dt} \leq bcd(R_0 - 1)E < 0$ if $R_0 - 1 < 0$.

Thus , this is true when $R_0 < 1$ which implies that $\frac{dL}{dt}$ is negative. Therefore the largest compact invariant set in Ω is singleton set E_0. Hence LaSalle's invariant principle [47] implies that E_0 is globally asymptotically stable.

4.4.3 Local Stability of Endemic Equilibrium point

To determine the local stability of the endemic equilibrium point $E_1 = (S^*, E^*, A^*, I^*, R^*)$ we use a linearization method. The Jacobian J matrix at the endemic equilibrium point is

$$J(E_1) = \begin{bmatrix} -k-\mu & 0 & \frac{-q\beta S^*}{N^*} & \frac{-\beta S^*}{N^*} & \theta \\ k & -b & \frac{q\beta S^*}{N^*} & \frac{\beta S^*}{N^*} & 0 \\ 0 & (1-p)\eta & -c & 0 & 0 \\ 0 & p\eta & 0 & -d & 0 \\ 0 & \varphi & \gamma & \alpha & -e \end{bmatrix} \tag{4.15}$$

where

$k = \frac{\beta(I^* + qA^*)}{N^*}, b = \eta + \varphi + \mu, c = \mu + \gamma + \zeta, d = \alpha + \mu + \zeta, e = \theta + \mu, N \leq \frac{\pi}{\mu}, S^* = \frac{N^*}{R_0}$

Theorem 4 *The endemic equilibrium point $E_1 = (S^*, E^*, A^*, I^*, R^*)$ of the system (4.1) is locally asymptotically stable if $R_0 > 1$.*

***Proof**: The characteristic equation of the Jacobian matrix (4.15) at the endemic equlibrium point is given by*

$$P(\lambda) = \lambda^5 + B_1\lambda^4 + B_2\lambda^3 + B_3\lambda^2 + B_4\lambda + B_5 = 0 \tag{4.16}$$

where the notation of the coefficients are:

$B_1 = b + c + d + e + k + \mu$

$B_2 = bc + bd + cd + ek + \mu e + (e + k + \mu)(b + c + d) - \frac{\beta\eta S^*}{N^*}[p(1 - q) + q]$

$B_3 = (b+c+d)+(e+k+\mu)(bc+bd+cd+(b+c+d)(ek+\mu e)-\frac{S^*}{N^*}[R_0bcd+\beta\eta(p(1 - q) + q)]$

$B_4 = (ek + \mu e)(bc + bd + cd + \frac{\beta\eta S^*}{N^*}(pq - p - q)) - \frac{R_0bcdS^*}{N^*}(e + k + \mu)$

$B_5 = \frac{\beta\eta S^* e}{N^*}(k + \mu)(pqd - pc - qd)$

where $k = \{\frac{\beta(I^*+qA^*)}{N^*} = \frac{bcde\pi R_0}{N^*[bcde-[pc\alpha\eta\theta+(1-p)\gamma\eta\theta d+\varphi\theta dc]]}(1 - \frac{1}{R_0})\}$

Then the eigenvalues of the characteristic equation (4.16) will be negative if it fulfill the Routh-Hurwitz criteria [46] that are $B_i > 0$ for $i = 1, 2, 3, 4, 5$ and the determinant of $p(\lambda) > 0$. From the Routh - Hurwitz criteria the determinant of the Hurwitz matrix becomes non negative if the following conditions holds true and it follows that all eigenvalues of the characteristic equation (4.16) has negative real part if and only if $B_i > 0, (i = 1, 2, 3, 4, 5)$ which implies that

$(i)B_1 > 0$ Since all the parameters in the models are positives.

(ii) $B_2 > 0 \Leftrightarrow bc + bd + cd + ek + \mu e + (e + k + \mu)(b + c + d) + \frac{\beta\eta qp}{R_0} > \frac{\beta\eta}{R_0}(p + q)$

(iii) $B_3 > 0 \Leftrightarrow (b+c+d)+(e+k+\mu)(bc+bd+cd+(b+c+d)(ek+\mu e)+\frac{\beta\eta}{R_0}(pqd+pq) > \frac{\beta\eta}{R_0}(pc + qd + p + q)$

(iv) $B_4 > 0 \Leftrightarrow e(k + \mu)(bc + bd + cd + \frac{\beta\eta qp}{R_0}) + (e + k + \mu)(\frac{\beta\eta qpd}{R_0}) > \frac{\beta\eta}{R_0}e(k + \mu)(p + q) + \frac{\beta\eta}{R_0}(e + k + \mu)(pc + qd)$

(v) $B_5 > 0 \Leftrightarrow e(\frac{\beta\eta qpd}{R_0})(k + \mu) > e\frac{\beta\eta q}{R_0}(k + \mu)(pc + qd))$.

and the determinant,

$D_1 = B_1 > 0$

$D_2 = B_1B_2 > 0$

$D_3 = B_1B_2 - B_3 > 0$

$D_4 = B_1B_2B_3 - B_3^2 - B_1^2B_4 > 0$

$D_5 = B_1B_2B_3B_4 + 2B_1B_4B_5 + B_2B_3B_5 - B_1B_2^2B_5 - B_1^2B_4^2 - B_3^2B_4 - B_5^2 > 0.$

Therefore the system (4.1) shows local asymptotic stability at E_1 when $R_0 > 1$ and conditions for D_1, D_2, D_3, D_4, D_5 are satisfied.

4.4.4 Global Stability of the Endemic Equilibrium Point

Theorem 5 *The endemic equilibrium point of the model equation(4.1) is globally asymptotically stable if* $R_0 > 1$.

Proof: *To show the result, we define the following Lyapunov function as:*

$$L(S^*, E^*, A^*, I^*, R^*) = [S - S^* - S^* \ln(\frac{S}{S^*})] + [E - E^* - E^* \ln(\frac{E}{E^*})] + [A - A^* - A^* \ln(\frac{A}{A^*})] + [I - I^* - I^* \ln(\frac{I}{I^*})] + [R - R^* - R^* \ln(\frac{R}{R^*})] \quad (4.17)$$

Then by taking the time derivative of $L(S^*, E^*, A^*, I^*, R^*)$, we obtain:

$\frac{dL}{dt} = (S' - \frac{S^*}{S}S') + (E' - \frac{E^*}{E}E') + (A' - \frac{A^*}{A}A') + (I' - \frac{I^*}{I}I') + (R' - \frac{R^*}{R}R')$

$= (1 - \frac{S^*}{S})\frac{dS}{dt} + (1 - \frac{E^*}{E})\frac{dE}{dt} + (1 - \frac{A^*}{A})\frac{dA}{dt} + (1 - \frac{I^*}{I})\frac{dI}{dt} + (1 - \frac{R^*}{R})\frac{dR}{dt}$

$= [1 - \frac{S^*}{S}][\pi + \theta R - (\lambda + \mu)S] + [1 - \frac{E^*}{E}][\lambda S - (\mu + \eta + \varphi)E] + [1 - \frac{A^*}{A}][(1 - p)\eta E - (\mu + \gamma)A] + [1 - \frac{I^*}{I}][p\eta E - (\mu + \alpha +)I] + [1 - \frac{R^*}{R}][\alpha I + \gamma A + \varphi E - (\theta + \mu)R]$

$= (\pi + \theta R + \lambda S^* + \mu S^* - \lambda S - \mu S - \pi\frac{S^*}{S} - \theta R\frac{S^*}{S}) + (\lambda S + \mu E^* + \eta E^* + \varphi E^* - \mu E - \eta E - \varphi E - \lambda S\frac{E^*}{E}) + (\eta E + \mu A^* + \gamma A^* + \frac{A^*}{A}p\eta E - p\eta E - \mu A - \gamma A - \frac{A^*}{A}\eta E) + (p\eta E\mu I^* + \alpha I^* - \mu I - \alpha I - \frac{I^*}{I}p\eta E) + (\alpha I + \gamma I + \varphi E + \theta R^* + \mu R^* - \theta R - \mu R - \alpha I\frac{R^*}{R} - \gamma A\frac{R^*}{R} - \varphi E\frac{R^*}{R})$

Now after some simplifications

$\frac{dL}{dt} = [\pi + (\lambda + \mu)S^* + \underbrace{(\mu + \eta + \varphi)}_{b}E^* + \frac{A^*}{A}p\eta E + \underbrace{(\mu + \gamma)}_{c}A^* + \underbrace{(\mu + \alpha)}_{d}I^* + \underbrace{(\theta + \mu)}_{e}R^*] - [\underbrace{(S + E + A + I + R)}_{N}\mu + \theta R\frac{S^*}{S} + \lambda S\frac{E^*}{E} + \frac{A^*}{A}\eta E + \frac{I^*}{I}p\eta E + \alpha I\frac{R^*}{R} + \gamma A\frac{R^*}{R} + \varphi E\frac{R^*}{R}]$

$= [\pi + (\lambda + \mu)S^* + bE^* + p\eta E\frac{A^*}{A} + cA^* + dI^* + eR^*] - [N\mu + \theta R\frac{S^*}{S} + \lambda S\frac{E^*}{E} + \eta E\frac{A^*}{A} + p\eta E\frac{I^*}{I} + (\alpha I + \gamma A + \varphi E)\frac{R^*}{R}], N \leq \frac{\pi}{\mu}$

$= [\pi + (\lambda + \mu)S^* + bE^* + p\eta E\frac{A^*}{A} + cA^* + dI^* + eR^*] - [\pi + \theta R\frac{S^*}{S} + \lambda S\frac{E^*}{E} + \eta E\frac{A^*}{A} + p\eta E\frac{I^*}{I} + \alpha I\frac{R^*}{R} + \gamma A\frac{R^*}{R} + \varphi E\frac{R^*}{R}]$

$= \underbrace{[(\lambda + \mu)S^* + bE^* + p\eta E\frac{A^*}{A} + cA^* + dI^* + eR^*]}_{M} - \underbrace{[\theta R\frac{S^*}{S} + \lambda S\frac{E^*}{E} + \eta E\frac{A^*}{A} + p\eta E\frac{I^*}{I} + \alpha I\frac{R^*}{R} + \gamma A}_{K}$

$\frac{dL}{dt} = M - K$

where $M = (\lambda + \mu)S^* + bE^* + p\eta E\frac{A^*}{A} + cA^* + dI^* + eR^*$

$K = \theta R\frac{S^*}{S} + \lambda S\frac{E^*}{E} + \eta E\frac{A^*}{A} + p\eta E\frac{I^*}{I} + \alpha I\frac{R^*}{R} + \gamma A\frac{R^*}{R} + \varphi E\frac{R^*}{R}$

$N = S + E + A + I + R$ and $N^* = S^* + E^* + A^* + I^* + R^*$

Thus if $K < M$, then $\frac{dL}{dt} < 0$. Nothing that $\frac{dL}{dt} = 0$ if and only if $S = S^*, E = E^*, A = A^*, I = I^*, R = R^*$. Therefore the largest compact invariant set in $\{(S^*, E^*, A^*, I^*, R^*) \in \Omega; \frac{dL}{dt} = 0\}$ is a singleton E_1 is the endemic equilibrium point of the system (4.1). By LaSalle's invariant principle [47], it implies that E_1 is globally asymptotically stable in Ω if $M < k$ and $R_0 > 1$.

4.5 Sensitivity Analysis

Sensitivity indices allow us to measure the relative change in variable when a parameter changes[36]. We carried out sensitivity analysis in order to determine the relative significance of model parameters on disease transmission. The analysis will enable us to find out parameters that have high impact on the basic reproduction number and which should be targeted by intervention strategies. We perform sensitivity analysis by calculating the sensitivity indices of the basic reproduction number R_0 in order to determine whether HPV can be spread in the population or not. These indices tell us how crucial each parameter is on the transmission of the HPV. Following [36, 38], we used the normalized forward sensitivity index also called elasticity as it is the backbone of nearly all other sensitivity analysis techniques [39] and are computationally efficient[40]. The normalized forward sensitivity index of the basic reproduction number, R_0 with respect to a parameter value, P is given by:

$$\Upsilon_p^{R_0} = \frac{\partial R_0}{\partial P} \times \frac{P}{R_0}. \tag{4.18}$$

To investigate which parameters have high impact on the R_0, we apply the approach presented in [48]. The explicit expression ofR_0 is given by

$$R_0 = \frac{\beta\eta(p(\mu+\gamma+\zeta)+q(\alpha+\mu+\zeta)(1-p))}{(\eta+\mu+\varphi)(\mu+\gamma+\zeta)(\alpha+\mu+\zeta)}.$$

Since R_0 depends only on nine parameters, we derive an analytical expression for its sensitivity to each parameter using the normalized forward sensitivity index as in [48] by taking the values of the paramters from table 4 in 6.1 and computed as follows:

$$\Upsilon_\beta^{(R_0)} = \frac{\partial R_0}{\partial \beta} \times \frac{\beta}{R_0} = 1,$$

$$\Upsilon_\eta^{(R_0)} = \frac{\partial R_0}{\partial \eta} \times \frac{\eta}{R_0} = \frac{\mu+\varphi}{\eta+\mu+\varphi},$$

$$\Upsilon_p^{(R_0)} = \frac{\partial R_0}{\partial p} \times \frac{p}{R_0} = \frac{[\mu+\gamma+\zeta-q(\alpha+\mu+\zeta)]p}{p(\mu+\gamma+\zeta)+q(\alpha+\mu+\zeta)(1-p)},$$

$$\Upsilon_q^{(R_0)} = \frac{\partial R_0}{\partial q} \times \frac{q}{R_0} = \frac{(\alpha+\mu+\zeta)(1-p)q}{p(\mu+\gamma+\zeta)+q(\alpha+\mu+\zeta)(1-p)},$$

$$\Upsilon_\mu^{(R_0)} = \frac{\partial R_0}{\partial \mu} \times \frac{\mu}{R_0} = \frac{[p+q(1-p)][(\eta+\mu+\varphi)(\mu+\gamma+\zeta)(\mu+\alpha+\zeta)]-[p(\mu+\gamma+\zeta)+q(\alpha+\mu+\zeta)(1-p)][(\mu+\gamma+\zeta)(\mu+\alpha+\zeta)+(\eta+\mu+\varphi)(\mu+}{(\eta+\mu+\varphi)(\mu+\gamma+\varphi)(\mu+\alpha+\zeta)}$$

$$\frac{\mu}{p(\mu+\gamma+\zeta)+q(\alpha+\mu+\zeta)(1-p)},$$

$$\Upsilon_\varphi^{(R_0)} = \frac{\partial R_0}{\partial \varphi} \times \frac{\varphi}{R_0} = \frac{-\varphi}{\mu+\eta+\varphi},$$

$$\Upsilon_{\zeta}^{(R_0)} = \frac{\partial R_0}{\partial \zeta} \times \frac{\zeta}{R_0} = \frac{[p+q(1-p)][(\mu+\gamma+\zeta)(\mu+\alpha+\zeta)]-[p(\mu+\gamma+\zeta)+q(\alpha+\mu+\zeta)(1-p)][2\mu+2\zeta+\alpha+\gamma]}{(\alpha+\mu+\zeta)(\mu+\gamma+\zeta)}$$

$$\times \frac{\zeta}{p(\mu+\gamma+\zeta)+q(\alpha+\mu+\zeta)(1-p)},$$

$$\Upsilon_{\gamma}^{(R_0)} = \frac{\partial R_0}{\partial \gamma} \times \frac{\gamma}{R_0} = \frac{-q(\alpha+\mu+\zeta)(1-p)\gamma}{(\mu+\gamma+\zeta)[p(\mu+\gamma+\zeta)+q(\alpha+\mu)(1-p)]},$$

$$\Upsilon_{\alpha}^{(R_0)} = \frac{\partial R_0}{\partial \alpha} \times \frac{\alpha}{R_0} = \frac{-(\mu+\gamma+\zeta)p\alpha}{(\mu+\alpha+\zeta)[p(\mu+\gamma+\zeta)+q(\alpha+\mu+\zeta)(1-p)]}.$$

Table 4.3: Sensitivity Indices of the Basic Model Parameters in R_0

Parameter Symbol	**Sensitivity indices**
β	+1
η	0.9943
q	0.8732
p	0.0626
ζ	-0.0151
α	-0.0549
μ	-0.3488
γ	-0.6288
φ	-0.9470

The sensitivity indices of the basic reproductive number with respect to the main parameters are arranged in table 4.3 above. Those parameters that have positive indices, β, η, q and p show that they have great impact on expanding the disease in the population if their values are increasing. Due to the reason that the basic reproduction number increases as their values increase, it means that the average number of secondary cases of infection increases in the population. Furthermore, those parameters in which their sensitivity indices are negative, $\zeta, \alpha, \mu, \gamma$ and φ have an influence of minimizing the burden of the disease in the community as their values increase while the others are left constant. And also as their values increase, the basic reproduction number decreases, which leads to minimizing the endemic nature of the disease in the community.

Chapter 5

An Optimal Control Problem for HPV

Control efforts are carried out to limit the spread of the disease and, in some cases, to prevent the emergence of drug resistance[4]. Most of the modern mathematical models that have been developed apply the optimal control theory[27]. Optimal control theory is one area of mathematics that is used extensively in the control of the spread of infection disease[31, 33]. In this thesis work, we consider a deterministic model for assessing the effect of vaccination on the susceptible individuals, screening on exposed individuals and treatement on both asymptomatic individuals and infective individuals in the symptomatic stage.

5.1 HPV Model with Optimal Control

In this section, our main focus is to setup an optimal control problem relative to the epidemic model (4.1). We introduce to SEAIR epidemic model (4.1) a control function $u_1(t)$ that represent the effort of vaccination to prevent susceptible individuals from exposing to disease by developing their natural immunity while the control function $u_2(t)$ represents, the effort of the screening for exposed individuals by effectively using a pap test to reduce transmission of HPV and $u_3(t)$ represent the effort of increasing the treatment rate to recover infected and asymptomatic individuals; it is aimed at increasing rate of treatment for infected and aymptomatic individuals. Thus $u_1(t)$, $u_2(t)$ and $u_3(t)$ are the first prevention(vaccination), second screening and third treatement control respectively at time t taking values between 0 and 100%. The objective is to use optimal control technique to minimize the number of exposed, asymptomatic and infected individuals respectively with optimal cost over a fixed period of time T. Thus, the transmission dynamic of HPV model with optimal control is governed by nonlinear system of differential equations as follows:

$$\begin{cases} \frac{dS}{dt} = \pi + \theta R - (1-u_1)\lambda S - \mu S, \\ \frac{dE}{dt} = (1-u_1)\lambda S - (1-u_2)\eta E - (u_2+\varphi)E - \mu E, \\ \frac{dA}{dt} = (1-u_2)(1-p)\eta E - (u_3+\gamma)A - (\mu+\zeta)A, \\ \frac{dI}{dt} = (1-u_2)p\eta E - (u_3+\alpha)I - (\mu+\zeta)I, \\ \frac{dR}{dt} = (u_3+\alpha)I + (u_3+\gamma)A + (u_2+\varphi)E - (\theta+\mu)R. \end{cases} \tag{5.1}$$

$S(0) = S_0 > 0, E(0) = E_0 \geq 0, A(0) = A_0 \geq 0, I(0) = I_0 \geq 0, R(0) = R_0 \geq 0.$

The optimal control problem is to minimize the objective (cost) functional (J) considering the costs of vaccination of susceptible individuals, screening of exposed individuals and treatment of both asymptomatic and acutely infected individuals.

The goal of the adopted strategy is to reduce exposed, asymptomatic and infected individuals with optimal cost. Mathematically, the optimal control problem consists of minimizing the objective functional J, on a fixed time interval T takes the form;

$$J(u_1(t), u_2(t), u_3(t)) = \int_0^T [M_1 E + M_2 A + M_3 I + \frac{1}{2}\sum_{i=1}^{3} k_i u_i^2(t)]dt \longrightarrow min \tag{5.2}$$

subject to

$$g(x,u,t) = \begin{cases} \frac{dS}{dt} = \pi + \theta R - (1-u_1)\lambda S - \mu S, \\ \frac{dE}{dt} = (1-u_1)\lambda S - (1-u_2)\eta E - (u_2+\varphi)E - \mu E, \\ \frac{dA}{dt} = (1-u_2)(1-p)\eta E - (u_3+\gamma)A - (\mu+\zeta)A, \\ \frac{dI}{dt} = (1-u_2)p\eta E - (u_3+\alpha)I - (\mu+\zeta)I, \\ \frac{dR}{dt} = (u_3+\alpha)I + (u_3+\gamma)A + (u_2+\varphi)E - (\theta+\mu)R, \end{cases} \tag{5.3}$$

with initial condition, $S(0) = S_0 > 0, E(0) = E_0 \geq 0, A(0) = A_0 \geq 0,$
$I(0) = I_0 \geq 0, R(0) = R_0 \geq 0$ and

$$\Omega_\epsilon = \{(u_1, u_2, u_3) : 0 \leq u_i \leq 1, t \in [0,T], i = 1,2,3\},$$

where $M_1, M_2, M_3, \frac{k_1}{2}, \frac{k_2}{2}, \frac{k_3}{2}$ are positive weights that balance the size of the integrand terms to reduce the dominance of any of the term in the integral. Such that the constant weight k_1, k_2 and k_3 measures the cost or effort required for the implementation of each of the three control measures adopted while M_1, M_2 and M_3 measures the relative importance of reducing the associated classes on the spread of the disease. The parameter T is the duration of time, in years of vaccination, screening and treatment progress.

We assumed that $0 \leq u_1 < 1$, since avoiding the contact between the entire susceptible and infectious individuals are impossible in reality. In practice, vaccinating the entire society is impossible due to many factors such as financial and human resource constraint. Similarly,

$0 \leq u_2 < 1$ because efficient implementation of pap test may not be in a proper ways and $0 \leq u_3 < 1$ because due to the failure of treatment.
Thus, the control takes values in the set

$$[0, 1) \times [0, 1) \times [0, 1) = [0, 1).$$

If $u_i = 0$ for $i = 1, 2, 3$ then no control measure is taken and the model equation (5.1) is equivalent to (4.1). On the other hand, if $u_i = 1$, for $i = 1, 2, 3$ implies our control is 100% success. But in the reality this case is not possible and our aim is to minimize the number of exposed, infected, asymptomatic and cost. Hence we are looking for the optimal control triple (u_1^*, u_2^*, u_3^*) such that

$$J(u_1^*, u_2^*, u_3^*) = min\{J(u_1, u_2, u_3) : u_1, u_2, u_3 \in \Omega_\epsilon\} \tag{5.4}$$

where Ω_ϵ is the set of admissible control as defined above. The solution of the optimal control problem is the vector function $x^*(.) = (S^*(.), E^*(.), A^*(.), I^*(.), R^*(.)) \in \mathbb{R}_+^5$ associated with an admissible control $u^* = (u_1^*, u_2^*, u_3^*) \in \Omega_\epsilon$ on the time interval $[0, T]$ that minimize the cost functional (5.2) where $u_i^*; i = 1, 2, 3$ are Lebesgue measurable function on $[0, 1]$ that is the control u_1^*, u_2^*, u_3^* are piecewise continuous and integrable.

5.2 Existence and Characterization of the Optimal Control

In this section, we examine conditions that can be assure the existence of a solution to the optimal control problem (5.2).

5.2.1 Existence of Optimal Control Solution

Theorem 6 *There exist an optimal control $u^* = (u_1^*, u_2^*, u_3^*)$ and a corresponding solution vector x^* to the state initial value problem (5.1) that minimizes the cost functional $J(u)$ of (5.2) over the set of admissible control Ω_ϵ.*
Proof : *The non trivial requirement on the set of admissible controls and the set of end conditions are followed by [28].*

i. The set of all solution to system (5.1) with corresponding control functions in Ω_ϵ is non-empty.
ii. The control set is convex and closed.
iii. The right hand side of the state system is bounded by a linearized function in the state and control variables.
iv. The integral of the objective function is convex.

v. There exist a constants $c_1, c_2 > 0$ and $\beta > 1$ such that the integrand of the objective functional satisfies, $M_1E+M_2A+M_3I+\frac{k_1}{2}u_1^2+\frac{k_2}{2}u_2^2+\frac{k_3}{2}u_3^2 \geq c_1(|u_1|^2+|u_2|^2+|u_3|^2)^{\frac{\beta}{2}}-c_2$.

In order to established condition (i), we consider the Picard-Lindelo̊f existence theorem [41]. If $g(x, u, t)$ is bounded, continuous, and lipschitz in the state variables, then there exists a unique solution corresponding to every admissible control Ω_ϵ . Hence, for any $u \in \Omega_\epsilon$ and the state variables, we have

$$0 < N \leq \frac{\pi}{\mu} \tag{5.5}$$

and non empty by model assumption. Furthermore, with the bounded established (5.5) it implies that the state system is continuous and bounded. It is possible to show the boundedness of the partial derivative with respect to the state variable i.e $\frac{\partial g}{\partial x}$ exist and finite, which established the system is Lipschitz with respect to the state variables [41]. This established the proof of condition (i).

For condition (ii) consider $\Omega_\epsilon = \{u \in R^3 : ||u|| \leq 1 - \varepsilon.$

Assume that $u_1, u_2 \in \Omega_\epsilon$ and $\lambda \in [0, 1]$, such that $||u_1|| \leq 1 - \varepsilon$ and $||u_2|| \leq 1 - \varepsilon$ then $||\lambda u_1 + (1 - \lambda)u_2|| \leq \lambda||u_1|| + (1 - \lambda)||u_2|| \leq 1 - \varepsilon$.

Hence, $0 \leq \lambda||u_1|| + (1 - \lambda)||u_2|| \leq 1 - \varepsilon, \forall u_1, u_2 \in \Omega_\epsilon$ and $\lambda \in [0, 1]$.

Thus the control set is convex and closed by definition.

To prove condition (iii), we consider the system (5.1). Then

$$\begin{gathered}\tfrac{dN}{dt} = \tfrac{dS}{dt} + \tfrac{dE}{dt} + \tfrac{dA}{dt} + \tfrac{dI}{dt} + \tfrac{dR}{dt},\\ = \pi - \mu N - \zeta(A + I) \leq \pi - \mu N\\ \tfrac{dN}{dt} + \mu N \leq \pi\\ \lim_{t\to\infty} sup\, N(t) \leq \tfrac{\pi}{\mu}.\end{gathered}$$

Therefore, all solutions of the model (5.1) are bounded. We can write system (5.1) in matrix form as

$$F(t, x, u) = G(t, x) + H(t, x)U$$

where

$$F(t,x,u) = \begin{bmatrix} \pi + \theta R - (1-u_1)\lambda S - \mu S \\ (1-u_1)\lambda S - (1-u_2)\eta E - (u_2+\varphi)E - \mu E \\ (1-u_2)(1-p)\eta E - (u_3+\gamma)A - (\mu+\zeta)A \\ (1-u_2)p\eta E - (u_3+\alpha)I - (\mu+\zeta)I \\ (u_3+\alpha)I + (u_3+\gamma)A + (u_2+\varphi)E - (\theta+\mu)R \end{bmatrix}$$

$$G(t,x) = \begin{bmatrix} \pi + \theta R - (\lambda+\mu)S \\ \lambda S - (\mu+\eta+\varphi)E \\ (1-p)\eta E - (\mu+\gamma+\zeta)A \\ p\eta E - (\mu+\alpha+\zeta)I \\ \alpha I + \gamma A + \varphi E - (\theta+\mu)R \end{bmatrix}$$

$$H(t,x) = \begin{bmatrix} \lambda S & 0 & 0 \\ -\lambda S & (\eta-1)E & 0 \\ 0 & -(1-p)\eta E & -A \\ 0 & -p\eta E & -I \\ 0 & E & I+A \end{bmatrix} \text{ and } U = \begin{bmatrix} u_1 \\ u_2 \\ u_3 \end{bmatrix}$$

It gives a linar function of control and state variable.
Then the norm of $F(t,x,u) = G(t,x) + H(t,x)U$ is

$$||F(t,x,u)|| = ||G(t,x) + H(t,x)U||$$
$$||F(t,x,u)|| \leq ||G(t,x)|| + ||H(t,x)U||$$

$$||F|| \leq ||G||||X(t)|| + ||H||||U(t)|| \leq max(||G||, ||H||)$$

This shows that the right hand side is bounded by the sum of the state and control variable. This complete the proof of condition (iii) which is bounded in the state and control variables.
(iv) The integrand in the objective functional which is a cost functional,

$$g(x,t,u) = M_1E + M_2A + M_3I + \frac{1}{2}\sum_{i=1}^{3} k_i u_i^2(t)$$
is an affine function.

Recall that any affine function is a convex and the sum of a convex function is a convex [42]. Therefore, $g(x,t,u)$ is convex on Ω_ϵ.
Proof of condition (v)
Given $g(x,t,u) = M_1E + M_2A + M_3I + \frac{1}{2}\sum_{i=1}^{3} k_i u_i^2(t)$.
$g(x,t,u) \geq \frac{1}{2}\sum_{i=1}^{3} k_i u_i^2(t)$,
$\geq c_1[\sum_{i=1}^{3} u_i^2(t)]^{\frac{\beta}{2}} - c_2$, where $c_1 = \frac{1}{2}min\{k_1,k_2,k_3\}$, $c_2 > 0$ and $\beta = 2$.
Thus,
$M_1E + M_2A + M_3I + \frac{k_1}{2}u_1^2 + \frac{k_2}{2}u_2^2 + \frac{k_3}{2}u_3^2 \geq c_1(|u_2|^2 + |u_1|^2 + |u_3|^2)^{\frac{\beta}{2}} - c_2$.
Since all the above conditions are satisfied, we conclude that there exists an optimal controls u_1^*, u_2^* and u_3^* such that (x, u^*) that minimize the cost functional of (5.2) over the set of admissible control Ω_ϵ.

5.2.2 Characterization of the Optimal Control Solutions

In order to derive the necessary conditions for the optimal control pair the Pontryagin's Maximum Principle[43] is used. According to the Pontryagin's Maximum Principle, if $u^*(.) \in \Omega_\epsilon$ (5.4) with fixed final time T, then there exists a non-trivial absolutely continuous mapping $\lambda : [0,T] \longrightarrow \mathbb{R}_+^5, \lambda = (\lambda_1(t), \lambda_2(t), \lambda_3(t), \lambda_4(t), \lambda_5(t))$ are the adjoint vector, such that

$$J(u_1(t), u_2(t), u_3(t)) = \int_0^T [M_1E(t) + M_2A(t) + M_3I(t) + \frac{1}{2}\sum_{i=1}^{3} k_i u_i^2(t)]dt$$

subject to

$$\sum_{i=1}^{5} \lambda_i(t) g_i(S, E, A, I, R, u_1, u_2, u_3, t).$$

Then

1. The Hamiltonian of the given system is defined as follows:
$H(t, S, E, A, I, R, u_1, u_2, u_3) = f(t, S, E, A, I, R, u_1, u_2, u_3) + \sum_{i=1}^{5} \lambda_i(t) g_i(t, S, E, A, I, R, u_1, u_2, u_3)$,
where $f(t, S, E, A, I, R, u_1, u_2, u_3) = M_1E(t) + M_2A(t) + M_3I(t) + \frac{1}{2}\sum_{i=1}^{3} k_i u_i^2(t)$ and
$g_i(t, S, E, A, I, R, u_1, u_2, u_3)$ stands for the right hand side of the constraints (5.2) for i=1,2...5.

2. The optimality condition of the system,

$$\begin{aligned} \frac{\partial H}{\partial u_1} &= 0, \\ \frac{\partial H}{\partial u_2} &= 0, \\ \frac{\partial H}{\partial u_3} &= 0. \end{aligned}$$

3. Hamiltonian system

$$\begin{cases} \frac{dS}{dt} = \frac{\partial H}{\partial \lambda_1}, \\ \frac{dE}{dt} = \frac{\partial H}{\partial \lambda_2}, \\ \frac{dA}{dt} = \frac{\partial H}{\partial \lambda_3}, \\ \frac{dI}{dt} = \frac{\partial H}{\partial \lambda_4}, \\ \frac{dR}{dt} = \frac{\partial H}{\partial \lambda_5}, \end{cases}$$

$$\begin{cases} \frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial S}, \\ \frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial E}, \\ \frac{d\lambda_3}{dt} = -\frac{\partial H}{\partial A}, \\ \frac{d\lambda_4}{dt} = -\frac{\partial H}{\partial I}, \\ \frac{d\lambda_5}{dt} = -\frac{\partial H}{\partial R}. \end{cases}$$

4. Minimality condition

$$H(x^*(t), u^*(t), \lambda(t)) = \min H(x^*(t), u^*(t), \lambda(t))$$

holds for almost all $t \in [0, T]$.

5. Moreover, the transversality condition
$\lambda_i(T) = 0$, for $i = 1, 2, 3, 4, 5$ also holds true.

Theorem 7 *The optimal control problem (5.4) with fixed final time T admits a unique optimal solution $(S^*, E^*, A^*, I^*, R^*)$ associated with an optimal control $u = (u_1, u_2, u_3)$ for all $t \in [0, T]$. Moreover, there exist adjoint function λ_i, for $i = 1, 2, 3, 4, 5$ such that*

$$\begin{cases} \frac{d\lambda_1}{dt} = (1-u_1)\lambda(\lambda_1-\lambda_2)+\mu\lambda_1, \\ \frac{d\lambda_2}{dt} = -M_1+(u_2+u_3+\eta+\varphi+\mu)\lambda_2-(1-u_2)(1-p)\eta\lambda_3-(1-u_2)p\eta\lambda_4-(u_3+\varphi)\lambda_5, \\ \frac{d\lambda_3}{dt} = -M_2+(1-u_1)\frac{\beta}{N}qS(\lambda_1-\lambda_2)+(u_3+\gamma+\mu+\zeta)\lambda_3-(u_3+\gamma)\lambda_5, \\ \frac{d\lambda_4}{dt} = -M_3+(1-u_1)\frac{\beta}{N}S(\lambda_1-\lambda_2)+(u_3+\alpha+\mu+\zeta)\lambda_4-(u_3+\alpha)\lambda_5, \\ \frac{d\lambda_5}{dt} = \lambda_5(\theta+\mu)-\lambda_1\theta, \end{cases}$$

with transiversality conditions $\lambda_i(T) = 0, i = 1, 2, 3, 4, 5$,.
Furthermore, the following properties holds:

$$u_1^* = min\{max\{0, \tfrac{\lambda^* S(\lambda_2-\lambda_1)}{k_1}\}, 1\} \text{ where } \lambda^* = \tfrac{\beta(I^*+qA^*)}{N},$$

$$u_2^* = min\{max\{0, \tfrac{(p\eta\lambda_4+(1-p)\eta\lambda_3-(\eta-1)\lambda_2-\lambda_5)E^*}{k_2}\}, 1\},$$

$$u_3^* = min\{max\{0, \tfrac{(\lambda_3-\lambda_5)A^*+(\lambda_4-\lambda_5)I^*}{k_3}\}, 1\},$$

Proof: *The Hamiltonian function associated with the system is defined as follows:*

$H(t, S, E, A, I, R, u_1, u_2, u_3) = M_1E(t) + M_2A(t) + M_3I(t) + \frac{1}{2}\sum_{i=1}^{3} k_iu_i^2(t) + \sum_{i=1}^{5}\lambda_i(t)g_i(t)$
$= (M_1E + M_2A + M_3I) + \frac{1}{2}(k_1u_1^2 + k_2u_2^2 + k_3u_3^2) + \lambda_1[\pi + \theta R - (1-u_1)\lambda S - \mu S] +$
$\lambda_2[(1-u_1)\lambda S - (1-u_2)\eta E - (u_2+\varphi)E - \mu E] + \lambda_3[(1-u_2)(1-P)\eta E - (u_3+\gamma)A -$
$(\mu+\zeta)A] + \lambda_4[(1-u_2)P\eta E - (u_3+\alpha)I - (\mu+\zeta)I] + \lambda_5[(u_3+\alpha)I + (u_3+\gamma)A + (u_2+$
$\varphi)E - (\theta+\mu)R]$
where $\lambda_i(t)$, for $i = 1, 2, 3, 4, 5$ are the adjoint functions to be determined suitably. The form of the adjoint equations and transversality conditions are standard results from PMP. The adjoint system can be obtained as follows:

$$\begin{cases} \frac{d\lambda_1}{dt} = -(\frac{\partial H}{\partial S}) = (1-u_1)\lambda(\lambda_1-\lambda_2)+\mu\lambda_1, \\ \frac{d\lambda_2}{dt} = -(\frac{\partial H}{\partial E}) = -M_1+((1-u_2)\eta+u_2+\varphi+\mu)\lambda_2-(1-u_2)(1-p)\eta\lambda_3-(1-u_2)p\eta\lambda_4-(u_2+\varphi \\ \frac{d\lambda_3}{dt} = -(\frac{\partial H}{\partial A}) = -M_2+(u_3+\gamma)(\lambda_3-\lambda_5)+(u_3+\zeta)\lambda_3 \\ \frac{d\lambda_4}{dt} = -(\frac{\partial H}{\partial I}) = -M_3+(u_3+\alpha)(\lambda_4-\lambda_5)+(\mu+\zeta)\lambda_3 \\ \frac{d\lambda_5}{dt} = -(\frac{\partial H}{\partial R}) = \theta(\lambda_5-\lambda_1)+\mu\lambda_5. \end{cases} \tag{5.6}$$

The state variables are not assigned at the final time T. Hence, following Lenhart, S.[31] the transversality conditions (or boundary conditions) becomes $\lambda_i(T) = 0$, for $i = 1, 2, 3, 4, 5$.
By the optimality condition, we have: $\frac{\partial H}{\partial u_i} = 0$, for $i = 1, 2, 3$
(i) $\frac{\partial H}{\partial u_1} = k_1 u_1 + S\lambda(\lambda_1 - \lambda_2) = 0$ at $u_1 = u_1^*(t)$ where$\lambda^* = \frac{\beta(I+qA)}{N}$,

$$u_1^*(t) = \frac{S^*\lambda^*(\lambda_2-\lambda_1)}{k_1}.$$

(ii) $\frac{\partial H}{\partial u_2} = k_2 u_2 + (\eta - 1)E\lambda_2 - (1-p)\eta E\lambda_3 - p\eta E\lambda_4 + E\lambda_5 = 0$ at $u_2 = u_2^*(t)$,

$$u_2^*(t) = \frac{(P\eta\lambda_4+(1-p)\eta\lambda_3-(\eta-1)\lambda_2-\lambda_5)E^*}{k_2}.$$

(iii) $\frac{\partial H}{\partial u_3} = k_3 u_3 - A\lambda_3 - I\lambda_4 + I\lambda_5 + A\lambda_5 + E\lambda_5 = 0$ at $u_3 = u_3^*(t)$,

$$u_3^* = \frac{(\lambda_3-\lambda_5)A^*+(\lambda_4-\lambda_5)I^*}{k_3}.$$

By using the bounds for the control $u_1(t)$, we get

$$u_1^*(t) = \begin{cases} \frac{S^*\lambda^*(\lambda_2-\lambda_1)}{k_1} \text{ if } 0 \leq \frac{S^*\lambda^*(\lambda_2-\lambda_1)}{k_1} \leq 1, \\ 0, \text{if } \frac{S^*\lambda^*(\lambda_2-\lambda_1)}{k_1} \leq 0, \\ 1, \text{if } \frac{S^*\lambda^*(\lambda_2-\lambda_1)}{k_1} \geq 1, \end{cases} \tag{5.7}$$

In compact notation:

$$u_1^* = min\{max\{0, \frac{\lambda^* S^*(\lambda_2 - \lambda_1)}{k_1}\}, 1\}. \tag{5.8}$$

By using the bounds for the control $u_2(t)$, we get

$$u_2^*(t) = \begin{cases} \frac{(P\eta\lambda_4+(1-p)\eta\lambda_3-(\eta-1)\lambda_2-\lambda_5)E^*}{k_2} \text{ if } 0 \leq \frac{(P\eta\lambda_4+(1-p)\eta\lambda_3-(\eta-1)\lambda_2-\lambda_5)E^*}{k_2} \leq 1, \\ 0, \text{ if } \frac{(P\eta\lambda_4+(1-p)\eta\lambda_3-(\eta-1)\lambda_2-\lambda_5)E^*}{k_2} \leq 0, \\ 1, \text{ if } \frac{(P\eta\lambda_4+(1-p)\eta\lambda_3-(\eta-1)\lambda_2-\lambda_5)E^*}{k_2} \geq 1, \end{cases} \tag{5.9}$$

In compact notation:

$$u_2^* = min\{max\{0, \frac{(P\eta\lambda_4 + (1-p)\eta\lambda_3 - (\eta-1)\lambda_2 - \lambda_5)E^*}{k_2}\}, 1\}. \tag{5.10}$$

By using the bounds for the control $u_3(t)$, we get

$$u_3^*(t) = \begin{cases} \frac{(\lambda_3-\lambda_5)A^*+(\lambda_4-\lambda_5)I^*}{k_3} \text{ if } 0 \leq \frac{(\lambda_3-\lambda_5)A^*+(\lambda_4-\lambda_5)I^*}{k_3} \leq 1, \\ 0, \text{ if } \frac{(\lambda_3-\lambda_5)A^*+(\lambda_4-\lambda_5)I^*}{k_3} \leq 0, \\ 1, \text{ if } \frac{(\lambda_3-\lambda_5)A^*+(\lambda_4-\lambda_5)I^*}{k_3} \geq 1, \end{cases} \tag{5.11}$$

In compact notation:

$$u_3^* = min\{max\{0, \frac{(\lambda_3 - \lambda_5)A^* + (\lambda_4 - \lambda_5)I^*}{k_3}\}, 1\}. \tag{5.12}$$

Using (5.8), (5.10), and (5.12) we obtain the following optimality system:

$$\frac{dS}{dt} = \pi + \theta R - (1 - min\{max\{0, \frac{\lambda^* S^*(\lambda_2 - \lambda_1)}{k_1}\}, 1\})\lambda S - \mu S,$$

$$\frac{dE}{dt} = (1 - [min\{max\{0, \frac{\lambda^* S^*(\lambda_2 - \lambda_1)}{k_1}\}, 1\}])\lambda S - (1 - [min\{max\{0, \frac{(P\eta\lambda_4 + (1-p)\eta\lambda_3 - (\eta-1)\lambda_2 - \lambda_5)E^*}{k_2}\}, 1\}])$$
$$(\eta E) - ([min\{max\{0, \frac{(P\eta\lambda_4 + (1-p)\eta\lambda_3 - (\eta-1)\lambda_2 - \lambda_5)E^*}{k_2}\}, 1\}] + \varphi)E - \mu E,$$

$$\frac{dA}{dt} = (1 - [min\{max\{0, \frac{(P\eta\lambda_4 + (1-p)\eta\lambda_3 - (\eta-1)\lambda_2 - \lambda_5)E^*}{k_2}\}, 1\}])(1-p)\eta E -$$
$$([min\{max\{0, \frac{(\lambda_3 - \lambda_5)A^* + (\lambda_4 - \lambda_5)I^*}{k_3}\}, 1\}] + \gamma)A - (\mu + \zeta)A,$$

$$\frac{dI}{dt} = (1 - [min\{max\{0, \frac{(P\eta\lambda_4 + (1-p)\eta\lambda_3 - (\eta-1)\lambda_2 - \lambda_5)E^*}{k_2}\}, 1\}])p\eta E -$$
$$([min\{max\{0, \frac{(\lambda_3 - \lambda_5)A^* + (\lambda_4 - \lambda_5)I^*}{k_3}\}, 1\}] + \alpha)I - (\mu + \zeta)I,$$

$$\frac{dR}{dt} = ([min\{max\{0, \frac{(\lambda_3 - \lambda_5)A^* + (\lambda_4 - \lambda_5)I^*}{k_3}\}, 1\}] + \alpha)I + [min\{max\{0, \frac{(\lambda_3 - \lambda_5)A^* + (\lambda_4 - \lambda_5)I^*}{k_3}\}, 1\}] +$$
$$\gamma)A + ([min\{max\{0, \frac{(P\eta\lambda_4 + (1-p)\eta\lambda_3 - (\eta-1)\lambda_2 - \lambda_5)E^*}{k_2}\}, 1\}] + \varphi)E - (\theta + \mu)R,$$

subject to the following initial conditions:
$S(0) = S_0, E(0) = E_0, A(0) = A_0, I(0) = I_0, R(0) = R_0$, and
$\lambda_1(T) = 0, \lambda_2(T) = 0, \lambda_3(T) = 0, \lambda_4(T) = 0, \lambda_5(T) = 0,$
This completes the proof.

Chapter 6

Numerical Simulations

6.1 Numerical Simulation of the System

Nonlinear problem may not easily solvable analytically and thus, instead numerical methods are used to approximate the solutions. In this section, we present numerically the behaviour of the solutions of the system (4.1) and (5.1) for different values of parameters given in the model. We conducted numerical simulation in order to investigate the effects of the control strategies on the transmission dynamics of HPV. To conduct the study, a set of meaningful values are assigned to the model parameters. These values are either taken from literature or assumed. Using the parameter values given in table 3 and the initial conditions $S(0) = 300, E(0) = 250, A(0) = 150, I(0) = 100$ and $R(0) = 50$. For the adjoint system we set terminal conditions $\lambda(T) = 0; i = 1, 2, , 4, 5$ where $T = 10$ is simulation time. We considered the numerical value of the controls $u_i; i = 1, 2, 3$ between zero and one as they are not 100% effective. The cost coefficients corresponding to control variables are estimated to be $k_1 = 0.5, k_2 = 10$ and $k_3 = 2$ and the relative importance of reducing the associated classes on the spread of the disease are $M_1 = 1, M_2 = 1, M_3 = 0$. Then the simulation process are performed using software MATLAB $R2015b$ with $ode45$ solver.

Table 6.1: The values of parameters used in the simulations

Parameter	Value	Reference
π	2	[2]
β	0.064	[2]
η	0.0024	[8]
α	0.016	[25]
φ	0.4	assumed
θ	0.0002	[17]
γ	0.054	assumed
q	1.002	assumed
p	0.067	assumed
μ	0.02	[1]
ζ	0.001	[17]

Using different combinations of the controls, such as one control only at a time, two controls at a time and also all controls at a time, that we analyse and compare numerical results from simulations with the following conditions.

- Using vaccination efforts (u_1) of susceptible population without screening $(u_2 = 0)$ of exposed population and treatment $(u_3 = 0)$ of infectious population.
- Using screening effort (u_2) of exposed population without vaccination $(u_1 = 0)$ of susceptible population and with no treatment $(u_3 = 0)$ of infectious population.
- Using treatment (u_3) of infectious population but without vaccination $(u_1 = 0)$ of susceptible population and no screening $(u_2 = 0)$ of exposed population .
- Using vaccination (u_1) of susceptible population, treatment (u_3) of infectious population and without screening $(u_2 = 0)$ of exposed population.
- Using vaccination (u_1) of susceptible population, screening (u_2) of exposed population and without treatment $(u_3 = 0)$ of infectious population.
- Using treatment (u_3) of infectious population, screening (u_2) of exposed population and without vaccination $(u_1 = 0)$ of susceptible population.
- Using all the three controls, vaccination (u_1) of susceptible, screening of exposed (u_2) and treatment of infectious (u_3) population at a time T.

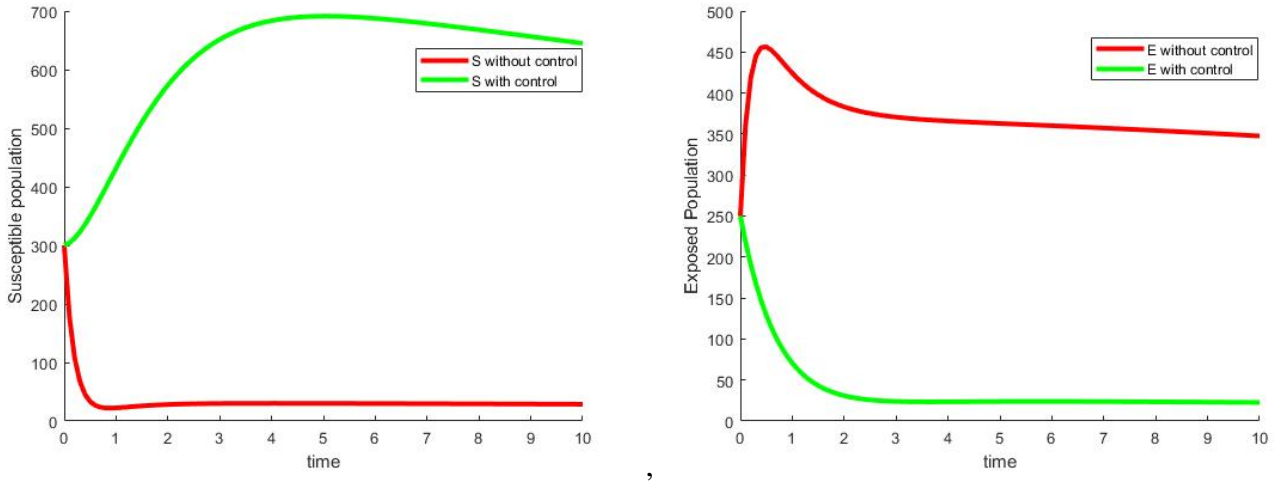

Figure 6.1: Illustrates the impact of optimal control on the susceptible and exposed population respectiveiy.

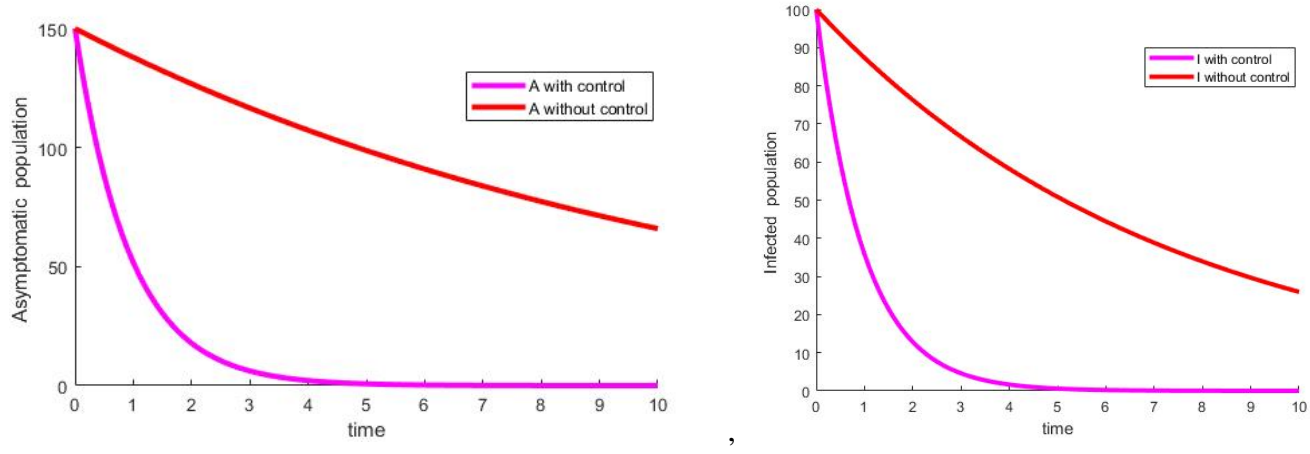

Figure 6.2: Illustrates the impact of optimal control on the asymptomatic and infected population respectively

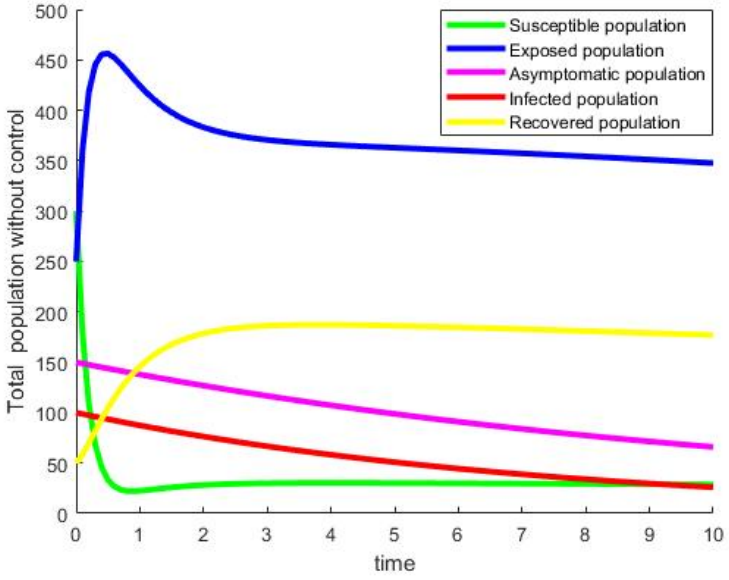

Figure 6.3: Illustrates the effets of the absence of optimal control on the total population

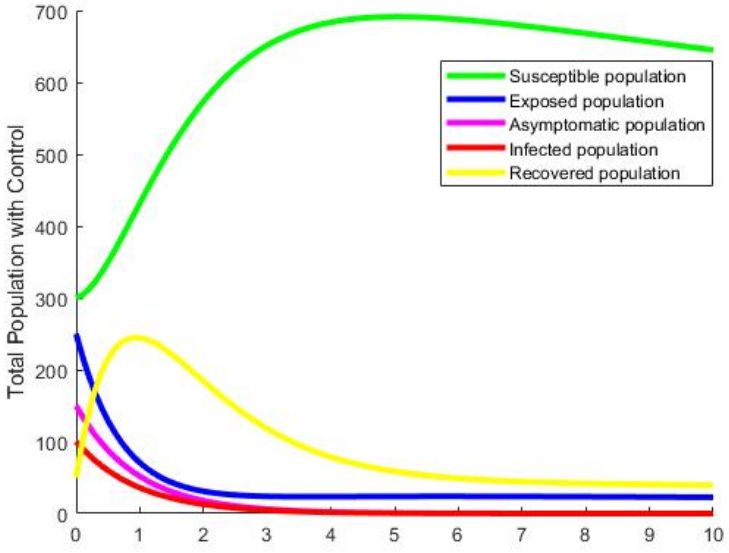

Figure 6.4: Illustrates the effets of the presence of optimal control on the total population.

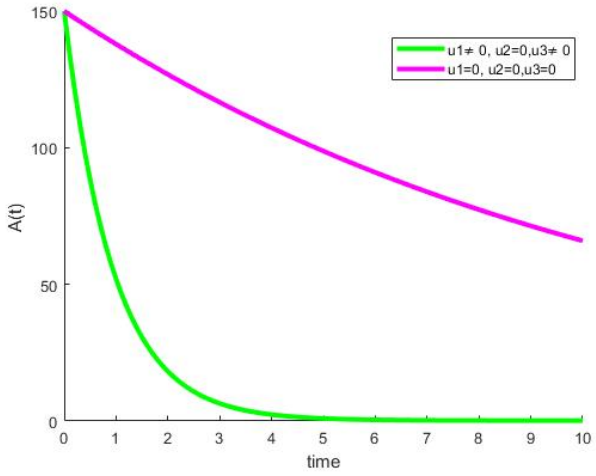

Figure 6.5: Illustrate the impact of vaccination and treatment on asymptomatic population .

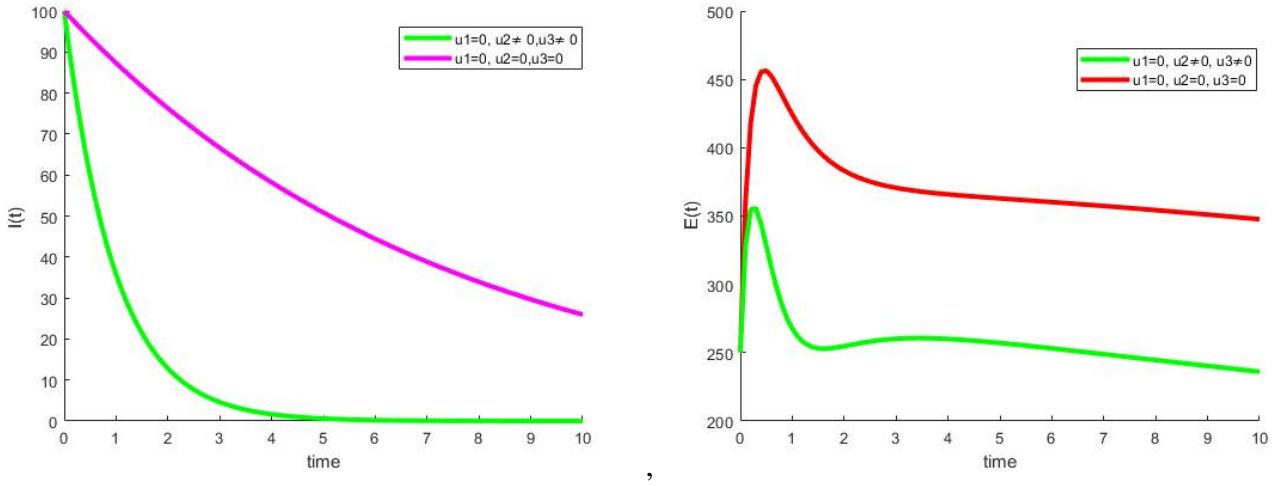

Figure 6.6: Illustrate the impact of screening and treatment on asymptomatic and exposed population respectively.

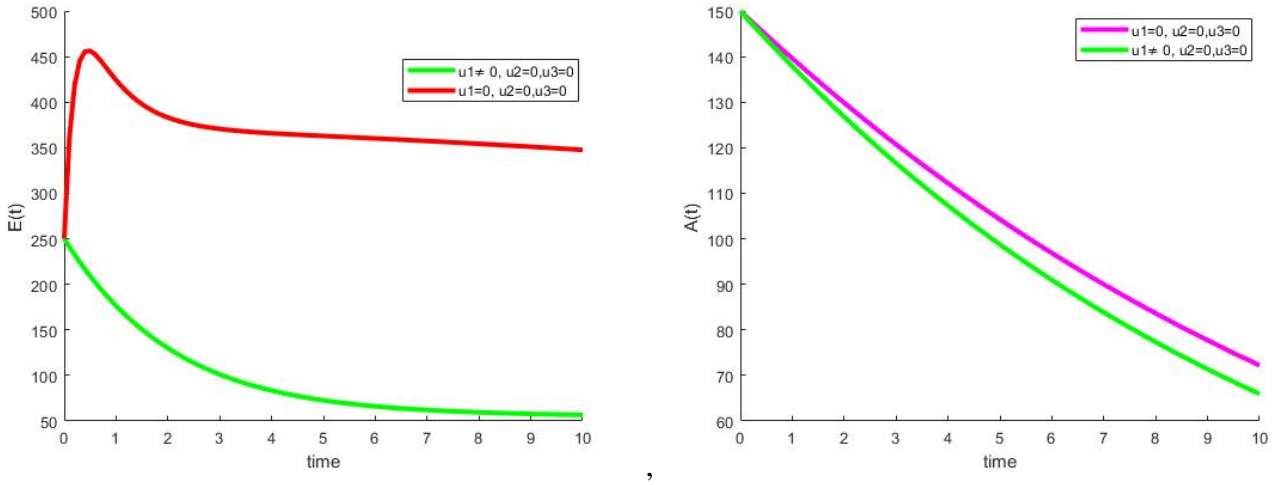

Figure 6.7: Illustrate the impact of vaccination on asymptomatic and exposed population.

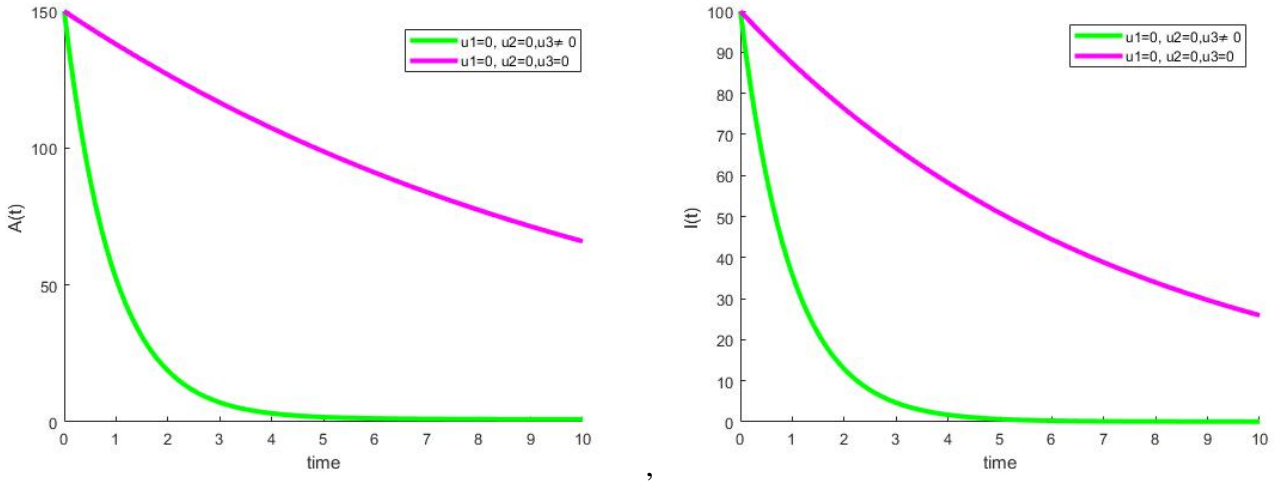

Figure 6.8: Illustrate the impact of treatment on asymptomatic and infected population respectively.

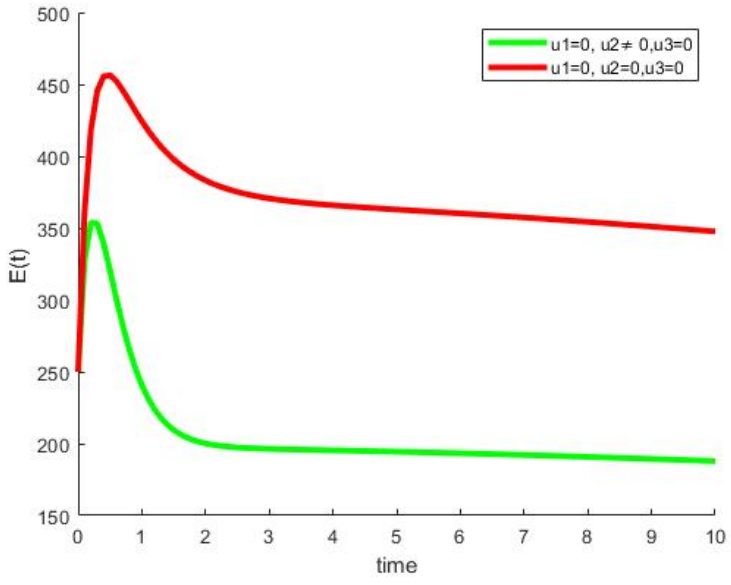

Figure 6.9: Illustrate the impact of screening on exposed population.

(i) Control with vaccination only

Vaccination minimizes the rate of joining of susceptible individuals into exposed as well as infectious compartments. We simulate the model by vaccination intervention only. From figure 6.7, we see that the decrease of exposed and infectious population due to the implementation of vaccination. This implies that optimized vaccination reduces the burden of HPV infection.

(ii) Control with screening only

Screening helps exposed population to move into the infectious classes and start to get treatment. Susceptible start to be infected and joins exposed class. If it is not screened it spread the disease. As a result from Figure 6.9 we see screening only might not be sufficient to eradicate the burden of HPV infection.

(iii) Control with treatment only

Figure 6.8, shows the decrease of infectious population due to the appropriately increasing of the treatment of HPV at early stage of development.

(v) Control with screening and treatment

We used screening and treatment controls as intervention. From Figures 6.6 we observe that optimal control of the combination of screening and treatment helps to bring down exposed as well as the infectious population which helps to control the disease in the population.

(vi) Control with vaccination and treatment

We used vaccination and treatment as intervention strategy, and Figure 6.5, show that, the number of exposed and also infectious goes down in the specified time. Therefore, this strategies is effective in controlinng the disease from the population in the specified time.

(vii) Control with vaccination, screening and treatment

We implement all the three controls strategies that helps to minimize the exposed , asymptomatic and infected population. From Figure 6.4, we observe that the number of the exposed and infectious populations decrease at the specified time due to the intervention strategies. Therefore, applying this strategy helps to control HPV infection in specified period of time in the population.

In general from this we have seen that Figure6.1, 6.2, 6.3, 6.4, 6.6, 6.7, 6.8, 6.9, shows that the impact of control on susceptible, exposed, asymptomatic and infected population respectively. It show that the density of susceptible population is increasing in the presence of the optimal control while the population of exposed, asymptomatic and infected population are damped down when control is applied. Thus, as expected the number of susceptible populatin $S(t)$ is increasing in the presence of control and at the same time the number of exposed $E(t)$, asymptomatic $A(t)$ and infected $I(t)$ populations are decreasing in the presence of control and increasing in the absence of control.

Chapter 7

Result and Discussion

7.1 Result and Discussion

In this thesis work, we have considered a special disease, HPV infection. We have developed a five-compartmental epidemic model, namely susceptible, exposed, asymptomatic, infective and recovered populations and investigated the dynamical behavior of this model. The model analysis showed that there exists a domain where the model is epidemiologically and mathematically well-posed. We have discussed about the invariant region in which the model solution is bounded. The existence and uniqueness of the solution of the model equation is shown by using Derrick and Groosman theorem[1] and positivity of the solution of the model is shown by a contradiction. With the next generation matrix method, we have found

$$R_0 = \frac{\beta\eta(p(\mu+\gamma+\zeta)+q(\alpha+\mu+\zeta)(1-p))}{(\eta+\mu+\varphi)(\mu+\gamma+\zeta)(\alpha+\mu+\zeta)}$$

as basic reproduction number of the system, which helps us to determine the dynamical behavior of the system. We have established two distinct equilibriums for the model with both local and global stability on the disease-free and endemic equilibrium points. The system (4.1) is locally asymptotically stable at the disease free equilibrium point E_0 when $R_0 < 1$. When $R_0 > 1$, the endemic equilibrium E_1 exists and the system becomes unstable at E_0 and locally asymptotically stable at E_1 under some conditions.

The main focus of this thesis work is to setup an optimal control problem relative to the epidemic model so as to minimize the exposed, asymptomatic and infective populations as well as to minimize the cost of control. We have considered three kinds of controls as the three controls reduce the transmission dynamic of HPV infection. The control functions u_1 (first vaccination control), u_2 (second screening control) and u_3 (the third treatment con-

trol) are designed in such away that they minimize the objective functional (cost function) as given in (5.2). It is observed that the optimal control is much more effective for reducing the number of exposed, asymptomatic and infective individuals which implies that using vaccination and increasing treatment can control the spread of HPV successfully. It can also be noticed that the prevention (vaccination) of susceptible population are very important before the beginning of the outbreak to control the spread of HPV and after the outbreak of HPV when susceptible individuals are exposed to HPV we control by screening individual and treat it.

Our model is not a case study. So it is difficult to choose parameter values from quantitative estimation. We have used hypothetical sets of parameter values to verify our analytical results. Our analysis and simulations using these parameter values indicate that the optimal control is efficient to reduce the spread of the disease and satisfies our analytical results. The important mathematical findings for the dynamical behavior of the HPV epidemic model are also numerically verified using a software MATLAB $R2015b$ with $ode45$ solver. Using different combinations of the controls, such as one control only at a time, two controls at a time and also all controls at a time, we analyse and compare numerical results from simulations. The simulation result illustrated that applying all the intervention strategy can successfully reduces the transmission dynamic of HPV disease from the population.

Chapter 8

Conclussion and Recommendation

8.1 Conclussion

In this thesis work, we develop mathematical model which describes the transmission dynamic of HPV with optimal control using a system of nonlinear ordinary differential equations. We performed the qualitative analysis of the model. Both local and global stability analysis of the equilibrium points of the model equations have been done using Jacobian matrix and Lyapunov functions respectively. Sensitivity analysis of the model have been studied and determine a parameter which plays greater role in the transmission dynamics of HPV. We have used three control vaccination (u_1), screening (u_2) and treatment (u_3) such that vaccination to susceptible populations, screening to exposed population and treatment to asymptomatic and infected populations to reduce the spread of HPV infection and using different combinations of the controls, such as one control only at a time, two controls at a time and also all the three controls at a time, we analyse and compare numerical results from simulations.

The optimal control have been derived by using the Pontryagin's maximum principle (PMP). Our model formulation is based on the effects of HPV infection in a population. As with many models, the mathematical model presented in this thesis should be treated with circumspection due to the assumptions made and the difficulty in the estimation of the model parameters. Parameters are dependent on the environmental conditions, so they are rarely constant. But for the simplification of our model we have assumed that these parameters are constant. There may be a time lag as a susceptible individual may take some time to be infected and also an infected individual may take some time to be infectious and symptomatic and again there may be a time lag to be recovered from the disease. Therefore, as a part of the future work, the model considered here can be refined to incorporate time delays in the system to make it more realistic.

8.2 Recommendation

The mathematical models on epidemic diseases are rather simple, but nevertheless they give insight into some of the consequences of public health policies. Controlling the spread of an epidemic disease is now a challenging and important issue to study. So, to predict and identify the cost-effective strategies to control the spread of HPV and minimize the cost of the control programme are the primary goals of health administrators, policy-makers and researchers. Since eradication of HPV infection remains a challenge especially in developing countries, but from results of this study we recommend that, the government should give a vaccination for susceptible before the out breaking of the disease and introduce education programmers on the importance of voluntary and routinely screening on HPV infection of exposed individual and give treatment for those who are already infected and infectious. Also, there is need to increase the number of hospitals to deal with HPV infection because HPV infection in long run results into different types of human cancers which pose serious health problem.

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Appendices

MATLAB CODES

1. SEAIR Model Without Control

function y = odeRungekutta order4(t,x1,x2,x3,x4,x5)

N=20356342; a=2; b=0.8; c=5; d=0.02; e=0.0024; f=0.4; p=0.067; q=1.002; g=0.054; h=0.001; s=0.016; R0=0.0052;

test = -1; deltaError = 0.0001; M = 100; t=linspace(0,10,M+1); T=10; h=T/M; h2=h/2; h6=h/6; x1=zeros(1,M+1); x2=zeros(1,M+1); x3=zeros(1,M+1); x4=zeros(1,M+1); x5=zeros(1,M+1);

x1(1)=300; x2(1)=250; x3(1)=150; x4(1)=100; x5(1)=50;

while(test ¡ 0) oldx1=x1; oldx2=x2; oldx3=x3; oldx4=x4; oldx5=x5; for i = 1:M k11=a+b*x5(i)-c*x1(i)-d*x1(i); k12=c*x1(i)-d*x2(i)-e*x2(i)-f*x2(i); k13=(1-p)*e*x2(i)-d*x3(i)-g*x3(i)-h*x3(i); k14=p*e*x2(i)-d*x4(i)-s*x4(i)-h*x4(i); k15=s*x4(i)+g*x3(i)+f*x2(i)-b*x5(i)-d*x5(i);

k21=a+b*(x5(i)+h2*k11)-c*(x1(i)+h2*k11)-d*(x1(i)+h2*k11); k22=c*(x1(i)+h2*k11)-d*(x2(i)+h2*k12)-e*(x2(i)+h2*k12)-f*(x2(i)+h2*k12); k23=(1-p)*e*(x2(i)+h2*k12)-d*(x3(i)+h2*k13)-g*(x3(i)+h2*k13); k24=p*e*(x2(i)+h2*k12)-d*(x4(i)+h2*k14)-s*(x4(i)+h2*k14)-h*(x4(i)+h2*k14); k25=s*(x4(i)+h2*k14)+g*(x3(i)+h2*k13)+f*(x2(i)+h2*k12)-b*(x5(i)+h2*k15)-d*(x5(i)+h2*k15);

k31=a+b*(x5(i)+h2*k25)-c*(x1(i)+h2*k21)-d*(x1(i)+h2*k21); k32=c*(x1(i)+h2*k21)-d*(x2(i)+h2*k22)-e*(x2(i)+h2*k22)-f*(x2(i)+h2*k22); k33=(1-p)*e*(x2(i)+h2*k22)-d*(x3(i)+h2*k23)-g*(x3(i)+h2*k23); k34=p*e*(x2(i)+h2*k22)-d*(x4(i)+h2*k24)-s*(x4(i)+h2*k24)-h*(x4(i)+h2*k24); k35=s*(x4(i)+h2*k24)+g*(x3(i)+h2*k23)+f*(x2(i)+h2*k22)-b*(x5(i)+h2*k25)-d*(x5(i)+h2*k25);

k41=a+b*(x5(i)+h2*k35)-c*(x1(i)+h2*k31)-d*(x1(i)+h2*k31); k42=c*(x1(i)+h2*k31)-d*(x2(i)+h2*k32)-e*(x2(i)+h2*k32)-f*(x2(i)+h2*k32); k43=(1-p)*e*(x2(i)+h2*k32)-d*(x3(i)+h2*k33)-g*(x3(i)+h2*k33); k44=p*e*(x2(i)+h2*k32)-d*(x4(i)+h2*k34)-s*(x4(i)+h2*k34)-h*(x4(i)+h2*k34); k45=s*(x4(i)+h2*k34)+g*(x3(i)+h2*k33)+f*(x2(i)+h2*k32)-b*(x5(i)+h2*k35)-d*(x5(i)+h2*k35);

x1(i+1) = x1(i) + h6*(k11 + 2*k21 + 2*k31 + k41); x2(i+1) = x2(i) + h6*(k12 + 2*k22 + 2*k32 + k42); x3(i+1) = x3(i) + h6*(k13 + 2*k23 + 2*k33 + k43); x4(i+1) = x4(i) + h6*(k14 + 2*k24 + 2*k34 + k44); x5(i+1) = x5(i) + h6*(k15 + 2*k25 + 2*k35 + k45); end

temp1 = deltaError*sum(abs(x1)) - sum(abs(oldx1 - x1)); temp2 = deltaError*sum(abs(x2)) - sum(abs(oldx2 - x2)); temp3 = deltaError*sum(abs(x3)) - sum(abs(oldx3 - x3)); temp4 = deltaError*sum(abs(x4)) - sum(abs(oldx4 - x4)); temp5 = deltaError*sum(abs(x5)) - sum(abs(oldx5 - x5));

test= min(temp1, min(temp2,min(temp3,min(temp4,min(temp5)))));

end y(1,:) = t; y(2,:) = x1; y(3,:) = x2; y(4,:) = x3; y(5,:) = x4; y(6,:) = x5; hold on plot(t,y(2,:),'b',t,y(3,:),'g',t,y(4,:),'r',t,y(5,:),'k',t,y(6,:),'m','linewidth',4)

plot(t,y(2,:),'r','linewidth',3) plot(t,y(3,:),'b','linewidth',3) plot(t,y(4,:),'g','linewidth',3) plot(t,y(5,:),'magenta','linewidth',3) plot(t,y(6,:),'y','linewidth',3)

plot(t,y(5,:),'r','linewidth',2) plot(t,y(6,:),'b','linewidth',2) plot(t,y(2,:),'g–',t,y(3,:),'y',t,y(4,:),'r–
',t,y(5,:),'b',t,y(6,:),'m','linewidth',3) plot(t,y(2,:),'g',t,y(3,:),'r','linewidth',3) plot(t,y(3,:),'y',t,y(4,:),'r','lin
plot(t,y(4,:),'r',t,y(5,:),'g',t, y(6,:),'y','linewidth',3) plot(t,y(4,:),'black','linewidth',3) plot(t,y(6,:),'y','linewi
xlabel('time') ylabel('Exposed Population ') legend('Susceptible population','Exposed pop-
ulation','Asymptomatic population','Infected population','Recovered population') hold on

2. SEAIR Model With Control

function y =Tem2(t,A1,A2,A3,M1,M2,M3,x1,x2,x3,x4,x5)

N=1000; a=2; b=0.8; c=5; d=0.02; e=0.0024; f=0.4; p=0.067; q=1.002; g=0.054; n=0.001;
s=0.016; R0=0.0052; test=-1; delta=0.0001; M=100; A1=1; A2=1; A3=0; B1=0.5; B2=10;
B3=2; r1=0; r2=0.99; t=linspace(0,10,M+1); T=10; h=T/M; h2=h/2; h6=h/6; u1=zeros(1,M+1);
u2=zeros(1,M+1); u3=zeros(1,M+1); x1=zeros(1,M+1); x2=zeros(1,M+1); x3=zeros(1,M+1);
x4=zeros(1,M+1); x5=zeros(1,M+1);

lambda1=zeros(1,M+1); lambda2=zeros(1,M+1); lambda3=zeros(1,M+1); lambda4=zeros(1,M+1);
lambda5=zeros(1,M+1);

x1(1)=300; x2(1)=250; x3(1)=150; x4(1)=100; x5(1)=50;

while(test ¡ 0) oldu1=u1; oldu2=u2; oldu3=u3; oldx1=x1; oldx2=x2; oldx3=x3; oldx4=x4;
oldx5=x5; oldlambda1=lambda1; oldlambda2=lambda2; oldlambda3=lambda3; oldlambda4=lambda4;
oldlambda5=lambda5;

for i=1:M First Runge-Kutta parameter k11=a+b*x5(i)-(1-u1(i))*c*x1(i)-d*x1(i); k12=(1-
u1(i))*c*x1(i)-(1-u2(i))*e*x2(i)-(u2(i)+f)*x2(i)-d*x2(i); k13=(1-u2(i))*(1-p)*e*x2(i)-(u3(i)+g)*x3(i)-
(d+n)*x3(i); k14=(1-u2(i))*p*e*x2(i)-(u3(i)+s)*x4(i)-(d+n)*x4(i); k15=(u3(i)+s)*x4(i)+(u3(i)+g)*x3(i)+(u
(b+d)*x5(i);

k21=a+b*(x5(i)+h2*k15)-(1-0.5*(u1(i)+u1(i+1)))*c*(x1(i)+h2*k11)-d*(x1(i)+h2*k11);
k22=(1-0.5*(u1(i)+u1(i+1)))*c*(x1(i)+h2*k11)-(1-0.5*(u2(i)+u2(i+1))*e*(x2(i)+h2*k12))-
(0.5*(u2(i)+u2(i+1))+f)*(x2(i)+h2*k12)-d*(x2(i)+h2*k12); k23=(1-0.5*(u2(i)+u2(i+1)))*(1-
p)*e*(x2(i)+h2*k12)-(0.5*(u3(i)+u3(i+1))+g)*(x3(i)+h2*k13)-(d+n)*(x3(i)+h2*k13); k24=(1-
0.5*(u2(i)+u2(i+1)))*p*e*(x2(i)+h2*k12)-(0.5*(u3(i)+u3(i+1))+s)*(x4(i)+h2*k14)-(d+n)*(x4(i)+h2*k14)
k25=(0.5*(u3(i)+u3(i+1))+s)*(x4(i)+h2*k14)+(0.5*(u3(i)+u3(i+1))+g)*(x3(i)+h2*k13)+(0.5*(u2(i)+u2(i+
(b+d)*(x5(i)+h2*k15);

k31=a+b*(x5(i)+h2*k25)-(1-0.5*(u1(i)+u1(i+1)))*c*(x1(i)+h2*k21)-d*(x1(i)+h2*k21);
k32=(1-0.5*(u1(i)+u1(i+1)))*c*(x1(i)+h2*k21)-(1-0.5*(u2(i)+u2(i+1))*e*(x2(i)+h2*k22))-
(0.5*(u2(i)+u2(i+1))+f)*(x2(i)+h2*k22)-d*(x2(i)+h2*k22); k33=(1-0.5*(u2(i)+u2(i+1)))*(1-
p)*e*(x2(i)+h2*k22)-(0.5*(u3(i)+u3(i+1))+g)*(x3(i)+h2*k23)-(d+n)*(x3(i)+h2*k23); k34=(1-
0.5*(u2(i)+u2(i+1)))*p*e*(x2(i)+h2*k22)-(0.5*(u3(i)+u3(i+1))+s)*(x4(i)+h2*k24)-(d+n)*(x4(i)+h2*k24)
k35=(0.5*(u3(i)+u3(i+1))+s)*(x4(i)+h2*k24)+(0.5*(u3(i)+u3(i+1))+g)*(x3(i)+h2*k23)+(0.5*(u2(i)+u2(i+
(b+d)*(x5(i)+h2*k25);

k41=a+b*(x5(i)+h*k35)-(1-0.5*(u1(i)+u1(i+1)))*c*(x1(i)+h*k31)-d*(x1(i)+h*k31); k42=(1-0.5*(u1(i)+u1(i+1)))*c*(x1(i)+h*k31)-(1-0.5*(u2(i)+u2(i+1))*e*(x2(i)+h*k32))-(0.5*(u2(i)+u2(i+1))+f)*(d*(x2(i)+h*k32); k43=(1-0.5*(u2(i)+u2(i+1)))*(1-p)*e*(x2(i)+h*k32)-(0.5*(u3(i)+u3(i+1))+g)*(x3(i)+h*(d+n)*(x3(i)+h*k33); k44=(1-0.5*(u2(i)+u2(i+1)))*p*e*(x2(i)+h*k32)-(0.5*(u3(i)+u3(i+1))+s)*(x4(i)+h*(d+n)*(x4(i)+h*k34); k45=(0.5*(u3(i)+u3(i+1))+s)*(x4(i)+h*k34)+(0.5*(u3(i)+u3(i+1))+g)*(x3(i)+h*k33(b+d)*(x5(i)+h*k35);

x1(i+1)=x1(i) + h6*(k11 + 2*k21 + 2*k31 + k41); x2(i+1)=x2(i) + h6*(k12 + 2*k22 + 2*k32 + k42); x3(i+1)=x3(i) + h6*(k13 + 2*k23 + 2*k33 + k43); x4(i+1)=x4(i) + h6*(k14 + 2*k24 + 2*k34 + k44); x5(i+1)=x5(i) + h6*(k15 + 2*k25 + 2*k35 + k45); end

for i=1:M j=M+2-i;

k11=c.*(1-u1(i)).*(lambda1(j)-lambda2(j))+d.*lambda1(j); k12=-A1+((1-u2(i).*e)+u2(i)+f+d).*lambda((1-u2(i)).*(1-p).*e)*lambda3(j)-((1-u2(i)).*p.*e).*lambda4(j)-(u2(j)+f).*lambda5(j); k13=-A2-(u3(i)+g).*(lambda3(j)-lambda5(j))+(d+n).*lambda3(j); k14=-A3-(u3(i)+s).*(lambda4(j)-lambda5(j))+(d+n).*lambda4(j); k15=b.*(lambda5(j)-lambda1(j))+d.*lambda5(j);

k21=c.*(1-0.5*(u1(i)+u1(i+1))).*((lambda1(j)-h2*k11)-(lambda2(j)-h2.*k12))+d.*(lambda1(j)-h2.*k11); k22=-A1+((1-0.5*(u2(i)+u2(i+1))).*e+0.5*(u2(i)+u2(i+1))+f+d).*(lambda2(j)-h2*k12)-(1-0.5*(u2(i)+u2(i+1))).*(1-p).*e.*(lambda3(j)-h2.*k13)-(1-0.5*(u2(i)+u2(i+1))).*p.*e.*(lambda4(j)-h2.*k14)*(0.5*(u2(i)+u2(i+1))+f).*(lambda5(j)-h2.*k15); k23=-A2-(0.5*(u3(i)+u3(i+1))+g).*(lambda3(j)-h2.*k13-(lambda5(j)-h2*k15))+(d+n).*(lambda3(j)-h2.*k13); k24=-A3-(0.5*(u3(i)+u3(i+1))+s).*(lambda4h2.*k14-(lambda5(j)-h2.*k15))+(d+n).*(lambda4(j)-h2.*k14); k25=b.*(lambda5(j)-h2.*k15-lambda1(j)-h2.*k11)+d.*(lambda5(j)-h2*k15);

k31=c.*(1-0.5*(u1(i)+u1(i+1))).*((lambda1(j)-h2.*k21)-(lambda2(j)-h2.*k22))+d.*(lambda1(j)-h2.*k21); k32=-A1+((1-0.5*(u2(i)+u2(i+1))).*e+0.5*(u2(i)+u2(i+1))+f+d).*(lambda2(j)-h2*k22)-(1-0.5*(u2(i)+u2(i+1))).*(1-p).*e.*(lambda3(j)-h2.*k23)-(1-0.5*(u2(i)+u2(i+1))).*p.*e.*(lambda4(j)-h2.*k24).*(0.5*(u2(i)+u2(i+1))+f).*(lambda5(j)-h2.*k25); k33=-A2-(0.5*(u3(i)+u3(i+1))+g).*(lambda3(jh2.*k23-(lambda5(j)-h2.*k25))+(d+n).*(lambda3(j)-h2.*k23); k34=-A3-(0.5*(u3(i)+u3(i+1))+s).*(lambdah2.*k24-(lambda5(j)-h2.*k25))+(d+n).*(lambda4(j)-h2.*k24); k35=b.*(lambda5(j)-h2.*k25-lambda1(j)-h2.*k21)+d.*(lambda5(j)-h2.*k25);

k41=c.*(1-0.5*(u1(i)+u1(i+1))).*((lambda1(j)-h.*k31)-(lambda2(j)-h.*k32))+d.*(lambda1(j)-h.*k31); k42=-A1+((1-0.5*(u2(i)+u2(i+1))).*e+0.5*(u2(i)+u2(i+1))+f+d).*(lambda2(j)-h*k32)-(1-0.5*(u2(i)+u2(i+1))).*(1-p).*e.*(lambda3(j)-h.*k33)-(1-0.5*(u2(i)+u2(i+1))).*p.*e.*(lambda4(j)-h.*k34)*(0.5*(u2(i)+u2(i+1))+f).*(lambda5(j)-h.*k35); k43=-A2-(0.5*(u3(i)+u3(i+1))+g).*(lambda3(j)-h.*k33-(lambda5(j)-h.*k35))+(d+n).*(lambda3(j)-h.*k33); k44=-A3-(0.5*(u3(i)+u3(i+1))+s).*(lambda4(jh.*k34-(lambda5(j)-h.*k35))+(d+n).*(lambda4(j)-h.*k34); k45=b*(lambda5(j)-h*k35-lambda1(j)-h*k31)+d*(lambda5(j)-h*k35)

lambda1(j-1)=lambda1(j)-(h/6*(k11+2*k21+2*k31+k41)); lambda2(j-1)=lambda2(j)-(h/6*(k12+2*k22lambda3(j-1)=lambda3(j)-(h/6*(k13+2*k23+2*k33+k43)); lambda4(j-1)=lambda4(j)-(h/6*(k14+2*k24+2*

lambda5(j-1)=lambda5(j)-(h/6*(k15+2*k25+2*k35+k45)); end

for i=1:M u1=min(r2,max(r1,(c*x1(j-1)*(lambda2(j-1)-lambda1(j-1)))/B1)); u1=0.5*(u1+oldu1); u2=min(r2,max(r1,(p*e*lambda4(j-1)+(1-p)*e*lambda3(j-1)-(e-1)*lambda2(j-1)-lambda5(j-1))*x2(j-1)/B2)); u2=0.5*(u2+oldu2); u3=min(r2,max(r1,(lambda3(j-1)-lambda5(j-1))*x3(j-1)+(lambda4(j-1)-lambda5(j-1))*x4(j-1)/B3)); u3=0.5*(u3+oldu3);

end

temp1 = delta*sum(abs(x1)) - sum(abs(oldx1 - x1)); temp2 = delta*sum(abs(x2)) - sum(abs(oldx2 - x2)); temp3 = delta*sum(abs(x3)) - sum(abs(oldx3 - x3)); temp4 = delta*sum(abs(x4)) - sum(abs(oldx4 - x4)); temp5 = delta*sum(abs(x5)) - sum(abs(oldx5 - x5)); temp6 = delta*sum(abs(u1))-sum(abs(oldu1-u1)); temp7=delta*sum(abs(u2))-sum(abs(oldu2-u2)); temp8=delta*sum(abs(u3))-sum(abs(oldu3-u3)); temp9=delta*sum(abs(lambda1))-sum(abs(oldlambda1-lambda1)); temp10=delta*sum(abs(oldlambda2-lambda2)); temp11=delta*sum(abs(lambda3))-sum(abs(oldlambda3-lambda3)); temp12=delta*sum(abs(lambda4))-sum(abs(oldlambda4-lambda4)); temp13=delta*sum(abs(lambda5))-sum(abs(oldlambda5-lambda5));

test= min(temp1, min(temp2,min(temp3,min(temp4,min(temp5,min(temp6,min(temp7, min(temp8,min(temp9,min(temp10,min(temp11,min(temp12,min(temp13)))))))))))));

end y(1,:) = t; y(2,:) = u1; y(3,:) = u2; y(4,:) = u3; y(5,:) = x1; y(6,:) = x2; y(7,:) = x3; y(8,:) = x4; y(9,:) = x5; y(10,:) = lambda1; y(11,:) = lambda2; y(12,:) = lambda3; y(13,:) = lambda4; y(14,:) = lambda5; hold on plot(t,y(2,:),'b',t,y(3,:),'g',t,y(4,:),'r',t,y(5,:),'k',t,y(6,:),'m','linewidth' plot(t,y(2,:),'r','linewidth',2)

plot(t,y(5,:),'r','linewidth',3) plot(t,y(6,:),'b','linewidth',3) plot(t,y(7,:),'magenta','linewidth',3) plot(t,y(8,:),'g','linewidth',3) plot(t,y(9,:),'y','linewidth',3) plot(t,y(2,:),'g–',t,y(3,:),'y',t,y(4,:),'r–','t,y(5,:),'b',t,y(6,:),'m','linewidth',3) plot(t,y(2,:),'g',t,y(3,:),'r','linewidth',3) plot(t,y(3,:),'y',t,y(4,:),'r','lin plot(t,y(4,:),'r',t,y(5,:),'g',t, y(6,:),'y','linewidth',3) plot(t,y(4,:),'g','linewidth',3) plot(t,y(6,:),'y','linewidth' xlabel('time') ylabel('E(t)') legend('u1=0,u2=0,u=0','u1=0,u2=0,u3=0')

hold on