KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY, KUMASI

THE EPIDEMIOLOGY OF HUMAN PAPILLOMA VIRUS INFECTION AND VACCINATION, ITS IMPACT ON CERVICAL CANCER IN GHANA

By

Twumasi, Robert Afrifa

(B.ED. Mathematics)

A THESIS SUBMITTED TO THE DEPARTMENT OF MATHEMATICS, KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF

M.PHIL APPLIED MATHEMATICS

May 10, 2014

Declaration

I hereby declare that this submission is my own work towards the award of the M. Phil degree and that, to the best of my knowledge, it contains no material previously published by another person nor material which had been accepted for the award of any other degree of the university, except where due acknowledgement had been made in the text.

Twumasi, Robert Afrifa	.....	.....
Student	Signature	Date

Certified by:

Rev. Dr. William Obeng Denteh	.....	.....
Supervisor	Signature	Date

Certified by:

Prof. S.k Amponsah	.....	.....
Head of Department	Signature	Date

Dedication

This work is dedicated to my late father Alexander Amankwah Afrifa, who worked assiduously to make me what I am now.

Abstract

This thesis is devoted to assess the impact of bivalent Human Papillomavirus (HPV) vaccine and Pap test on prevalence of carcinogenic HPV 16/18 types in Ghanaian females. For this purpose, a non-linear dynamic SIR model of homogeneous transmission for HPV 16/18 type's infection is developed, which accounts for immunity due to vaccination in particular. The recovery class was R partitioned into two compartments, temporal recovery R_T and permanent recovery R_p . We propose ODE equations to study HPV infection in the general female population. Since HPV infection and its vaccination is age dependent, we propose PDE equations to study their behavior in two age groups, adolescent $(9-25)$ and adult 25 and above. The vaccinated reproduction number R_0 for general female population was derived using the approach described by Diekmann (2010) called the Next Generation Operator approach. We used a theory by Kermsck and McKendrick (1927) to derived basic reproductive number R_0 for the adolescent and adult female population. The two models proposed were analyzed using quantitative method, with regard to steady-state stability and sensitivity analysis. Precisely, the stability of the models is investigated depending on the value for R_0 for the disease free steady-state and Routh-Hurwitz criterion employed to study the stability of the endemic steady-state. Prevalence data are used to fit a numerical HPV model, so as to assess infection rates.

We also support our theoretical analysis with numerical simulations. This provides a framework for future research and public-health policy to determine the dependence of HPV vaccination programs on age, as well as how the vaccine and Pap test can reduce the number of infections and deaths due to cervical cancer.

Acknowledgements

First and foremost, I would like to express my profound gratitude to God Almighty for providing me with good health, protection and knowledge throughout the study of this programme. I am also indebted to my supervisor Rev. Dr. William Obeng Denteh, and my mentor Mr. Barnes for their constructive contributions to this thesis. I also owe a debt of gratitude and appreciation to the lecturers of the department of mathematics, knust, especially Dr. Edward Prempeh and Dr. F.T Oduro, for their encouragement and invaluable contribution towards the success of this study I am also grateful to my course mates Sammy, Sir Wallas and Yaro. Special thanks as well goes to my lovely sisters Awo and Bene, my mum Madam Deborah Boadu and all those who helped me in diverse ways throughout my education. To God be the glory.

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Chapter 1

Introduction

1.1 Introduction

Viruses are very small organisms - most cannot even be seen with a regular microscope. They cannot reproduce on their own. They must enter a living cell, which becomes the host cell, and hijack the cell's machinery to make more viruses. Viruses can enter the body through the mucous membranes, such as the nose, mouth, the lining of the eyes, or the genitals. They can also enter through the skin and any breaks in the skin. Once inside, they find their specific type of host cell to infect. For example, cold and flu viruses find and invade cells that line the respiratory tract (nose, sinuses, breathing tubes, and lungs). HPVs are called papilloma viruses because some of the HPV types cause warts or papilloma's, which are non-cancerous tumors. The papilloma viruses are attracted to and are able to live only in squamous epithelial cells in the body. Of the more than 150 known strains, about 3 out of 4 (75 percent) HPV types cause warts on skin, such as that of the arms, chest, hands, and feet. These are the common warts. The other 25 percent of the HPV types are mucosal types of HPV. "Mucosal" refers to the body's mucous membranes, or the moist surface layers that line organs and cavities of the body that open to the outside. For example, the vagina and anus have this moist mucosal layer. The mucosal HPV types are also called the genital (or anogenital) type HPVs because they often affect the anal and genital area. The mucosal HPVs prefer the moist squamous cells found in this area.

Genital Human papillomavirus (HPV) is one of the most common sexually transmitted infections and has been shown in epidemiological and molecular studies

to be a necessary etiologic agent for cervical cancer. Most people who become infected with HPV do not even know that they have it. Human papilloma viruses (HPVs) are a group of more than 150 related viruses. Each HPV virus in the group is given a number, which is called an HPV type. The HPV types 16-18 are the most common high-risk type, accounting for more than half (56 percent) of all cervical cancers. Persistent infection with high-risk types of HPV is the most important risk factor for cervical cancer. Other risk factors for HPV and Cervical cancer include having sexual partners, having a weakened immune system and not getting a regular Pap test. The long premalignant course of HPV infection means that screening programs can detect and treat early disease and prevent progression to cervical cancer. At the advanced stage of HPV infection normal cells in the body turns abnormal and leads to cancer. Infections with carcinogenic HPV at the cervix cause cervical cancer in females. Women who have many sexual partners or who have sex with men who have had many other partners have a greater risk.

Mathematical modeling of a disease is a rapidly growing field reflecting interdisciplinary cooperation of mathematics and biology in solving complex real life problems. Mathematical models have become a viable approach to analyzing biological phenomenon and evaluating the impact of public health intervention strategies to suggest the optimal course of action in the ongoing fight against persistent and emerging infectious diseases.

1.1.1 Mode of Transmission

Human papilloma viruses is commonly transmitted through sexual means, although non-sexual modes of transmission of the infection that is through a handshake and kissing are also possible but very controversial since more research is required in that direction. Genital or sexual contact with one who is infected is the main cause of transmission in a healthy person. The virus is acquired two

to three weeks after coming into contact with an infected person. In most cases, sexual transmission of the virus is through vaginal or anal intercourse. Oral sex transmission of the virus is also very common. The virus is also transmitted through skin- to- skin contact. Touching someone or something infected by the virus and then touching one's genital without washing the hand is one of the methods of transmission. An infected mother can pass this infection to her baby in rare cases during delivery. This infection is manifested in children in the form of warts in the throat or voice box of the babies.

1.1.2 Signs and Symptoms of HPV infection

The early stages of HPV infection may be completely asymptomatic until it is quite advanced and hard to treat. Vaginal bleeding, contact bleeding, or rarely a vagina mass may indicate the presence of malignancy. Also, moderate pain during sexual intercourse and vaginal discharge are symptoms of HPV infection.

1.1.3 Prevention

Primary prevention of HPV infection begins with HPV vaccination of girls aged 9-25 years, before they become sexually active. After many years of testing, two HPV vaccines have been approved by the USA Food and Drugs Administration (FDA). They are Gardasil and Cervarix which reduce the risk of cancerous or precancerous changes of the cervix and perineum by about 93 percent. HPV vaccines are typically given to female age 9 to 25 as the vaccine is greatly effective if given before infection occurs. The vaccines have been shown to be effective for at least 4 to 20 years, and it is believed they will be effective for longer; however, the duration of effectiveness and whether a booster will be needed is unknown.

The vaccine is a course of three injections at 0, 2 and 6 months so there is a question about uptake. If an individual does not complete the course, they will need to start the course from the beginning again to be protected. The bivalent

HPV vaccine Cervarix has been licensed for use in Ghana. Condoms are thought to offer some protection against HPV infection. Evidence on whether condoms protect against HPV infection is mixed.

1.1.4 Treatment

Although there is currently no medical treatment for Human papilloma virus infections, the cellular changes that come from an HPV infection can be treated. For example, genital warts can be treated. Pre-cancerous cell changes caused by HPV can be detected by Pap tests and treated. Cervical, anal, and genital cancers can also be treated. Getting the HPV vaccine before being exposed to HPV will prevent High risked HPV 16-18 types that cause HPV infections. Limiting the number of sex partners and avoiding sex with people who have had many other sexual partners decreases a person's risk of exposure to HPV. Human papilloma virus infections are very common, these afore mentioned precautionary measures are no guarantee that a person will not get HPV. Still, these measures may help reduce the number of times a person is exposed to HPV.

High-risk HPV persistent infections will progress to cancer and when cervical cancer is diagnosed in the early stages, it can be easily treated; however treating advanced cervical.
cancer is very challenging. Treatment of precancerous and cancerous changes caused by the virus, reduce the viral load and consequently transmission.

1.2 Problem Statement

The Age - standardized mortality rate for cervical cancer in Ghana is more than three times the global cervical cancer mortality rate. Cervical cancer is the leading cause of cancer death among women in Ghana. The cervical cancer incidence and mortality rates in Ghana are among the highest in the world. These rates

have been rapidly increasing in contrast to the decreasing cervical cancer incidence and mortality rates in developed countries.

The World Health Organization (WHO) predicts that by the year 2025, 5000 new cases of cervical cancer and 3361 cervical cancer death will occur annually in Ghana. Despite these staggering statistics cervical cancer prevention is not commonly promoted in Ghana. Cervical cancer is highly preventable with good vaccination programs.

1.3 Objective of the study

The objectives of the study are;

- To propose an SIR model with two different recovery compartments, temporal recovery and permanent recovery.
- To propose an SIR's model with age - dependent.
- To study the stability of equilibrium states of the models.
- Perform sensitivity analysis on the model parameters.

1.4 Methodology

We modify a SIR compartmental model developed by Kernack-McKendrick (1927) to describe the epidemiology of HPV infection and its impact on cervical cancer in Ghana. Our new SIR models will be used in epidemiology to calculate the amount of susceptible, infected, temporally recovered and permanently recovered under the two equilibrium states: the disease - free equilibrium state and endemic equilibrium states in Ghana. The model equations will be solved using quantitative method and MatLab software. Sensitivity analysis shall be performed on the model equations to determine the effect of the parameter values on the spread of the HPV infection.

1.5 Justification

This thesis intends to contribute to the research information on Human papillomavirus infection that leads to cervical cancer disease in the country, so that it can help in further research work in this area. The thesis seeks to suggest whether or not the vaccination program measures and treatment option available to check the spread of Human papillomavirus infection and its treatment in the country is enough or more work is needed to be done in order to control the infection and reduce cervical cancer from becoming endemic. Such estimates can enable policy makers to evaluate different disease containments and medical response plans. Based on the above information, it is very important for health policy makers to have access to outbreak models in different scenarios to predict the speed of the infection under different circumstances.

1.6 Thesis organization

This thesis is organized into five main chapters. Chapter 1 presents the introduction of the thesis. This consists of the background of the study, the research problem statement, objectives of the research, justification and organization of the thesis. Chapter 2 is the literature review of related works, which looks at briefly work done by other researchers on the disease. Chapter 3 is the formulation of the mathematical models, the systems of ordinary differential equations (ODEs) and systems of partial differential equations (PDEs) and the approach for solving them. Chapter 4 contains analysis of the two models. Chapter 5 looks at Summary, Conclusions and Recommendation of the analyzed models.

Chapter 2

Introduction

2.1 Introduction

Harper and Paavonen (2008) have observed that a virus is a causal factor in the development of cervical cancer. Sexually transmitted strains of the human papillomavirus (HPV) are thought to affect about 80 percent of the sexually active female population at some point during their lives.

Adams et al., (2007) observed that of these, about 10-20 percent has a persistent infection (the definition of this differs greatly in the literature, but most sources put it as somewhere between 6 months and 2 or more years), and say an infection last 2 or more years. The likelihood of developing pre-cancerous lesions increases with long-term infection; for type HPV-16, there is a 40 percent chance of cervical intraepithelial neoplasia (CIN) after infection lasting 5 or more years.

Leggatt and Frazer (2007) explained that the connection between HPV and cervical cancer has been suspected since the 1970s, a discovery that was aided by the knowledge that papillomaviruses cause cancer in animals. Studies showed that HPV could be found in 99.7 percent of cervical cancer tumours, leading the International Agency for Research on Cancer (IARC) in 1995 to classify types HPV-16 and HPV-18 as carcinogenic.

Heather(1998), further studies led to HPV types -31, -33, -35, -45 also being classified as carcinogenic, but it is types -16 and -18 that are considered to be the most prevalent of the carcinogenic types throughout the world, causing about 70

percent of all cervical cancer.

Agosti and Goldie (2007), is of the view that because worldwide, cervical cancer is the second most common form of cancer, with 493,000 deaths attributed to it in 2002, it is important to investigate the disease.

Thomas et al., (2006) say that presently, 80 percent of deaths from HPV infection which leads to cervical cancer occur in developing countries, with the proportion expected to rise to 90 percent by the year 2020. It is one of the biggest causes of number of years of life lost.

Nicola Low et al., (2006) concluded that the current processes for prevention and cure of cervical cancer and HPV rely mainly on screening. In the United Kingdom, Pap smears are used to test for abnormalities in the cells at the cervix, as this could be an indication of pre-cancerous lesions. Women are advised to be tested at regular intervals, the intervals differing depending on age.

Thomas et al., (2006), this has been a successful policy - since the introduction of Pap smears 50 years ago, cases of cervical cancer have been reduced by approximately 50 percent. However, there are flaws in the system.

Sue (2006) believes screening does not always reveal the presence of HPV-DNA, and while there are tests that will do this more effectively, they are then less effective at identifying pre-cancerous cells.

Adams et al., (2007) observed that not all women will be screened; the rate of screening seems to be falling in the population as a whole, and some sectors of the community traditionally have a poor uptake rate. He lectured that two prophylactic vaccines have been developed that protect against some strains of

HPV, with a view to dramatically reducing the cases of cervical cancer. The vaccines have been produced by Merck and GlaxoSmithKline; the Merck vaccine protects against strains $-6, -11, -16, -18$, and the GlaxoSmithKline vaccine protects against strains $-16 and -18$.

Markman (2007) observed that these vaccines are widely welcomed, as in testing they have shown close to 100 percent efficacy against these strains of HPV. Hildesheim et al. (2003), studied Human papillomavirus (HPV) vaccination which was introduced into the routine immunization schedule in the United States in late 2006 for females aged 11 or 12 years, with catch - up vaccination recommended for those aged 13 - 26 years. They used statistical methods and observed that in 2010, 3 dose vaccine coverage was only 32 percent among 13 - 17 year olds. Reduction in the prevalence of HPV types targeted by the quadrivalent vaccine (HPV -6, -11, -16, and -18) will be one of the first measures of vaccine impact. They analyzed HPV prevalence data from the era 2007 - 2010) and the prevaccine era (2003-2006) that were collected during National Health and Nutrition Examination Surveys. HPV prevalence was determined by the Linear Array HPV Assay in cervical vaginal swab samples from females aged 14 - 59 years; 4150 provided samples in (2003-2006), and 4253 provided samples in 2007 - 2010. Their results shows that among females aged 14 - 19 years, the vaccine - type HPV prevalence (HPV-6, -11, -16, or -18) decreased from 11.5 percent (95 percent confidence interval [CI], 9.2 - 14.4) in 2003-2006 to 5.1 percent 95 percent CI, 3.8-6.6 in 2007-2010, a decline of 56 percent (95 percent CI, 38 - 69). Among other age groups, the prevalence did not differ significantly between the 2 time periods ($P > .05$). The vaccine effectiveness of at least 1 dose was 82 percent (95 percent CI, 53 - 93). They finally arrived at a conclusion that within 4 years of vaccine introduction, the vaccine - type HPV prevalence decreased among females aged 14 - 19 years despite low vaccine uptake. The estimated vaccine effectiveness was high.

Mark Jit et al. (2008), observed that by preventing strains -16 and -18, these vaccines could play a major part in reducing cervical cancer, but there are other factors to be considered. The cost of the vaccine is very high, and will almost certainly be prohibitive for some countries; for the UK, vaccine cost has been estimated (without administration costs) at approximately £ 60 per dose. Secondly, the vaccine is a course of three injections at 0, 2 and 6 months so there is a question about uptake. If an individual does not complete the course, they will need to start the course from the beginning again to be protected, which would be costly. However, the cost of screening and treatment (if necessary) is also expensive, as is the treatment of genital warts. From an uptake viewpoint, questions also need to be raised about how do we make sure the vaccination programs are dully followed to make sure girls receive their dose in full.
As evidence begins to emerge about a connection between HPV and other genital cancers, it may indicate that males should also be vaccinated. Another consideration is whether the vaccine could have a negative effect on the cervical cancer rates; as HPV strains -16 and -18 only cause about 70 percent of all cervical cancer, there is some concern that other carcinogenic strains will take their place. Another concern is that women will assume they are fully protected once they have been vaccinated and so no longer need smears, although it will still be crucial that women are screened.

Raphael et al., (2006) observed that the issues still to be addressed, which included duration of protection, the optimal age for vaccination, and how to implement the vaccine. These ideas provide a starting point for developing a model to address some of the pertinent questions surrounding the HPV vaccine.

Heather (1998) suggested that natural infection does not induce a strong antibody response and that the vaccine will need to induce a strong response for prophylaxis to occur, and a study done in Costa Rica found no evidence of pro-

tective immunity, and suggested that the immune response from natural infection may not be strong enough to provide immunity.

Other issues arise, for example the majority of HPV infections are asymptomatic, so people do not seek treatment, and therefore the true scale of the disease may never be known. The strains that can display symptoms - namely, strains such as -6 and -11 that cause genital warts are not considered being carcinogenic, so it is the more dangerous strains that may be undetected. However, even if detected, much uncertainty remains. For example, will the patient go on to develop cervical cancer? How long will it take for pre-cancerous lesions (which may or may not lead to cancer) to manifest? This has been measured at anything from a few months to several years. If lesions do develop, what is the likelihood that they will progress to the more serious pre-cancerous stages, or indeed, to cancer itself? These are currently all unknown quantities, and need to be taken into account when developing a model. Studies have been undertaken to try and determine more accurately the answers to these questions, but the results tend to vary wildly, leaving us without a clear picture.

Trottier and Franco (2006) pronounced it is not yet fully understood what causes an HPV infection to progress to cervical cancer. The length of time it takes for any lesions that develop to progress to cancer, if indeed they do at all, is very variable; they can take anything from a few months to several years. It is also thought the Human Leukocyte Antigens may play a part in a person's susceptibility to cancer. There are risk factors involved; a person's age and sexual history (number of lifetime partners, recent partners) are considered strong indicators of the likelihood of contracting cervical cancer. Burchell (2008), other factors that could increase the risk of developing cervical cancer are viral load, other sexually transmitted infections (STIs), circumcision (may help reduce transmissibility), and condom use.

However, the evidence is not always particularly strong, and at times is contra-

dictory. Issues that still need to be explored is the natural history of the virus, and the viral load pattern.

Baseman and Koutsky (2005) observed that it is also not clear what can cause an HPV infection to become persistent, or lead to cervical cancer, other than the HPV type and its variant. It is thought that the host's immune system probably plays a part. If reinfection does occur, it is not clear whether this has anything to do with developing into a persistent infection. While most women with HPV recover and do not develop cervical cancer, an individual is 13 times more likely to develop a high-grade squamous intraepithelial lesion (HSIL) from a persistent infection. From here, $\frac{1}{3} to \frac{2}{3}$ women with HSIL will go on to develop cervical cancer if the HSIL is not treated.

In the early 20th century, epidemiologists noted that cervical cancer behaves like a sexually transmitted disease. It was much more common in prostitutes than in housewives and virtually non-existent in religious sisters.

Murray (2002) have observed that mathematical modeling of biological situations has been done for centuries, with evidence from as early as the 11th and 12th centuries confirming that attempts were made to describe a biological situation in mathematical terms.

Anderson and May (1992) observed that from these early days, the use of mathematics in aiding our biological understanding has grown tremendously. One area in which mathematical modeling has proved very useful is that of epidemiology, modeling the spread of a disease through a population. It has been used to great effect in many situations and can be used in both a descriptive and predictive role. In particular, sexually transmitted infections (STIs) have generally been of modeling interest - they have some very specific characteristics that need to be considered, such as separation of genders, or contact structure.

Kermack - McKendrick (1927) has explained that an epidemic, which acts on a short temporal scale, may be described as a sudden outbreak of a disease that infects a substantial portion of the population in a region before it disappears. Epidemics usually leave many members untouched. Often these attacks recur with intervals of several years between outbreaks, possibly diminishing in severity as populations develop some immunity. Throughout history, epidemics have had major effects on the course of events. One of the early triumphs of mathematical epidemiology was the formulation of a simple model that predicted behavior very similar to this behavior, observed in countless epidemics.

Another important distinction is between epidemics and endemic situations. An epidemic acts on a short time scale and may be described as a sudden outbreak of a disease that infects a substantial portion of the population in a region before it disappears. Epidemics usually leave many members untouched. In an endemic situation, a disease becomes established in a population and remains for a long time.

Baseman and Koutsky (2005) have observed that prior to building a model, it is important to understand how the human papillomavirus works, and also how the vaccine works. One of the difficulties facing researchers is that very little is known about this virus. It is not clear for example whether the virus ever leaves the system once infected, or whether it enters a latent period. It is also not clear why some people and not others have a persistent infection, although it is suspected this is due in part to the strain of the virus and in part to the host's susceptibility to the disease. Another problem is that if a woman presents with an HPV infection at two or three consecutive screening sessions, it is very difficult to know whether it is the same infection each time or a different infection. However, as not all women with persistent HPV infections go on to develop cancer; other risk factors such as smoking and the number of full-term pregnancies are

thought to play a part. Also, is it not clear whether an individual can develop natural immunity to the virus once infected. The immune response to HPV is not completely understood.

Hughes et al., (2002) proposed two models:- one examines the transmission of HPV in a population, the development into cancer (this is an ODE model), and the effect of the vaccine; the other looks at the effect of reducing cervical intraepithelial neoplasia (CIN) and (cervical) cancer through the use of the vaccine, which is an ODE/PDE model. They employ the use of different sexual activity groups as a means of dividing the population, a concept that other models also use. Whether the vaccine reduces susceptibility, transmissibility of disease or mean duration of infectiousness is considered. The models assume an arbitrary age at which people enter the susceptible class, that is an arbitrary age at which they become sexually active. They used numerical method and found that if the vaccine protects against -16 and -18, other high-risk types will fill the gap and so cancers caused by them will increase. They assume a mean immunity of 10 years with a vaccine that is 75 percent effective. They concluded that vaccinating women is about 75 percent as effective as vaccinating men and women, but this again may need to be checked against what is now known about the vaccine.

Lee and Tameru (2012) developed a mathematical model of HPV for African American women (AAW) in the United States and give quantitative insight into current U.S. prevention and mitigations against cervical cancer. In their work they considered a compartmental mathematical model of the cycle of HPV that includes the choices individuals make once they become infected; treatment versus no treatment was developed. Using this mathematical model they evaluated the impact of human papillomavirus (HPV) on a given population and determined what could decrease the rate at which AAW become infected. All state equations in the model were approximated using the Runge-Kutta 4th order nu-

merical approximation method using MatLab software. They found that the basic reproductive number R_{0U} is directly proportional to the rate of infectivity of HPV and the contact rate in which a human infects another human with HPV. The R_{0U} was indirectly proportional to the recovery rate plus the mortality by natural causes and the disease. The second R_{0T} is also directly proportional to the rate of infectivity of HPV and contact rate in which humans infect another human with HPV and indirectly proportional to the recovery rate plus the mortality from HPV related cause and natural causes. Based on the data of AAW for the parameters; they found that R_{0U} and R_{oT} were 0.519798 and 0.070249 respectively. As both of these basic reproductive numbers are less than one, infection cannot therefore get started in a fully susceptible population, however, if mitigation is to be implemented effectively it should focus on the HPV untreated population as is greater than 0.5.

They concluded from their Mathematical models, that individual and population perspectives will help decision makers to evaluate different prevention and mitigation measures of HPV and deploy synergistically to improve cancer outcomes. Integrating the best available epidemiologic data, computer- based mathematical models used in a decision-analytic framework can identify those factors most likely to influence outcomes and can help in formulating decisions that need to be made amidst considerable lack of data and uncertainty.

Laureen Ribassin-Majed et al (2012) work is devoted to assess the impact of quadrivalent Human Papillomavirus (HPV) vaccine on prevalence of non-oncogenic HPV 6/11 types in French males and females. For this purpose, a non-linear dynamic model of heterosexual transmission for HPV 6/11 types infection was developed, which accounts for immunity due to vaccination in particular. The vaccinated reproduction number R_v was derived using the approach described by Diekmann (2010) called the Next Generation Operator approach. The model proposed was analysed, with regard to existence and uniqueness of the solution,

steady-state stability. Precisely, the stability of the model was investigated depending on the sign of number $R_V - 1$ is. Prevalence data were used to fit a numerical HPV model, so as to assess infection rates. Their approach suggests that 10 years after introducing vaccination, the prevalence of HPV 6/11 types in females will be halved and that in males will be reduced by one quarter, assuming a sustained vaccine coverage of 30 percent among females. Using the formula they derived for the vaccinated reproduction number, they show that the non-oncogenic HPV 6/11 types would be eradicated if vaccine coverage in females is kept above 12 percent.

Sally B. Rose et al., (2010) conducted a research to describe parents' preferences on where their daughter(s) receive the human papillomavirus (HPV) vaccine, at what age, and their information needs. They used statistical sampling method by distributing 3123 questionnaires to parents recruited from 14 schools in 2008, prior to the start of the school-based vaccination program. Outcome measures were that preferred age and place of vaccination and information needs of parents and their daughters. They performed tests for significance to determine whether parental preferences differed by ethnic group (Maori, Pacific, New Zealand European and, Other'). They obtain results which suggest that 25 percent response rate was achieved (769/3123). Receipt of the HPV vaccine in a clinic setting were preferred by 40 percent of parents; 25 percent preferred vaccination at school. Fifty percent preferred vaccination to occur at age 13 or older; 28 percent thought ages 10, 11 or 12 appropriate. One in three parents wanted more information and 65 percent said they would seek information from their family doctor before deciding on the vaccine for their daughter(s). After their work they suggested that a program delivered jointly in primary care and school settings, that are appropriately resourced for follow-up and information-sharing, would increase vaccine coverage. The rationale for vaccination at age 12 needs to be made clear to parents and evidence-based information needs to be delivered

appropriately to parents and girls.

Van Velde et al., (2001), in their paper, introduced an SIRS epidemic model with vertical transmission, where the death rate of the population is in density dependent, that is, dependent on the population size to study HPV vaccine effectiveness. They assumed that there exists an infection related death rate. The authors furthered show the existence of nonnegative solutions of the model, and also give a detailed stability analysis of disease free and positive fixed points was also discussed. With the numerical method they employed in their work they concluded that HPV vaccine should be given to women before they become sexually active to reduce HPV infection.

Many of the other models touch on slightly different aspect Kohli et al. (2007) use a Markov process model to assess the impact of vaccination, carrying it through to consider the effect on CIN and cervical cancer. Their conclusions suggest that 100 percent coverage of pre-teenage girls could lead to around a 75 percent drop in deaths from cervical cancer, but that the benefits of vaccination would decrease as the age of vaccination increased.

Goldie et al., (2003) use a computer-based simulation model to assess the effect of vaccination on the prevalence of HPV and pre-cancerous stages. This model again uses Markov processes to model the situation. Under certain assumptions, this model shows that a vaccine administered at age 13, even with differing efficacy levels, could have a significant effect on the incidence of cervical cancer. They also find that the proportion vaccinated is a key factor in the overall reduction of cervical cancer.

Barnabas et al., (2006) construct an SIR compartmental, deterministic model dealing with infection of HPV and potential progression to cervical cancer. This

model allows for an HPV sufferer to become immune. They assume a type-specific lifelong immunity once an individual has recovered, but allow for a, gradual loss of a detectable antibody response', as tests may not be sensitive enough to detect very low levels of antibodies, and this assumption therefore allows for a comparison with test results. The model also divides the population into age groups with a 5 year spread (i.e. 0-4yrs, 5-9yrs etc.), and also into sexual activity groups (four groups relating to the rate at which an individual changes their sexual partner). The model is studied numerically, as the population is divided into a large number of different classes. Their results are similar to other conclusions, in that vaccinating men made very little difference, and what was important was vaccinating the girls before they became sexually active and achieving a high level of coverage. They did, however, assume the vaccine would offer lifelong protection, or that it would be supplemented with boosters, so if this assumption does not hold, the results could be quite different.

Llamazares and Smith (2008) is the only paper explicitly to include a compartment for non-sexually active individuals, although it focuses on female-only vaccination, so does not mirror this with an equivalent non-sexually active male class. They concentrate on the impact of the efficacy and, take' of the vaccine on the overall success of the vaccine. The second part of the thesis relates to the most cost-effective way to introduce the vaccine, and indeed whether vaccination is cost-effective. A comparison of the current cost-effectiveness analyses suggests that the important assumptions are those such as the effectiveness of the vaccine, smear tests and the model used for predictions. Expansions to the models include ideas such as different options in using the vaccine and epidemiological variables. The vaccine cannot replace screening, as types -16 and -18 only account for about 70 percent of cervical cancer. In the USA there is a high cost to screening as they use expensive testing methods and screen frequently, so the vaccine along with a reduction in the screening program may benefit them. Cost effectiveness anal-

yses often include reduced quality of life as a cost, although this value could be underestimated if aspects such as the effect the illness and treatment has on the rest of the family are not included. Although all models produce slightly different conclusions, the general consensus is that the vaccine is cost-effective under certain conditions. It is agreed that screening will still be necessary, so this is taken into account. Most of the studies agree that there is little extra benefit in vaccinating males as well as females, and that a catch-up program is probably not particularly cost-effective.

Kim et al., (2007) look at the effect of vaccinating males as well as females, specifically in Brazil. This study used statistical methods and found that, even with vaccination of males (pre-adolescents), there was very little overall benefit. Cervical cancer rates would drop slightly in this situation, but the drop was marginal compared to the increased cost of vaccination. Indeed, the paper concludes that, if a choice must be made between vaccinating boys and increasing the level of vaccination in females, the latter option should be taken first.

Kjaer et al., (2001) looked at the transmission of HPV infection among a group of young women who were either monogamous or without sexual experience and who changed their behavior during the follow-up. The results support the importance of the sexual transmission of HPV infection: the prevalence of HPV infection was 0 percent among the virgins, but increased to 35.4 percent after they became sexually active. Likewise, the HPV prevalence of HPV in monogamous women increased from 14.8 percent to 34.6 percent after sexual activity with a new partner.

Taira et al. (2004) used decision analysis software to model HPV transmission dynamics, and then assesses the cost-effectiveness of including males in the vaccination strategy. They also found that, although it is cost-effective to vaccinate the females, there is little benefit in also vaccinating males. However, they did

show that under certain conditions, such as low vaccine coverage, or low vaccine efficacy, vaccinating males would be cost-effective.

Developing age-structured models for infectious diseases is discussed at length in Anderson and May (1992). It often adds another level of accuracy to a model as behaviors (e.g. contact structures) and transmissibility of a disease can change as an individual ages. Age is usually introduced into a model as a variable, and is often combined with time as a variable to create a set of partial differential equations, as in Ruanne (2006).The inclusion of age as a variable allows many parameters, which would otherwise be constant in a time-dependent model, to be age-dependent. The models also stratify their population into age groups, and calculate forces of infection that are dependent on these age groups.

From the study of the literatures, we have the impression that a new approach would be to build a model that partitions the recovery individuals into two, that is permanent recovered and temporally recovered. We want to be able to consider the vaccination for only females, so our model does not allows for the inclusion of a protected male class. We model the infection as an SIR model.
If full course of the vaccine means protection from the disease then we present an SIR compartmental model with the R compartment partitioned into permanent recovered and temporally recovered compartments.
Age-structured models are of particular use in modeling sexually transmitted diseases since sexual activity often varies significantly by age, and individuals usually contact others of a similar age.

We also extend our study to consider age since the administration of the HPV vaccine is age dependent. We develop an age- and time-dependent system of PDEs in Chapter 3 to allow for the inclusion of age-dependent parameters.

Chapter 3

Methodology

Based on the biology of HPV and its vaccination, researchers across the globe have tried to develop a mathematical model that captures the dynamics of HPV and its vaccination. Researchers have developed models by considering possible scenarios which individuals might take in regards to HPV infection and its vaccination.

Revealing the literatures across the globe has modeled the Human papillomavirus (HPV) using SIR model or its variants. The models for HPV and its vaccination do not reflect the realities on the ground since a person recovers fully from the HPV after receiving all the three dose of HPV vaccine.

As at now, the Recovery, R compartment has not been partitioned into two as a susceptible can move to recovery compartment either temporarily or permanently based on the number of doses of HPV vaccine received. Anyone who has either received one or two but not all three doses of the vaccine has recovered temporarily since the person is at a risk of contracting the HPV virus. Anyone who has received all three dose of HPV vaccine recovers permanently.

In this chapter we present a vaccinated SIR model with two different Recovery groups to study the epidemiology of high-risk $HPV-16-18$ types which causes cervical cancer in Ghana based on the biology of HPV and its vaccination. We divide the recovery class R into two sub classes; permanent recovery population,R_p and temporal recovery population,R_T . We also use our model to study the effect of HPV infection on females within the age 9-25 that are more

sexually active and adult 25 and above that are less sexually active since infection is age dependent.

3.1 Model Assumptions

- Recovery is in two compartments, temporal and permanent.
- Population size is constant.
- The individuals in the population mix homogeneously.
- The rate at which people acquire the virus is proportional to the product of susceptible and infective present.

Our model is shown as a flow diagram below.

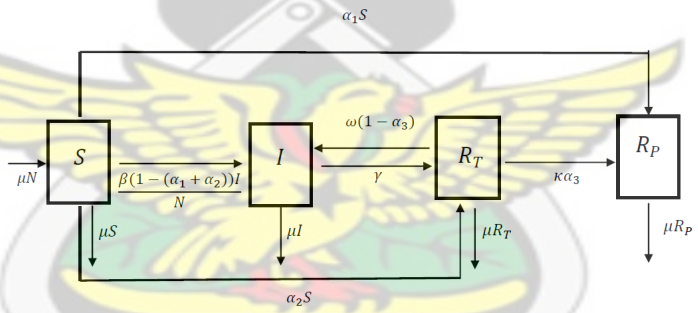

Figure 3.1: Compartmental diagram for HPV infection

$$\begin{aligned}
\frac{dS}{dt} &= \mu N - \frac{\beta(1-(\alpha_1+\alpha_2))SI}{N} - ((\alpha_1+\alpha_2)+\mu)S \\
\frac{dI}{dt} &= \frac{\beta(1-(\alpha_1+\alpha_2))SI}{N} - (\mu+\gamma)I + \omega(1-\alpha_1)R_T \\
\frac{dR_T}{dt} &= \alpha_2 S + \gamma I - (\omega(1-\alpha_3)+\alpha_3 k+\mu)R_T \\
\frac{dR_p}{dt} &= \alpha_3 k + \alpha_1 S - \mu R_p
\end{aligned} \tag{3.1}$$

with initial conditions given as follows,

$S(0) = S_0 > 0, I(0) = I_0 > 0, R_T(0) = R_T > 0, R_p(0) = R_p > 0$

Where S is number of susceptible humans, I is number of Infectious humans, R_T is number of temporally recovered humans,R_p is number of permanently recovered

humans, P is rate of proportion,β is contact rate between the non-vaccinated susceptible individuals and the infected individuals per unit time, γ is rate at which an infectious individual temporally recover per unit time, k is rate at which individuals permanently recover per unite time. In general any member of the human population is born into the susceptible class, S at a rate μ. The proportion of individuals in the susceptible class that have received all three dose of vaccine is given by $\alpha_1 S$. The proportion of individuals in the susceptible class that have received only one or two dose of vaccine is given by $\alpha_1 S$. The proportion of individuals in the susceptible class that is non-vaccinated is given by $(1-(\alpha_1+\alpha_2))S$. The proportion of temporally recovered individuals that receives all three dose of vaccine is given by $\alpha_3 R_T$ and the proportion of temporally recovered individuals that could not receive all three dose of vaccine is given by $(1-\alpha_3)R_T$.

Individuals are born only into the susceptible class through birth rate μ. When the non- vaccinated individual in the susceptible class comes into contact with infected human population, they become infective and moves into the infected class I . Those in the infective class, upon viral clearance or treatment of precancerous lesions moves into the temporally recovered class R_T. Vaccinated individuals in the susceptible class moves to the temporally recovered class R_T, when they receive only one or two dose of HPV vaccine. In the temporally recovered class R_T individuals moves to the permanently recovered class R_p upon receiving all three dose of HPV vaccine and individuals who could not receive all the three dose of vaccine moves to the infected class I. An infected individual who after receiving treatment recovers temporally may move back into the infected class with time and get re-infected. Humans in all the various population class leaves the class through natural death rate μ.

We non - dimensionalize the variables in the system of equations (3.1) by using the following equations

$$s = \frac{S}{N}, \frac{I}{N}, r_p = \frac{R_p}{N}, r_T = \frac{r_T}{N}, \tau = kt, \psi = \frac{\mu}{k}, \phi = \frac{\omega}{k}, \xi = \frac{\beta}{k},$$
$$\varphi = \frac{\gamma}{k}, \eta = \frac{\alpha_1}{k}, \rho = \frac{\alpha_2}{k}, \vartheta = \frac{\alpha_3}{k} \tag{3.2}$$
$$s + i + r_T + r_p = 1,\ \alpha_1, \alpha_2, \alpha_3 \in [0, 1]$$

A new system of differential equations is obtained from (3.1) by using the system of equations (3.2).

$$\begin{aligned}
\frac{ds}{d\tau} &= \psi - \xi(1 - (\eta + \rho))si - ((\eta + \rho) + \psi)s \\
\frac{di}{d\tau} &= \xi(1 - (\eta + \rho))si - (\psi + \vartheta)i + \phi(1 - \vartheta)r_t \\
\frac{dr_T}{d\tau} &= \rho S + \varphi i - (\phi(1 - \vartheta) + \vartheta + \psi)r_T \\
\frac{dr_p}{d\tau} &= \vartheta r_T + \eta s - \psi r_p
\end{aligned} \tag{3.3}$$

$$S(0) = s_0, i(0) = i_0, r_T = r_T > 0, r_p(0) = r_p > 0$$

Table 3.1: Initial values for the population

GENERAL FEMALE POPULATION	Values
Susceptible (S)	0.53
Infective (I)	0.08
Temporal recovery (R_T)	0.21
Permanent recovery (R_p)	0.18
AGED STRUCTURD FEMALE POPULATION	Values
Susceptible (S)	0.70
Infective (I)	0.05
Temporal recovery (R_T)	0.30
Permanent recovery (R_p)	0.25

We obtain the equilibriums for the system of equations as follows

Let; $\frac{ds}{d\tau} = \frac{di}{d\tau} = \frac{dr_T}{d\tau} = \frac{dr_p}{d\tau} = 0$

$$\psi - \xi(1 - (\eta + \rho))si - ((\eta + \rho) + \psi)s = 0$$
$$\xi(1 - (\eta + \rho))si - (\psi + \vartheta)i + \phi(1 - \vartheta)r_t = 0$$

$$\rho s+\varphi i-(\phi(1-\vartheta)+\vartheta+\psi)r_T = 0 \tag{3.4}$$
$$\vartheta r_T + \eta s - \psi r_p = 0$$

Solving equations (3.4) simultaneously we obtain two solutions as infectious-free equilibrium state of equation (3.5)

$$(s_1^*, i_1^*, r_T^*, r_p^*) = (1, 0, 0, 0) \tag{3.5}$$

and two endemic equilibrium states of equation (3.6) and (3.7)

$$(s_1^*, i_1^*, r_{T1}^*, r_{p1}^*) = (\frac{\psi}{\xi(1-((\eta+\rho))i_1^*+(\eta+\rho)+\psi}, \frac{-[\xi(1-((\eta+\rho))(\phi(1-\vartheta)+\vartheta+\psi)-((\eta+\rho)+\psi)(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)]}{2[\xi(1-((\eta+\rho))\phi\psi(1-\vartheta)-(1-((\eta+\rho))(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)]} +$$
$$\frac{\sqrt{[\xi(1-((\eta+\rho))(\phi(1-\vartheta)+\vartheta+\psi)-((\eta+\rho)+\psi)(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)]^2-4[\xi(1-((\eta+\rho))\phi\psi(1-\vartheta)-(1-((\eta+\rho))(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)\phi(1-\varphi)\rho\psi]}}{2[\xi(1-((\eta+\rho))\phi\psi(1-\vartheta)-(1-((\eta+\rho))(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)]},$$
$$\frac{\rho s_1^*+\varphi i_1^*}{(\phi(1-\vartheta)+\vartheta+\psi)}, \frac{\rho r_{T1}^*+\eta s_1^*}{\psi}) \tag{3.6}$$

and

$$(s_2^*, i_2^*, r_{T2}^*, r_{p2}^*) = (\frac{\psi}{\xi(1-((\eta+\rho))i_2^*+(\eta+\rho)+\psi}, \frac{-[\xi(1-((\eta+\rho))(\phi(1-\vartheta)+\vartheta+\psi)-((\eta+\rho)+\psi)(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)]}{2[\xi(1-((\eta+\rho))\phi\psi(1-\vartheta)-(1-((\eta+\rho))(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)]} +$$
$$\frac{\sqrt{[\xi(1-((\eta+\rho))(\phi(1-\vartheta)+\vartheta+\psi)-((\eta+\rho)+\psi)(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)]^2-4[\xi(1-((\eta+\rho))\phi\psi(1-\vartheta)-(1-((\eta+\rho))(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)\phi(1-\varphi)\rho\psi]}}{2[\xi(1-((\eta+\rho))\phi\psi(1-\vartheta)-(1-((\eta+\rho))(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)]},$$
$$\frac{\rho s_2^*+\varphi i_2^*}{(\phi(1-\vartheta)+\vartheta+\psi)}, \frac{\rho r_{T2}^*+\eta s_2^*}{\psi}) \tag{3.7}$$

Given $\psi - \xi(1-(\eta+\rho))si - ((\eta+\rho)+\psi)s = f_1$

$$\xi(1-(\eta+\rho))si - (\psi+\varphi)i + \phi(1-\vartheta)r_t = f_2$$
$$\rho S+\varphi i-(\phi(1-\vartheta)+\vartheta+\psi)r_T = f_3 \tag{3.8}$$
$$\vartheta r_T + \eta s - \psi r_p = f_4$$

The Jacobian matrix for equation 3.8 is given as

$$J(s, i, r_T, r_p) = \begin{pmatrix} \frac{\partial f_1}{\partial s} & \frac{\partial f_1}{\partial i} & \frac{\partial f_1}{\partial r_T} & \frac{\partial f_1}{\partial r_p} \\ \frac{\partial f_2}{\partial s} & \frac{\partial f_2}{\partial i} & \frac{\partial f_2}{\partial r_T} & \frac{\partial f_2}{\partial r_p} \\ \frac{\partial f_3}{\partial s} & \frac{\partial f_3}{\partial i} & \frac{\partial f_3}{\partial r_T} & \frac{\partial f_3}{\partial r_p} \\ \frac{\partial f_4}{\partial s} & \frac{\partial f_4}{\partial i} & \frac{\partial f_4}{\partial r_T} & \frac{\partial f_4}{\partial r_p} \end{pmatrix} \tag{3.9}$$

Now using (3.9) we have;

$$J(s,i,r_T,r_p)=$$

$$\begin{pmatrix} -\xi(1-(\eta+\rho))i-((\eta+\rho)+\psi) & -\xi(1-(\eta+\rho))s & 0 & 0 \\ \xi(1-(\eta+\rho))i & \xi(1-(\eta+\rho))s-(\psi+\varphi) & \phi(1-\vartheta) & 0 \\ \rho & \varphi & -(\phi(1-\vartheta)+\vartheta+\psi) & 0 \\ \eta & 0 & \vartheta & -\psi \end{pmatrix} \tag{3.10}$$

3.2 The infectious-free equilibrium state

At infectious free equilibrium state $(s_2^*, i_2^*, r_{T2}^*, r_{p2}^*) = (1,0,0,0)$, equation (3.10) becomes

$$J(s_2^*, i_2^*, r_{T2}^*, r_{p2}^*) = \begin{pmatrix} -\psi) & -\xi & 0 & 0 \\ 0 & \xi-(psi+\varphi) & \phi(1-\vartheta) & 0 \\ \rho & \varphi & -(\phi(1-\vartheta)+\vartheta+\psi) & 0 \\ 0 & 0 & \vartheta & -\psi \end{pmatrix} \tag{3.11}$$

The Reproductive ratio R_0 is the expected number of individuals infected by a single infected individual over the duration of the infectious period in a population that is entirely susceptible. We use the next generation operator approach to obtain R_0

$$F = \begin{pmatrix} \xi & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

$$V = \begin{pmatrix} \psi+\varphi & -\phi(1-\vartheta) & 0 \\ -\varphi & \phi(1-\vartheta) & 0 \\ \rho & \varphi & -(\phi(1-\vartheta)+\vartheta+\psi) \quad 0 \\ 0 & -\vartheta & \psi \end{pmatrix}$$

$det(V) = \psi(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)$

$$V^T = \begin{pmatrix} \psi(\phi(1-\vartheta)+\vartheta+\psi) & \psi\phi(1-\vartheta) & 0 \\ \psi\varphi & \psi(\psi+\varphi) & 0 \\ \vartheta\varphi & \vartheta(\psi+\varphi) & (\psi+\varphi)(\phi(1-\vartheta+\vartheta+\psi)+\varphi\phi(1-\vartheta) \end{pmatrix}$$

$$V^{-1} = \begin{pmatrix} \psi(\phi(1-\vartheta)+\vartheta+\psi) & \psi\phi(1-\vartheta) & 0 \\ \psi\varphi & \psi(\psi+\varphi) & 0 \\ \vartheta\varphi & \vartheta(\psi+\varphi) & (\psi+\varphi)(\phi(1-\vartheta+\vartheta+\psi)+\varphi\phi(1-\vartheta) \end{pmatrix}^{(\frac{1}{\psi(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)})}$$

$$V^{-1} = \begin{pmatrix} \frac{1}{\psi+\varphi} & \frac{\phi(1-\vartheta)}{(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)} & 0 \\ \frac{\varphi}{(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)} & \frac{1}{(\phi(1-\vartheta)+\vartheta+\psi)} & 0 \\ \frac{\varphi\vartheta}{(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)} & \frac{\vartheta}{(\psi(\phi(1-\vartheta)+\vartheta+\psi))} & \frac{(\psi+\varphi)(\phi(1-\vartheta+\vartheta+\psi)+\varphi\phi(1-\vartheta)}{\psi(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)} \end{pmatrix}$$

$$K = FV^{-1}$$

$$K = \begin{pmatrix} \xi & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} \frac{1}{\psi+\varphi} & \frac{\phi(1-\vartheta)}{(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)} & 0 \\ \frac{\varphi}{(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)} & \frac{1}{(\phi(1-\vartheta)+\vartheta+\psi)} & 0 \\ \frac{\varphi\vartheta}{(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\phi)} & \frac{\vartheta}{(\psi(\phi(1-\vartheta)+\vartheta+\psi))} & \frac{(\psi+\varphi)(\phi(1-\vartheta+\vartheta+\psi)+\varphi\phi(1-\vartheta)}{\psi(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)} \end{pmatrix}$$

$$K = \begin{pmatrix} \frac{\xi}{(\psi+\varphi)} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

The basic reproductive number for our model is given as;

$$R_0 = \frac{\xi}{\psi+\varphi} \tag{3.12}$$

This shows that the basic reproductive number of our model is directly proportional to contact rate in which a human infects another human with HPV and

inversely proportional to the recovery rate plus the mortality rate.

If $R_0 < 1$on the average each infected individual infect less than one other individual and the infection dies out. If $R_0 > 1$ on the average each infected individual infect more than one individual so we would expect the infection to spread.

3.3 The Endemic equilibrium state

3.3.1 Case 1

At the first endemic equilibrium state we substituting equation (3.6) into equation (3.10)which yields

$$J(s_1^*, i_1^*, r_{T1}^*, r_{p1}^*) = \begin{pmatrix} -\xi(1-(\eta+\rho))i_1^* - ((\eta+\rho)+\psi) & -\xi(1-(\eta+\rho))s_i^* & 0 & 0 \\ \xi(1-(\eta+\rho))i_1^* & \xi(1-((\eta+\rho))s_i^* - (\psi+\varphi) & \phi(1-\vartheta) & 0 \\ \rho & \varphi & -(\phi(1-\vartheta)+\vartheta+\psi) & 0 \\ \eta & 0 & \vartheta & \psi \end{pmatrix} \quad (3.13)$$

From equation (3.13) we calculating $det|J - \lambda I| = 0$

$$det = \begin{pmatrix} -\xi(1-(\eta+\rho))i_1^* - ((\eta+\rho)+\psi) - \lambda & -\xi(1-(\eta+\rho))s_i^* & 0 & 0 \\ \xi(1-(\eta+\rho))i_1^* & \xi(1-((\eta+\rho))s_i^* - (\psi+\varphi) - \lambda & \phi(1-\vartheta) & 0 \\ \rho & \varphi & -(\phi(1-\vartheta)+\vartheta+\psi) & 0 \\ \eta & 0 & \vartheta & -\psi-\lambda \end{pmatrix} = 0 \quad (3.14)$$

Solving equation(3.14) we obtain

$\lambda^4+[(\phi(1-\vartheta)+\vartheta+\psi)-(\xi(1-(\eta+\rho))s_1^*-(\psi+\varphi))-(\xi(1-(\eta+\rho))i_1^*)-((\eta+\rho)+\psi)-\psi]\lambda^3+[((\phi(1-\vartheta)+\vartheta+\psi)\psi)+(-\xi(1-(\eta+\rho)))i_1^*-((\eta+\rho)+\psi)(\xi(1-(\eta+\rho))s_1^*-(\psi+\varphi))-(-\xi(1-(\eta+\rho))i_1^*-((\eta+\rho)+\psi)(\phi(1-\vartheta)+\vartheta+\psi))+(\xi(1-(\eta+\rho))s_1^*(\xi(1-(\eta+\rho))i_1^*)-(\xi(1-(\eta+\rho))s_1^*-(\psi+\varphi)((\phi(1-\vartheta)+\vartheta)+\psi))-((-\xi(1-(\eta+\rho))i_1^*-((\eta+\rho)+\psi)-\psi))(\psi)]\lambda^2+[(-\xi(1-(\eta+\rho)))i_1^*-((\eta+\rho)+\psi)(\xi(1-(\eta+\rho))s_1^*-(\psi+\varphi))((\phi(1-\vartheta)+\vartheta)+\psi)+((-\xi(1-(\eta+\rho)))i_1^*-((\eta+\rho)+\psi)(\xi(1-(\eta+\rho))s_1^*-(\psi+\varphi)))(\psi)-((-\xi(1-(\eta+\rho)))i_1^*-((\eta+\rho)+\psi))((\phi(1-\vartheta)+\vartheta)+\psi)(\psi)-(\xi(1-(\eta+\rho)))s_1^*((\phi(1-\vartheta)+\vartheta)+\psi)(\psi)+(\xi(1-(\eta+\rho))s_1^*(\xi(1-(\eta+\rho))i_1^*((\phi(1-\vartheta)+\vartheta)+\psi)+(\xi(1-(\eta+\rho)))s_1^*((\xi(1-(\eta+\rho)))i_1^*)(\psi)]\lambda+(-\xi(1-(\eta+\rho))i_1^*-((\eta+\rho)+\psi)(\xi(1-(\eta+\rho))s_1^*-(\psi+\varphi)((\phi(1-\vartheta)+\vartheta)+\psi)+(\xi(1-(\eta+\rho))s_1^*(\xi(1-(\eta+\rho))i_1^*)((\phi(1-\vartheta)+\vartheta)+\psi)(\psi)$

$$= 0 \tag{3.15}$$

In equation (3.15) we let

$A_1 = (\phi(1-\vartheta)+\vartheta)+\psi) - ((\xi(1-(\eta+\rho))s_1^*) - (\psi+\varphi)) - (\xi(1-(\eta+\rho)i_1^*) - ((\eta+\rho)\psi) - \psi)$

$A_2 = ((\phi(1-\vartheta)+\vartheta)+\psi)(\psi) + (-(\xi(1-(\eta+\rho))i_1^*) - ((\eta+\rho)+\psi))(\xi(1-(\eta+\rho))s_1^* - (\psi+\varphi)) - (-\xi(1-(\eta+\rho))i_1^* - ((\eta+\rho)+\psi)((\phi(1-\vartheta)+\vartheta)+\psi)) + (\xi(1-(\eta+\rho))s_1^*(\xi(1-(\eta+\rho))i_1^*) - ((\xi(1-(\eta+\rho))s_1^*) - (\psi+\varphi))((\phi(1-\vartheta)+\vartheta)+\psi) - (\xi(1-(\eta+\rho))i_1^*) - ((\eta+\rho)+\psi) - \psi)(\psi)$

$A_3 = (-(\xi(1-(\eta+\rho))i_1^*) - ((\eta+\rho)+\psi))(\xi(1-(\eta+\rho))s_1^* - (\psi+\varphi))(\phi(1-\vartheta)+\vartheta)+\psi) + (-\xi(1-(\eta+\rho))i_1^*) - ((\eta+\rho)+\psi))(\xi(1-(\eta+\rho))s_1^* - (\psi+\varphi))(\psi) - (-\xi(1-(\eta+\rho))i_1^* - ((\eta+\rho)+\psi)((\phi(1-\vartheta)+\vartheta)+\psi))(\psi) - (\xi(1-(\eta+\rho))s_1^*(\phi(1-\vartheta)+\vartheta)+\psi)(\psi) + (\xi(1-(\eta+\rho))s_1^*(\xi(1-(\eta+\rho))i_1^*)((\phi(1-\vartheta)+\vartheta)+\psi) + (\xi(1-(\eta+\rho))s_1^*(\xi(1-(\eta+\rho))i_1^*)(\psi)$

$A_4 = (-(\xi(1-(\eta+\rho))i_1^*) - ((\eta+\rho)+\psi))(\xi(1-(\eta+\rho))s_1^* - (\psi+\varphi))(\phi(1-\vartheta)+\vartheta)+\psi) + (\xi(1-(\eta+\rho))s_1^*(\xi(1-(\eta+\rho))i_1^*)(\phi(1-\vartheta)+\vartheta)+\psi)(\psi)$

Now equation (3.15) becomes

$$\lambda^4 + A_1\lambda^2 + A_2\lambda^2 + A_3\lambda + A_4 \tag{3.16}$$

Using Routh-Hurwitz criterion, the equilibrium for equation (3.16) is locally stable if the following conditions are satisfied:

$A_1 > 0, A_3 > 0, A_4 > 0, A_1A_2A_3 > A_3^2 + A_1^2A_4$

Otherwise the endemic equilibrium state is unstable.

3.3.2 Case 2

At the second endemic equilibrium state we substituting equation (3.7) into equation (3.10) which yields

$$J(s_1^*, i_1^*, r_{T1}^*, r_{p1}^*) = \begin{pmatrix} -\xi(1-(\eta+\rho))i_1^* - ((\eta+\rho)+\psi) & -\xi(1-(\eta+\rho))s_i^* & 0 & 0 \\ \xi(1-(\eta+\rho))i_1^* & \xi(1-((\eta+\rho))s_i^* - (\psi+\varphi) & \phi(1-\vartheta) & 0 \\ \rho & \varphi & -(\phi(1-\vartheta)+\vartheta+\psi) & 0 \\ \eta & 0 & \vartheta & -\psi \end{pmatrix} \tag{3.17}$$

From equation (3.17) we calculating $det|J - \lambda I| = 0$

$$det = \begin{pmatrix} -\xi(1-(\eta+\rho))i_1^* - ((\eta+\rho)+\psi) - \lambda & -\xi(1-(\eta+\rho))s_i^* & 0 & 0 \\ \xi(1-(\eta+\rho))i_1^* & \xi(1-((\eta+\rho))s_i^* - (\psi+\varphi) - \lambda & \phi(1-\vartheta) & 0 \\ \rho & \varphi & -(\phi(1-\vartheta)+\vartheta+\psi) & 0 \\ \eta & 0 & \vartheta & -\psi-\lambda \end{pmatrix} = 0 \tag{3.18}$$

Solving equation (3.18) we obtain

$$\lambda^4+[(\phi(1-\vartheta)+\vartheta+\psi)-(\xi(1-(\eta+\rho))s_2^*-(\psi+\varphi))-(\xi(1-(\eta+\rho))i_2^*)-((\eta+\rho)+\psi)-\psi]\lambda^3+[((\phi(1-\vartheta)+\vartheta+\psi)\psi)+(-\xi(1-(\eta+\rho)))i_2^*-((\eta+\rho)+\psi)(\xi(1-(\eta+\rho))s_2^*-(\psi+\varphi))-(-\xi(1-(\eta+\rho))i_2^*-((\eta+\rho)+\psi)(\phi(1-\vartheta)+\vartheta+\psi))+(\xi(1-(\eta+\rho))s_2^*(\xi(1-(\eta+\rho))i_2^*)-(\xi(1-(\eta+\rho))s_2^*-(\psi+\varphi)((\phi(1-\vartheta)+\vartheta)+\psi))-((-\xi(1-(\eta+\rho))i_2^*-((\eta+\rho)+\psi)-\psi))(\psi)]\lambda^2+[(-\xi(1-(\eta+\rho)))i_2^*-((\eta+\rho)+\psi)(\xi(1-(\eta+\rho))s_2^*-(\psi+\varphi))((\phi(1-\vartheta)+\vartheta)+\psi)+((-\xi(1-(\eta+\rho)))i_2^*-((\eta+\rho)+\psi)(\xi(1-(\eta+\rho))s_2^*-(\psi+\varphi)))(\psi)-((-\xi(1-(\eta+\rho)))i_2^*-((\eta+\rho)+\psi))((\phi(1-\vartheta)+\vartheta)+\psi)(\psi)-(\xi(1-(\eta+\rho)))s_2^*((\phi(1-\vartheta)+\vartheta)+\psi)(\psi)+(\xi(1-(\eta+\rho))s_2^*(\xi(1-(\eta+\rho))i_2^*((\phi(1-\vartheta)+\vartheta)+\psi)+(\xi(1-(\eta+\rho)))s_2^*((\xi(1-(\eta+\rho)))i_2^*)(\psi)]\lambda+(-\xi(1-(\eta+\rho))i_2^*-((\eta+\rho)+\psi)(\xi(1-(\eta+\rho))s_2^*-(\psi+\varphi)((\phi(1-\vartheta)+\vartheta)+\psi)+(\xi(1-(\eta+\rho))s_2^*(\xi(1-(\eta+\rho))i_2^*)((\phi(1-\vartheta)+\vartheta)+\psi)(\psi)=0 \tag{3.19}$$

In equation (3.19) we let

$$B_1 = (\phi(1-\vartheta)+\vartheta)+\psi)-((\xi(1-(\eta+\rho))s_2^*)-(\psi+\varphi))-(\xi(1-(\eta+\rho)i_2^*)-((\eta+\rho)\psi)-\psi)$$

$$B_2 = ((\phi(1-\vartheta)+\vartheta)+\psi)(\psi)+(-(\xi(1-(\eta+\rho))i_2^*)-((\eta+\rho)+\psi))(\xi(1-(\eta+\rho))s_1^*-(\psi+\varphi))-(-\xi(1-(\eta+\rho))i_2^*-((\eta+\rho)+\psi)((\phi(1-\vartheta)+\vartheta)+\psi))+(\xi(1-(\eta+\rho))s_2^*(\xi(1-(\eta+\rho))i_2^*)-((\xi(1-(\eta+\rho))s_2^*)-(\psi+\varphi))((\phi(1-\vartheta)+\vartheta)+\psi)-(\xi(1-(\eta+\rho))i_2^*)-((\eta+\rho)+\psi)-\psi)(\psi)$$

$$B_3 = (-(\xi(1-(\eta+\rho))i_2^*)-((\eta+\rho)+\psi))(\xi(1-(\eta+\rho))s_2^*-(\psi+\varphi))(\phi(1-\vartheta)+\vartheta)+\psi)+(-\xi(1-(\eta+\rho))i_2^*)-((\eta+\rho)+\psi))(\xi(1-(\eta+\rho))s_2^*-(\psi+\varphi))(\psi)-(-\xi(1-(\eta+\rho))i_2^*-((\eta+\rho)+\psi)((\phi(1-\vartheta)+\vartheta)+\psi))(\psi)-(\xi(1-(\eta+\rho))s_2^*(\phi(1-\vartheta)+\vartheta)+\psi)(\psi)+(\xi(1-(\eta+\rho))s_2^*(\xi(1-(\eta+\rho))i_2^*)((\phi(1-\vartheta)+\vartheta)+\psi)+(\xi(1-(\eta+\rho))s_1^*(\xi(1-(\eta+\rho))i_2^*)(\psi)$$

$$B_4 = (-(\xi(1-(\eta+\rho))i_2^*)-((\eta+\rho)+\psi))(\xi(1-(\eta+\rho))s_2^*-(\psi+\varphi))(\phi(1-\vartheta)+$$

$\vartheta) + \psi) + (\xi(1-(\eta+\rho))s_2^*(\xi(1-(\eta+\rho))i_2^*)(\phi(1-\vartheta)+\vartheta)+\psi)(\psi)$

Now equation (3.19) becomes

$$\lambda^4 + B_1\lambda^3 + B_2\lambda^2 + B_3\lambda + B_4 = 0 \tag{3.20}$$

Using Routh-Hurwitz criterion, the equilibrium for equation (3.20) is locally stable if the following conditions are satisfied:

$B_1 > 0, B_3 > 0, B_4 > 0, B_1B_2B_3 > B_3^2 + B_1^2B_4$

Otherwise the endemic equilibrium state is unstable.

3.4 System of partial differential equations

Now since infection is age-dependent we present the partial differential equation of our model and analyze the stability of both infectious - free equilibrium state and endemic equilibrium state

$$\frac{\partial S}{\partial t} + \frac{\partial S}{\partial a} = \mu(a)N - \frac{\beta(t,a)(1-a_1+a_2)SI}{N} - ((a_1+a_2)+\mu(a))S$$

$$\frac{\partial I}{\partial t} + \frac{\partial I}{\partial a} = \frac{\beta(t,a)(1-a_1+a_2)SI}{N} - (\mu(a)+\gamma(t,a)I + \omega(t,+a_1)R_T \tag{3.21}$$

$$\frac{\partial R_T}{\partial t} + \frac{\partial R_T}{\partial a} = a_2S + \gamma(t,a)I - (\omega(t,a)(1-a_3) + a_3k + \mu(a))R_T$$

$$\frac{\partial R_p}{\partial t} + \frac{\partial R_p}{\partial a} = a_3k(t,\alpha) + a_1S\mu(\alpha)R_p$$

All variables and parameters are as described above.

We non-dimensionalize equations (3.21) by using equation (3.9)to obtain;

$$\frac{\partial s}{\partial \tau} + \frac{\partial s}{\partial a} = \psi(a) - \xi(\tau,a)(1-(\eta+\rho)+\psi(a))s$$

$$\frac{\partial i}{\partial \tau}+\frac{\partial i}{\partial a} = \xi(\tau,a)(1-(\eta+\rho))si-(\psi(a)+\varphi(\tau,a))i+\phi(\tau,a)(1-\vartheta)r_T \tag{3.22}$$

$$\frac{\partial r_T}{\partial \tau} + \frac{\partial r_T}{\partial a} = \rho s + \vartheta(\tau,a)i - (\phi(\tau,a)(1-\varphi) + \varphi + \psi(a))r_T$$

$$\frac{\partial r_p}{\partial \tau} + \frac{\partial r_p}{\partial a} = \vartheta r_T + \eta s - \psi(\alpha)r_p$$

with the age-dependent death rate $\psi(a)$ defining initial conditions at age $(a = 9)$

$$s(\tau,a) = \int_a^\infty \psi(a)N(\tau,a)d\tau, i(\tau,a) = r_T(\tau,a) = r_p(\tau,a) = 0 \tag{3.23}$$

and appropriate initial conditions at time $\tau = 0$ The force of $\xi(\tau,a)$infection is defined by

$$\xi(\tau,a) = \int_a^\infty k(a,u)i(\tau,u)du \tag{3.4}$$

and is the rate at which susceptible of age a become infected at time τ

We obtain the equilibriums for the system of equations (3.22)as follows

we let

$$\frac{\partial s}{\partial \tau} + \frac{\partial s}{\partial \tau} + \frac{\partial s}{a} = \frac{\partial i}{\partial \tau} + \frac{\partial i}{\partial a} = \frac{\partial r_T}{\partial \tau} + \frac{\partial r_T}{\partial \tau} = \frac{\partial r_p}{\partial \tau} + \frac{\partial r_p}{\partial a} = 0$$

that is; $\psi(a) - \xi(\tau,a)(1-(\eta+\rho))si - ((\eta+\rho))si - ((\eta+\rho)) + \psi(a)s = 0$

$$\xi(\tau,a)(1-(\eta+\rho)si - (\psi(a)+\varphi(\tau,a))i + \psi(\tau,a))i + \phi(\tau,a)(1-\vartheta)r_T = 0$$

$$\rho s + \varphi(\tau,a)i - (\phi(\tau,a)(1-\vartheta) + \vartheta + \psi(a))r_T = 0 \tag{3.25}$$

$$\vartheta r_T + \eta s - \psi(a) r_p = 0$$

We solve the system of equations (3.25) simultaneously to obtain two solutions as infectious-free equilibrium state of equation (3.26)

$$(s_2^*(\tau,\alpha), i_2^*(\tau,\alpha), r_{T2}^*(\tau,\alpha) r_{p2}^*(\tau,\alpha)) =$$

$$(1, 0, 0, 0) \tag{3.26}$$

and two endemic equilibrium point of equation (3.26) $(s_2^*(\tau,\alpha), i_2^*(\tau,\alpha), r_{T2}^*(\tau,\alpha) r_{p2}^*(\tau,\alpha)) = (\frac{\psi}{\xi(1-((\eta+\rho))i_1^*+(\eta+\rho)+\psi}, \frac{-[\xi(1-((\eta+\rho))(\phi(1-\vartheta)+\vartheta+\psi)}{2[\xi(1-((\eta+\rho))\phi\psi(1-\vartheta)-\xi(1}$

$$\frac{\sqrt{[\xi(1-((\eta+\rho))(\phi(1-\vartheta)+\vartheta+\psi)-((\eta+\rho)+\psi)(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)]^2-4[\xi(1-((\eta+\rho))\phi\psi(1-\vartheta)-(1-((\eta+\rho))(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)\phi(1-\varphi)\rho\psi]}}{2[\xi(1-((\eta+\rho))\phi\psi(1-\vartheta)-(1-((\eta+\rho))(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)]},$$

$$\frac{\rho s_2^* + \varphi i_2^*}{(\phi(1-\vartheta)+\vartheta+\psi)}, \frac{\rho r_{T2}^* + \eta s_2^*}{\psi}) \tag{3.27}$$

and $(s_2^*(\tau,\alpha), i_2^*(\tau,\alpha), r_{T2}^*(\tau,\alpha) r_{p2}^*(\tau,\alpha)) =$

$$(\frac{\psi}{\xi(1-((\eta+\rho))i_2^*+(\eta+\rho)+\psi}, \frac{-[\xi(1-((\eta+\rho))(\phi(1-\vartheta)+\vartheta+\psi)-((\eta+\rho)+\psi)(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)]}{2[\xi(1-((\eta+\rho))\phi\psi(1-\vartheta)-\xi(1-((\eta+\rho))(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)]} +$$

$$\frac{\sqrt{[\xi(1-((\eta+\rho))(\phi(1-\vartheta)+\vartheta+\psi)-((\eta+\rho)+\psi)(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)]^2-4[\xi(1-((\eta+\rho))\phi\psi(1-\vartheta)-(1-((\eta+\rho))(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)\phi(1-\varphi)\rho\psi]}}{2[\xi(1-((\eta+\rho))\phi\psi(1-\vartheta)-(1-((\eta+\rho))(\psi+\varphi)(\phi(1-\vartheta)+\vartheta+\psi)]},$$

$$\frac{\rho s_2^* + \varphi i_2^*}{(\phi(1-\vartheta)+\vartheta+\psi)}, \frac{\rho r_{T2}^* + \eta s_2^*}{\psi}) \tag{3.28}$$

3.5 The infectious-free equilibrium state

Steady state (time-independent) solutions of equation (3.23) are functions of age,α They may be computed by solving the set of ordinary differential equations.

$$\frac{ds}{da} = \psi(a) - \xi(a)(1 - (\eta+\rho)si - ((\eta+\rho) + \psi(a))s$$

$$\frac{di}{d\tau} = \xi(a)(1-(\eta+\rho))si - (\psi(a)+\varphi(a))i + \phi(a)(1-\vartheta)r_T \tag{3.29}$$

$$\frac{dr_T}{da} = \rho s + \vartheta(a)i - (\phi a)(1-\vartheta) + \vartheta + \psi(a))r_T$$

$$\frac{dr_p}{da} = \vartheta r_T + \eta s - \psi(a) r_p$$

Together with

$$s(0) = \int_a^\infty \psi(a)N(a)da, i(0) = r_T(0) = r_p(0) = 0 \tag{3.30}$$

and

$$\xi(a) = \int_a^\infty k(a,u)i(u)du \tag{3.31}$$

These expressions are obtained from equation (3.23) by suppressing all dependence of the variables on , but the notation for dependent variables has been changed to aid clarity of exposition

$$(s(\tau,a) = s(a), i(\tau,a) = i(a), r_T(\tau,a) = r_T(a), r_p(\tau,a) = r_p(a), \xi(\tau,a) = \xi(a))$$

Equation (3.29) may be integrated to obtain

$$s(a) = \int_a^b \psi(a)i(0)\frac{\xi(a)}{\psi(a)} \tag{3.32}$$

$$i(a) = \int_a^b \frac{s(u)\xi(a)}{\psi(a)+\varphi(a)} \tag{3.33}$$

In other to derive a formula for the basic reproductive ratio of the infection at the steady state infection-free age distribution of susceptible is $s(u) = N(u)$ Making this substitution into equation 3.33 and using 3.31 the steady state age distribution of infective at the beginning of an endemic then satisfies

$$i(a) = \int_a^b k(u,w)i(w)\int_a^b \frac{N(u)}{\psi(a)+\varphi(a)}dudw \tag{3.34}$$

For separable mixing the kernel $k(u,w) = f(u)g(w)$ for some functions f and g Substituting this in equation 3.34 leads to

$$i(a) = \int_a^\infty f(u)\frac{N(u)}{\psi(a)+\varphi(a)}\int_a^b g(w)i(w)d(u)d(w) \tag{3.35}$$

The second integral in equation (3.35) is independent of a hence $i(a) = c_0\chi(a)$

where

$$\chi(a) = \int_a^\infty f(u)\frac{N(u)}{\psi(a)+\varphi(a)}du \tag{3.36}$$

and c_0 is a constant. It then follows that the infection can persist when $R_0 > 1$ and infection dies out $R_0 < 1$ when where

$$R_0 = \int_a^\infty \chi(w)g(w)d(w) \tag{3.37}$$

3.6 The Endemic equilibrium state

3.6.1 Case 1

Given

$$\xi(\alpha) - \xi(\tau,\alpha)(1-(\eta+\rho))si - ((\eta+\rho)\psi)s = g_1$$

$$\xi(\tau,\alpha)(1-(\eta+\rho)si - (\psi+\varphi(\tau,\alpha))i + \phi(1-\vartheta)r_T = g_2$$

$$\rho s + \varphi(\tau,\alpha)i - (\phi(\tau,\alpha)(1-\vartheta)+\vartheta+\psi(\alpha))r_T = g_3 \tag{3.38}$$

$$\vartheta(\tau,\alpha)r_T + \eta s - \psi(\alpha)r_p = g_4$$

The Jacobian matrix for equation (3.38) is given as

$$J(s(\tau,\alpha), i(\tau,\alpha), r_T(\tau,\alpha), r_p(\tau,\alpha)) = \begin{pmatrix} \frac{\partial g_1}{\partial s} & \frac{\partial g_1}{\partial i} & \frac{\partial g_1}{\partial r_T} & \frac{\partial g_1}{\partial r_p} \\ \frac{\partial g_2}{\partial s} & \frac{\partial g_2}{\partial i} & \frac{\partial g_2}{\partial r_T} & \frac{\partial g_2}{\partial r_p} \\ \frac{\partial g_3}{\partial s} & \frac{\partial g_3}{\partial i} & \frac{\partial g_3}{\partial r_T} & \frac{\partial g_3}{\partial r_p} \\ \frac{\partial g_4}{\partial s} & \frac{\partial g_4}{\partial i} & \frac{\partial g_4}{\partial r_T} & \frac{\partial g_4}{\partial r_p} \end{pmatrix} \tag{3.39}$$

Now using (3.39) we have

$$J(s(\tau,\alpha), i(\tau,\alpha), r_T(\tau,\alpha), r_p(\tau,\alpha)) =$$
$$\begin{pmatrix} -\xi(\tau,\alpha)(1-(\eta+\rho))i + ((\eta+\rho)+\psi(\alpha)) & -\xi(1-(\eta+\rho))s & 0 & 0 \\ \xi(\tau,\alpha)(1-(\eta+\rho))i & \xi(1-(\eta+\rho))s - (\psi(\alpha)+\varphi) & \phi(1-\vartheta) & 0 \\ \rho & \varphi & -(\phi(1-\vartheta)+\vartheta+\psi(\alpha)) & 0 \\ \eta & 0 & \vartheta & -\psi(\alpha) \end{pmatrix} \tag{3.40}$$

At the first endemic equilibrium state we substituting equation (3.27) into equation (3.40) which yields

$$J(s^*(\tau,\alpha), i^*(\tau,\alpha), r_T^*(\tau,\alpha), r_p^*(\tau,\alpha)) =$$
$$\begin{pmatrix} -\xi(\tau,\alpha)(1-(\eta+\rho))i_1^* + ((\eta+\rho)+\psi(\alpha)) & -\xi(1-(\eta+\rho))s_1^* & 0 & 0 \\ \xi(\tau,\alpha)(1-(\eta+\rho))i_1^* & \xi(1-(\eta+\rho))s_1^* - (\psi(\alpha)+\varphi) & \phi(1-\vartheta) & 0 \\ \rho & \varphi & -(\phi(1-\vartheta)+\vartheta+\psi(\alpha)) & 0 \\ \eta & 0 & \vartheta & -\psi(\alpha) \end{pmatrix} \tag{3.41}$$

From equation (3.41) we calculating $det|J-\lambda I| = 0$

$$det \begin{pmatrix} -\xi(\tau,\alpha)(1-(\eta+\rho))i_1^* + ((\eta+\rho)+\psi(\alpha)) - \lambda & -\xi(1-(\eta+\rho))s_1^* & 0 & 0 \\ \xi(\tau,\alpha)(1-(\eta+\rho))i_1^* & \xi(1-(\eta+\rho))s_1^* - (\psi(\alpha)+\varphi) - \lambda & \phi(1-\vartheta) & 0 \\ \rho & \varphi & -(\phi(1-\vartheta)+\vartheta+\psi(\alpha)) - \lambda & 0 \\ \eta & 0 & \vartheta & -\psi(\alpha) - \lambda \end{pmatrix} = 0 \tag{3.42}$$

Solving equation (3.42) we obtain

$\lambda^4 + [(\phi(\tau,\alpha)(1-\vartheta)+\vartheta+\psi(\alpha)) - (\xi(\tau,\alpha)(1-(\eta+\rho))s_1^*(\tau,\alpha) - (\psi(\alpha)+\varphi(\tau,\alpha))) - (\xi(\tau,\alpha)(1-(\eta+\rho))i_1^*(\tau,\alpha)) - ((\eta+\rho)+\psi(\alpha)) - \psi(\alpha)]\lambda^3 + [((\phi(1-\vartheta)+\vartheta+\psi)\psi) + (-\xi(1-(\eta+\rho)))i_1^*(\tau,\alpha) - ((\eta+\rho)+\psi)(\xi(\tau,\alpha)(1-(\eta+\rho))s_1^*(\tau,\alpha) - (\psi+\varphi)) - (-\xi(\tau,\alpha)(1-(\eta+\rho))i_1^*(\tau,\alpha) - ((\eta+\rho)+\psi)(\phi(\tau,\alpha)(1-\vartheta)+\vartheta+\psi)) + (\xi(\tau,\alpha)(1-(\eta+\rho))s_1^*(\tau,\alpha)(\xi(1-(\eta+\rho))i_1^*)(\tau,\alpha) - (\xi(\tau,\alpha)(1-(\eta+\rho))s_1^*(\tau,\alpha) - (\psi+\varphi(\tau,\alpha))((\phi(\tau,\alpha)(1-\vartheta)+\vartheta)+\psi)) - ((-\xi(\tau,\alpha)(1-(\eta+\rho))i_1^*(\tau,\alpha) - ((\eta+\rho)+\psi)-\psi))(\psi)]\lambda^2 + [(-\xi(1-(\eta+\rho)))i_1^*(\tau,\alpha) - ((\eta+\rho)+\psi)(\xi(\tau,\alpha)(1-(\eta+\rho))s_1^*(\tau,\alpha) - (\psi+\varphi))((\phi(\tau,\alpha)(1-\vartheta)+\vartheta)+\psi) + ((-\xi(\tau,\alpha)(1-(\eta+\rho)))i_1^*(\tau,\alpha) - ((\eta+\rho)+\psi)(\xi(\tau,\alpha)(1-(\eta+\rho))s_1^*(\tau,\alpha) - (\psi+\varphi(\tau,\alpha))))(\psi) - ((-\xi(\tau,\alpha)(1-(\eta+\rho)))i_1^*(\tau,\alpha) - ((\eta+\rho)+\psi))((\phi(\tau,\alpha)(1-\vartheta)+\vartheta)+\psi)(\psi) - (\xi(\tau,\alpha)(1-(\eta+\rho)))s_1^*(\tau,\alpha)((\phi(\tau,\alpha)(1-\vartheta)+\vartheta)+\psi)(\psi) + (\xi(\tau,\alpha)(1-(\eta+\rho))s_1^*(\tau,\alpha)(\xi(\tau,\alpha)(1-(\eta+\rho))i_1^*(\tau,\alpha)((\phi(\tau,\alpha)(1-\vartheta)+\vartheta)+\psi) + (\xi(\tau,\alpha)(1-(\eta+\rho)))s_1^*(\tau,\alpha)((\xi(1-(\eta+\rho)))i_1^*(\tau,\alpha))(\psi)]\lambda +$

$$(-\xi(\tau,\alpha)(1-(\eta+\rho))i_1^*(\tau,\alpha)-((\eta+\rho)+\psi)(\xi(\tau,\alpha)(1-(\eta+\rho))s_1^*(\tau,\alpha)-(\psi+\varphi)((\phi(1-\vartheta)+\vartheta)+\psi)+(\xi(1-(\eta+\rho))s_2^*(\xi(1-(\eta+\rho))i_1^*(\tau,\alpha))((\phi(1-\vartheta)+\vartheta)+\psi)(\psi)=0 \tag{3.43}$$

In equation (3.43) we let

$$C_1 = (\phi(\tau,\alpha)(1-\vartheta)+\vartheta)+\psi(\alpha))-((\xi(\tau,\alpha)(1-(\eta+\rho))s_1^*)(\tau,\alpha)-(\psi(\alpha)+\varphi(\tau,\alpha)))-(\xi(\tau,\alpha)(1-(\eta+\rho)i_1^*)(\tau,\alpha)-((\eta+\rho)\psi(\alpha))-\psi(\alpha))$$

$$C_2 = ((\phi(1-\vartheta)+\vartheta)+\psi)(\psi)+(-(\xi(1-(\eta+\rho))i_1^*(\tau,\alpha))-((\eta+\rho)+\psi))(\xi(\tau,\alpha)(1-(\eta+\rho))s_1^*(\tau,\alpha)-(\psi+\varphi))-(-\xi(\tau,\alpha)(1-(\eta+\rho))i_1^*(\tau,\alpha)-((\eta+\rho)+\psi)((\phi(\tau,\alpha)(1-\vartheta)+\vartheta)+\psi))+(\xi(\tau,\alpha)(1-(\eta+\rho))s_1^*(\tau,\alpha)(\xi(1-(\eta+\rho))i_1^*(\tau,\alpha))-((\xi(\tau,\alpha)(1-(\eta+\rho))s_1^*(\tau,\alpha))-(\psi+\varphi(\tau,\alpha)))((\phi(\tau,\alpha)(1-\vartheta)+\vartheta)+\psi)-(\xi(\tau,\alpha)(1-(\eta+\rho))i_1^*(\tau,\alpha))-((\eta+\rho)+\psi)-\psi)(\psi)$$

$$C_3 = (-(\xi(1-(\eta+\rho))i_1^*(\tau,\alpha))-((\eta+\rho)+\psi))(\xi(\tau,\alpha)(1-(\eta+\rho))s_1^*(\tau,\alpha)-(\psi+\varphi))(\phi(\tau,\alpha)(1-\vartheta)+\vartheta)+\psi)+(-\xi(\tau,\alpha)(1-(\eta+\rho))i_1^*(\tau,\alpha))-((\eta+\rho)+\psi))(\xi(\tau,\alpha)(1-(\eta+\rho))s_1^*(\tau,\alpha)-(\psi+\varphi(\tau,\alpha)))(\psi)-(-\xi(\tau,\alpha)(1-(\eta+\rho))i_1^*(\tau,\alpha)-((\eta+\rho)+\psi)((\phi(1-\vartheta)+\vartheta)+\psi))(\psi)-(\xi(\tau,\alpha)(1-(\eta+\rho))s_1^*(\tau,\alpha)(\phi(\tau,\alpha)(1-\vartheta)+\vartheta)+\psi)(\psi)+(\xi(\tau,\alpha)(1-(\eta+\rho))s_1^*(\tau,\alpha)(\xi(\tau,\alpha)(1-(\eta+\rho))i_1^*(\tau,\alpha))((\phi(1-\vartheta)+\vartheta)+\psi)+(\xi(\tau,\alpha)(1-(\eta+\rho))s_1^*(\xi(\tau,\alpha)(1-(\eta+\rho))i_1^*(\tau,\alpha)(\psi)$$

$$C_4 = (-(\xi(\tau,\alpha)(1-(\eta+\rho))i_1^*(\tau,\alpha))-((\eta+\rho)+\psi))(\xi(\tau,\alpha)(1-(\eta+\rho))s_1^*(\tau,\alpha)-(\psi+\varphi))(\phi(1-\vartheta)+\vartheta)+\psi)+(\xi(\tau,\alpha)(1-(\eta+\rho))s_1^*(\tau,\alpha)(\xi(1-(\eta+\rho))i_1^*(\tau,\alpha))(\phi(1-\vartheta)+\vartheta)+\psi)(\psi)$$

Now equation (3.43) becomes

$$\lambda^4+C_1\lambda^3+C_2\lambda^2+C_3\lambda+C_4 \tag{3.44}$$

Using Routh-Hurwitz criterion, the equilibrium for equation (3.43) is locally stable if the following conditions are satisfied:

$$C_1>0, C_3>0, C_4>0, C_1C_2C_3>C_3^2+C_1C_4$$

Otherwise the endemic equilibrium state is unstable.

3.6.2 Case 2

At the second endemic equilibrium state we substituting equation (3.25) into equation (3.28) which yields

$$J(s_2^*(\tau,\alpha), i_2^*(\tau,\alpha), r_{T2}^*(\tau,\alpha), r_{p2}^*(\tau,\alpha)) = \begin{pmatrix} -\xi(\tau,\alpha)(1-(\eta+\rho))i_2^* + ((\eta+\rho)+\psi(\alpha)) & -\xi(1-(\eta+\rho))s_2^* & 0 & 0 \\ \xi(\tau,\alpha)(1-(\eta+\rho))i_2^* & \xi(1-(\eta+\rho))s_2^* - (\psi(\alpha)+\varphi) & \phi(1-\vartheta) & 0 \\ \rho & \varphi & -(\phi(1-\vartheta)+\vartheta+\psi(\alpha)) & 0 \\ \eta & 0 & \vartheta & -\psi(\alpha) \end{pmatrix} \tag{3.45}$$

From equation (3.45) we calculating $det|J-\lambda I| = 0$

$$det \begin{pmatrix} -\xi(\tau,\alpha)(1-(\eta+\rho))i_2^* + ((\eta+\rho)+\psi(\alpha)) - \lambda & -\xi(1-(\eta+\rho))s_2^* & 0 & 0 \\ \xi(\tau,\alpha)(1-(\eta+\rho))i_2^* & \xi(1-(\eta+\rho))s_2^* - (\psi(\alpha)+\varphi) - \lambda & \phi(1-\vartheta) & 0 \\ \rho & \varphi & -(\phi(1-\vartheta)+\vartheta+\psi(\alpha)) - \lambda & 0 \\ \eta & 0 & \vartheta & -\psi(\alpha)-\lambda \end{pmatrix} = 0 \tag{3.46}$$

Solving equation (3.46) we obtain

$$\lambda^4 + [(\phi(\tau,\alpha)(1-\vartheta)+\vartheta+\psi(\alpha)) - (\xi(\tau,\alpha)(1-(\eta+\rho))s_2^*(\tau,\alpha) - (\psi(\alpha)+\varphi(\tau,\alpha))) - (\xi(\tau,\alpha)(1-(\eta+\rho))i_2^*(\tau,\alpha)) - ((\eta+\rho)+\psi(\alpha)) - \psi(\alpha)]\lambda^3 + [((\phi(1-\vartheta)+\vartheta+\psi)\psi) + (-\xi(1-(\eta+\rho)))i_2^*(\tau,\alpha) - ((\eta+\rho)+\psi)(\xi(\tau,\alpha)(1-(\eta+\rho))s_2^*(\tau,\alpha) - (\psi+\varphi)) - (-\xi(\tau,\alpha)(1-(\eta+\rho))i_2^*(\tau,\alpha) - ((\eta+\rho)+\psi)(\phi(\tau,\alpha)(1-\vartheta)+\vartheta+\psi)) + (\xi(\tau,\alpha)(1-(\eta+\rho))s_2^*(\tau,\alpha)(\xi(1-(\eta+\rho))i_2^*)(\tau,\alpha) - (\xi(\tau,\alpha)(1-(\eta+\rho))s_1^*(\tau,\alpha) - (\psi+\varphi(\tau,\alpha))((\phi(\tau,\alpha)(1-\vartheta)+\vartheta)+\psi)) - ((-\xi(\tau,\alpha)(1-(\eta+\rho))i_2^*(\tau,\alpha) - ((\eta+\rho)+\psi)-\psi))(\psi)]\lambda^2 + [(-\xi(1-(\eta+\rho)))i_1^*(\tau,\alpha) - ((\eta+\rho)+\psi)(\xi(\tau,\alpha)(1-(\eta+\rho))s_2^*(\tau,\alpha) - (\psi+\varphi))((\phi(\tau,\alpha)(1-\vartheta)+\vartheta)+\psi) + ((-\xi(\tau,\alpha)(1-(\eta+\rho)))i_2^*(\tau,\alpha) - ((\eta+\rho)+\psi)(\xi(\tau,\alpha)(1-(\eta+\rho))s_2^*(\tau,\alpha) - (\psi+\varphi(\tau,\alpha))))(\psi) - ((-\xi(\tau,\alpha)(1-(\eta+\rho)))i_2^*(\tau,\alpha) - ((\eta+\rho)+\psi))((\phi(\tau,\alpha)(1-\vartheta)+\vartheta)+\psi)(\psi) - (\xi(\tau,\alpha)(1-(\eta+\rho)))s_2^*(\tau,\alpha)((\phi(\tau,\alpha)(1-\vartheta)+\vartheta)+\psi)(\psi) + (\xi(\tau,\alpha)(1-(\eta+\rho))s_2^*(\tau,\alpha)(\xi(\tau,\alpha)(1-(\eta+\rho))i_2^*(\tau,\alpha)((\phi(\tau,\alpha)(1-\vartheta)+\vartheta)+\psi) + (\xi(\tau,\alpha)(1-(\eta+\rho)))s_2^*(\tau,\alpha)((\xi(1-(\eta+\rho)))i_2^*(\tau,\alpha))(\psi)]\lambda + (-\xi(\tau,\alpha)(1-(\eta+\rho))i_2^*(\tau,\alpha) - ((\eta+\rho)+\psi)(\xi(\tau,\alpha)(1-(\eta+\rho))s_2^*(\tau,\alpha) - (\psi+$$

$\varphi)((\phi(1-\vartheta)+\vartheta)+\psi)+(\xi(1-(\eta+\rho))s_2^*(\xi(1-(\eta+\rho))i_2^*(\tau,\alpha))((\phi(1-\vartheta)+\vartheta)+\psi)(\psi) =$

$0 \qquad (3.47)$

In equation (3,47) we let

$D_1 = (\phi(\tau,\alpha)(1-\vartheta)+\vartheta)+\psi(\alpha)) - ((\xi(\tau,\alpha)(1-(\eta+\rho))s_2^*)(\tau,\alpha) - (\psi(\alpha)+$

$\varphi(\tau,\alpha))) - (\xi(\tau,\alpha)(1-(\eta+\rho)i_2^*)(\tau,\alpha) - ((\eta+\rho)\psi(\alpha)) - \psi(\alpha))$

$D_2 = ((\phi(1-\vartheta)+\vartheta)+\psi)(\psi)+(-(\xi(1-(\eta+\rho))i_2^*(\tau,\alpha))-((\eta+\rho)+\psi))(\xi(\tau,\alpha)(1-$

$(\eta+\rho))s_2^*(\tau,\alpha)-(\psi+\varphi))-(-\xi(\tau,\alpha)(1-(\eta+\rho))i_2^*(\tau,\alpha)-((\eta+\rho)+\psi)((\phi(\tau,\alpha)(1-$

$\vartheta)+\vartheta)+\psi)) + (\xi(\tau,\alpha)(1-(\eta+\rho))s_2^*(\tau,\alpha)(\xi(1-(\eta+\rho))i_2^*(\tau,\alpha)) - ((\xi(\tau,\alpha)(1-$

$(\eta+\rho))s_2^*(\tau,\alpha)) - (\psi+\varphi(\tau,\alpha)))((\phi(\tau,\alpha)(1-\vartheta)+\vartheta)+\psi) - (\xi(\tau,\alpha)(1-(\eta+$

$\rho))i_2^*(\tau,\alpha)) - ((\eta+\rho)+\psi)-\psi)(\psi)$

$D_3 = (-(\xi(1-(\eta+\rho))i_2^*(\tau,\alpha)) - ((\eta+\rho)+\psi))(\xi(\tau,\alpha)(1-(\eta+\rho))s_2^*(\tau,\alpha) -$

$(\psi+\varphi))(\phi(\tau,\alpha)(1-\vartheta)+\vartheta)+\psi) + (-\xi(\tau,\alpha)(1-(\eta+\rho))i_2^*(\tau,\alpha)) - ((\eta+\rho)+$

$\psi))(\xi(\tau,\alpha)(1-(\eta+\rho))s_2^*(\tau,\alpha)-(\psi+\varphi(\tau,\alpha)))(\psi)-(-\xi(\tau,\alpha)(1-(\eta+\rho))i_2^*(\tau,\alpha)-$

$((\eta+\rho)+\psi)((\phi(1-\vartheta)+\vartheta)+\psi))(\psi) - (\xi(\tau,\alpha)(1-(\eta+\rho))s_2^*(\tau,\alpha)(\phi(\tau,\alpha)(1-$

$\vartheta)+\vartheta)+\psi)(\psi)+(\xi(\tau,\alpha)(1-(\eta+\rho))s_2^*(\tau,\alpha)(\xi(\tau,\alpha)(1-(\eta+\rho))i_2^*(\tau,\alpha))((\phi(1-$

$\vartheta)+\vartheta)+\psi) + (\xi(\tau,\alpha)(1-(\eta+\rho))s_2^*(\xi(\tau,\alpha)(1-(\eta+\rho))i_2^*(\tau,\alpha)(\psi)$

$D_4 = (-(\xi(\tau,\alpha)(1-(\eta+\rho))i_2^*(\tau,\alpha))-((\eta+\rho)+\psi))(\xi(\tau,\alpha)(1-(\eta+\rho))s_2^*(\tau,\alpha)-$

$(\psi+\varphi))(\phi(1-\vartheta)+\vartheta)+\psi)+(\xi(\tau,\alpha)(1-(\eta+\rho))s_2^*(\tau,\alpha)(\xi(1-(\eta+\rho))i_2^*(\tau,\alpha))(\phi(1-$

$\vartheta)+\vartheta)+\psi)(\psi)$

Now equation (3.47) becomes

$\lambda^4+D_1\lambda^3+D_2\lambda^2+D_3\lambda+D_4 \qquad (3.48)$

Using Routh-Hurwitz criterion, the equilibrium for equation (3.48) is locally stable if the following conditions are satisfied:

$D_1 > 0, D_3 > 0, D_4 > 0, D_1D_2D_3 > D_3^2 + D_1D_4$

Otherwise the endemic equilibrium state is unstable.

3.7 Sensitivity Analysis

Sensitivity analysis is the study of the uncertainty in the output of a mathematical model or system (numerically or otherwise). Sensitivity analysis can be useful for a range of purposes including, Testing the robustness of the results of a model or system in the presence of uncertainty, Increasing the understanding between the relationships of the input and output variables in a model or system, Uncertainty reduction; sensitivity analysis identify model inputs that causes significant uncertainty in the output, therefore it should be the focus of attention if the robustness is to be increased, Searching for errors in the model or system by encountering unexpected relationships between inputs and outputs, Model simplification; fixing model inputs that have no effect on the output, or identifying and removing redundant parts of the model structure, Enhancing communication from modelers to decision makers, for example making recommendations more credible, understandable, compelling or persuasive. Sensitivity indices allow us to measure the relative change in a variable when a parameter changes. The normalized forward sensitivity index of a variable with respect to a parameter is the ratio of the relative change in the variable to the relative change in the parameter. When the variable is a differentiable function of the parameter, the sensitivity index may be alternatively defined using partial derivatives defined as

$$\Gamma_p^{r_0} = \frac{\partial R_0}{\partial p} \times \frac{p}{R_0}$$

We perform a sensitivity analysis on our model based on our assumptions to ascertain the robustness of the results we will obtain in the next chapter and also to make recommendations credible enough for decision makers.

Chapter 4

Model Analysis and Discussion of Results

4.1 Stability Analysis

4.1.1 Stability of equilibrium state for the Ode's model

By substituting the parameter values for general female population in table (4.1) below into equation (3.12)

$R_0 = \frac{0.964}{0.186+0.66} = 1.66$

$R_0 \approx 2$

Since $R_0 > 1$ the disease free equilibrium is unstable and an endemic will occur when an infected person is introduced into the general female population. The infected person on an average is capable of infecting more than one susceptible. This is because the transmission rate is greater than the temporal recovery rate.

Table 4.1: Parameters and their descriptions for general female population Source: Ghana Statistical Service Report (2007)

Parameter	Parameter description	Typical values
ψ	Birth and dearth rate	0.186
ξ	Rate at which female get infected	0.968
φ	Temporal recovery rate in female	0.395
k	Permanently recovery rate	0.7
η	Proportion of female who have 3 doses	0.094
ρ	Proportion of female with 1 and 3 doses	0.281
ϑ	female receiving full dose after 1 and 2 dose	0.025
ϕ	Rate of re-infection in general female after partial doses	0.003

Using the parameter values given in table 4.1 below on equations (3.6) and (3.7) gives two endemic equilibrium states as;

$(s_1^*, i_1^*, r_{T1}^*, r_{p1}^*) = (0.34, -0.05, 0.34, 0.69)$ and

$(s_2^*, i_2^*, r_{T2}^*, r_{p2}^*) = (0.258, 0.392, 0.991, 1.628)$

The first endemic equilibrium state is left from the analysis since it is not biologically meaningful. Therefore we analyse the stability of only the second endemic equilibrium state.

Using the characteristics equation (3.20) which was evaluated at this endemic equilibrium state and the parameter values;

We obtain;

$$\lambda^4 + 0.674\lambda^3 + 0.697\lambda^2 + 0.256\lambda + 0.088 = 0 \tag{4.1}$$

$B_1 > 0, B_3 > 0, B_4 > 0, B_1B_2B_3 > 0.120B_3^2 + B_1^2B_4 = 0.106$ Using the Routh-Hurwitz criterion on equation (4.1) the endemic equilibrium state is locally asymptotically stable since all criterions is satisfied.

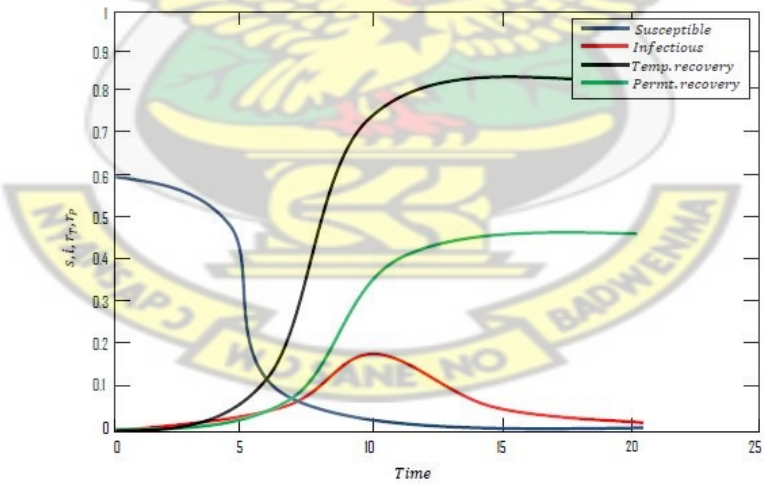

Figure 4.1: State variable of the ODE system with initial conditions and parameters

4.2 Sensitivity analysis

4.2.1 Sensitivity analysis of the endemic equilibrium state for the ODE's model with increased and decreased parameters.

We increase all parameter values for the general female population except the death rate as

$\xi = 0.68, \varphi = 0.53, \eta = 0.12, \rho = 0.46, , \vartheta = 0,051, \phi = 0.06, \psi = 0.186, \xi_A = 0.675, \varphi_A = 0.371, \eta_A = 0.071, \rho_A = 0.062, \vartheta_A = 0.052, \phi_A = 0.056$

Using the characteristics equation (3.19) and the new parameter values.

We obtain;

$$\lambda^4 + 1.796\lambda^3 + 1.239\lambda^2 + 0.470\lambda + 0.164 = 0 \tag{4.2}$$

$B_1 > 0, B_3 > 0, B_4 > 0, B_1B_2B_3 = 0.660, B_3^2 + B^2B_4 = 0.750$

Using the Routh Hurwitz criterion on equation (4.2) the endemic equilibrium state is unstable since all the conditions do not hold.

Table 4.2: Sensitivity indices of R_0 evaluated at the general female parameter values

Parameter	Sensitivity index
ξ	+0.5
φ	+0.49

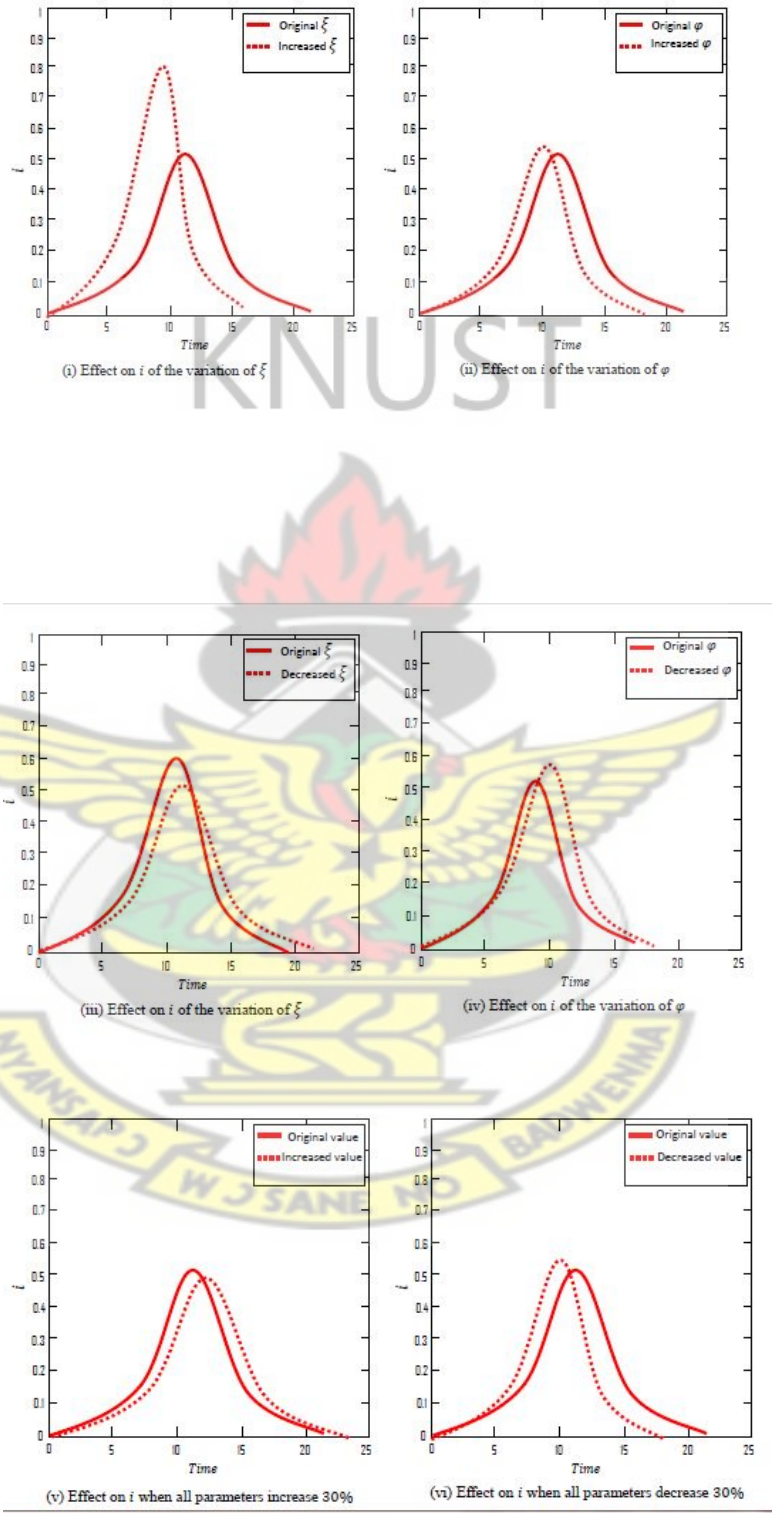

Figure 4.2: State variables of the infective class with increased and decreased parameters

Table 4.3: Parameters and their descriptions for adolescent and adult population

Parameter	Parameter description	Typical values
ψ	Birth and dearth rate	0.186
k	Permanent recovery rate for adolescent	0.7
ξ_α	Rate at which adolescent gets infected	0.713
ξ_A	Rate at which adult gets infected	0.583
φ_α	Temporal recovery rate in adolescent	0.0.692
φ_A	Temporal recovery rate in adult	0.098
η_α	Proportion of adolescent who have 3 doses	0.187
η_A	Proportion of adolescent who have 3 doses	0.007
ρ_α	Proportion of adolescent with 1 and 2 doses	0.527
ρ_A	Proportion of adult with 1 and 2 doses	0.034
ϑ_α	adolescent receiving full dose after 1 and 2 dose	0.049
ϑ_A	adult receiving full dose after 1 and 2 dose	0.009
ϕ_α	Rate of re - infection in adolescent after partial doses	0.019
ϕ_A	Rate of re - infection in adults after partial doses	0.004

4.3 Stability Analysis

4.3.1 Stability of equilibriums state for the PDE's model

By substituting the parameter values for adolescent population in table (4.2) above into equation (3.36)

$R_0 = 1.812$

$R_0 \approx 2$

Since $R_0 > 1$, the disease free equilibrium state for the adolescent population is unstable and the disease will persist when an infected person is introduced into the population. On an average an infected individual will infect more than one susceptible.

We study the behavior of the endemic equilibrium states of the adolescent population. Using the parameter values for the adolescent population as given above on equations (3.27) and (3.28) gives two endemic equilibrium states as;

$(s_1^*, i_1^*, r_{T1}^*, r_{p1}^*) = (0.29, -0.26, 0.09, 0.55)$ and

$(s_2^*, i_2^*, r_{T2}^*, r_{p2}^*) = (2.15, 1.31, 3.90, 13.20)$

The first endemic equilibrium state is left from the analysis since it is not biologically meaningful. Therefore we analyse the stability of only the second endemic equilibrium state. Using the characteristics equation (3.44) which was evaluated at this endemic equilibrium state and the parameter values;

We obtain;

$$\lambda^4+1.41\lambda^3+2.10\lambda^2+0.55\lambda+0.54 = 0 \tag{4.4}$$

$D_1 > 0, D_3 > 0, D_4 > 0, D_1D_2D_3 = 1.45, D_3^2 + D^2D_4^2 = 1.37$

Using the Routh-Hurwitz criterion on equation the endemic equilibrium state is locally asymptotically stable since all criterions is satisfied.

Now substituting the parameter values for adult population in table 4.2 above into equation (3.36)

$R_0 = 0.812$

Since $R_0 < 1$ the disease free equilibrium state for the adult population is asymptotically stable and the disease will die out when an infected person is introduced into the population. On an average an infected individual will infect less than one susceptible. We study the behaviour of the endemic equilibrium states of the adult population. Using the parameter values for the adult population as given above on equations (3.27) and (3.28) gives two endemic equilibrium states as;

$(s_1^*, i_1^*, r_{T1}^*, r_{p1}^*) = (0.85, -2.02 \times 10^{-3}, 0.15, 0.88)$

and

$(s_2^*, i_2^*, r_{T2}^*, r_{p2}^*) = (0.35, 0.66, 0.39, 0.07)$

and The first endemic equilibrium state is left from the analysis since it is not biologically meaningful. Therefore we analyse the stability of only the second endemic equilibrium state. Using the characteristics equation (3.41) which was evaluated at this endemic equilibrium state and the parameter values;

We obtain;

$$\lambda^4+0.03\lambda^3+0.22\lambda^2+0.07\lambda+0.01 = 0 \tag{4.5}$$

$D_1 > 0, D_3 > 0, D_4 > 0, D_1D_2D_3 = 3.84 \times 10^{-4}, D_3^2 + D^2D_4 = 4.37 \times 10^{-3}$

Using the Routh - Hurwitz criterion on equation (4.5) in the endemic equilibrium state is unstable since all criterion's are not satisfied.

Figure 4.2(a) State variable of the PDE system with initial conditions and parameters for adolescent (solid lines) and adult (dashed lines) population.

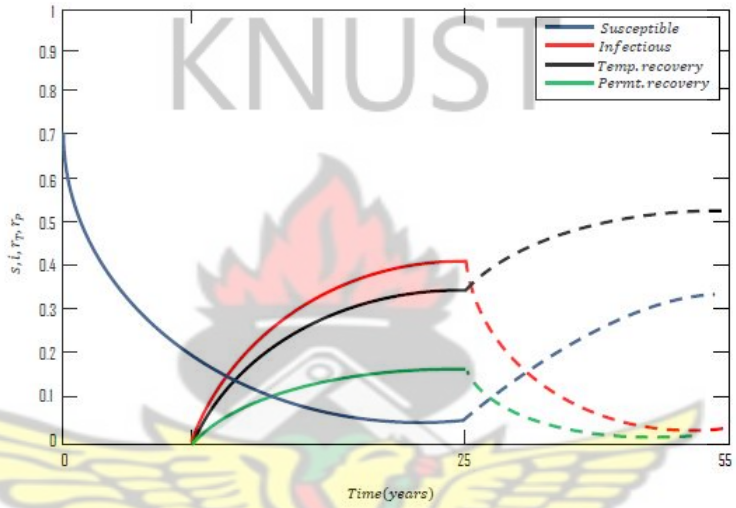

Figure 4.3:

4.4 Sensitivity analysis for the adolescent and adult population

4.4.1 Sensitivity analysis of endemic equilibrium for the PDE's model with increased and decreased parameters

We increased all parameter values for the adolescent and adult population except the death rate as

$\xi_\alpha = 0.813, \varphi_\alpha = 0.742, \eta_\alpha = 0.316, \rho_\alpha = 0.721, \vartheta_\alpha = 0.102, \phi_\alpha = 0.031, \psi =$

$0.186, \xi_A = 0.675\varphi_A = 0.371, \eta_A = 0.071, \rho_A = 0.062, \vartheta_A = 0.052, \phi_A = 0.056$

Using the characteristics equation (3.41) and the new parameter values for the adolescent population.

We obtain;

$$\lambda^4 + 0.617\lambda^3 + 1.475\lambda^2 + 0.267\lambda + 0.193 = 0 \tag{4.6}$$

$D_1 > 0, D_3 > 0, D_4 > 0, D_1 D_2 D_3 = 0.194, D_3^2 + D^2 D_1^2 D_4 = 0.145$

Since all the Routh-Hurwitz criterion conditions holds for equation (4.6) the endemic equilibrium state is asymptotically stable.

Now using the characteristics equation (3.41) and the new parameter values for the adult population,

We obtain;

$$\lambda^4 + 0.07\lambda^3 + 0.49\lambda^2 + 0.14\lambda + 0.04 = 0 \tag{4.7}$$

$D_1 > 0, D_3 > 0, D_4 > 0, D_1 D_2 D_3 = 4.8 \times 10^{-3}, D_3^2 + D^{2_1} D_4 = 0.020$

Using the Routh-Hurwitz criterion on equation (4.7) the endemic equilibrium state is unstable since all criterions are not satisfied.

Table 4.4: Sensitivity indices of R_0 evaluated at the adolescent and adult female parameter values

Parameter	Sensitivity index
ξ_a	+0.5
φ_a	+0.52
ξ_A	+0.5
φ_A	+0.81

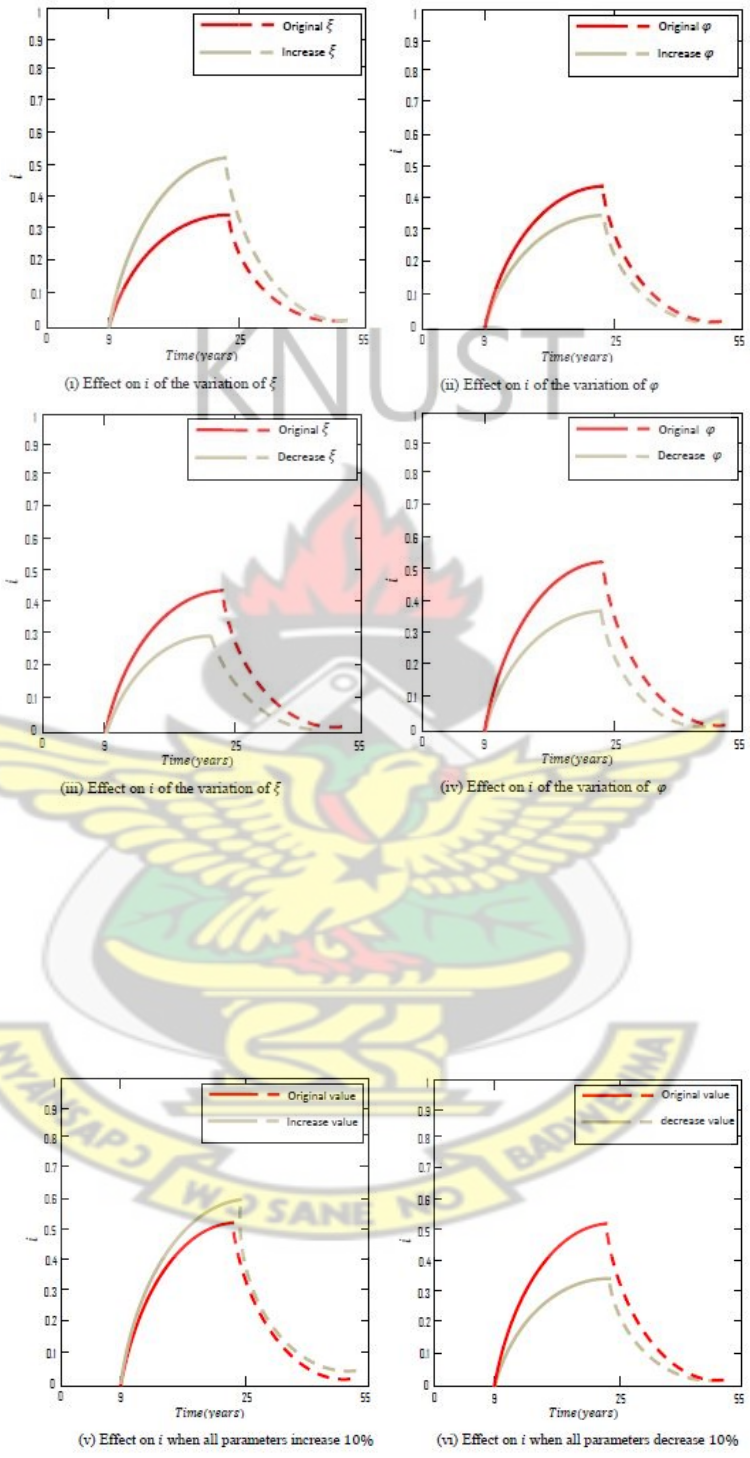

Figure 4.4: State variables of the infective class with increased and decreased parameters

4.5 Discussion of Results

In our thesis, we use ordinary differential equation obtained from our propose SIR model to predict the spread of HPV infection in general female population in the presence of HPV vaccine in Ghana. We also use standard partial differential equation obtained from our propose SIR model to compare the spread of HPV infection in both adolescents aged 9-25 and adults aged 25 and above in the absence of HPV vaccine. We discussed the existence and stability of the disease free and endemic equilibrium state for both the ordinary differential equations and partial differential equations of our model and performed sensitivity analysis on the parameters.

We estimate the basic reproductive ratio for the general female population in the presence vaccination using the systems of ODE's to be $R_0 > 1$ which indicates that the pathogen is able to invade the general female population and cervical cancer cases will increase in the future. We also estimated the basic reproductive ratio for only adolescents using the systems of PDE's to be $R_0 > 1$ which indicates that each infected individual in the adolescent population, on an average, more than one new infected individual, and therefore, predictable that the infection will persist in the adolescent population. In the adult population we calculated $R_0 < 1$ which indicates that the pathogen will die out in the adult population and cervical cancer cases will decrease in the future. This means that the vaccination programs put in place for adolescent should be intensified. Since vaccination is not effective in adult, cervical cancer screening should be intensified. Since HPV vaccine has no adverse effect on adults but adolescent, if the vaccination program is intensified for the adolescent in the country will have a great impact in reducing HPV infection and further reduce the spread of cervical cancer cases in Ghana.

Two endemic equilibrium states were found for all the various population groups and was observed that in each case the first endemic equilibrium states was not biologically meaningful so only the second endemic equilibrium states were used for the analysis. In the general female population the endemic equilibrium was locally asymptotically stable.

In the adolescent population the endemic equilibrium state was locally asymptotically stable. In the adult population the endemic equilibrium state was unstable. We performed sensitivity analysis on our models to see how our model parameters influence our models.

In figure 4.1 we observe that the susceptible reduce with time and approaches zero but do not disappear. The infective grows but reduces with time. The temporal and permanent recovery increases exponentially with time.

In figure 4.2 we compare the behaviour of the adolescent and adult population and observed that as the adolescent who are susceptible reduces that of the adult increases and as the adolescent infectious increases the infected adult reduces. Again both the temporal adolescent and adult population grows as time increases. The permanent recovery for the adolescent population increases whiles that of the adult population decreases with time.

We observed from our analysis that the transmission rate (ξ)and the temporal recovery rate φ are the main parameters to consider in controlling HPV infection in Ghana if death rate is assumed constant.

From the sensitivity index analysis for the general female population, for example $\Gamma_{\xi}^{R_0}$ means that increasing (or decreasing)ξ by 30 percent increases(or decreases) always R_0 by 15 percent in the general female population.

In this situation the infected humans also increases (or decreases) accordingly, as can be seen in Figure 4.2 (i - iv). Figure 4.2 (v-vi) presents the comparison of the infected humans when the original parameters are considered and all the paramters are increased (or decrease) by 30 percent

From the sensitivity index analysis for the adolescent population example $\Gamma_{\xi}^{R_0}$ means that increasing (or decreasing) ξ by 10 percent increases(or decreases) always R_0 by 5 percent in both the adolescent and adult female population. In this situation the infected humans also increases (or decreases) accordingly, as can be seen in Figure 4.4 (i-iv). Figure 4.4 (v-vi) presents the comparison of the infected humans when the original parameters are considered and all the paramters are increased (or decrease) by 10 percent

Chapter 5

Conclusion and Recommendations

5.1 Introduction

In this chapter we deal with the conclusion and give necessary recommendation for further studies about the results obtained from chapter four.

5.2 Conclusions

The derivation and analysis of the modified SIR mathematical model SIR_TR_T enabled a better understanding of the dynamics of the spread of Human Papilloma Virus infection and reduction of cervical cancer cases in Ghana.

The reproductive ratio is greater than one for the general female population which indicates that epidemic can occur. However, the disease will die out if the reproductive ratio is less than.
Numerical simulations analysis was extensively helpful in the determination of the effect of the various parameters especially the transmission rate and recovery rate on the spread of the infection and disease.

Our model was studied by evaluating the sensitivity indices of the basic reproductive number R_0 in order to determine the relative importance of the parameters in the disease transmission. From the sensitivity index analysis for example $\Gamma_{\xi}^{R_0} = +0.5$ means that increasing (or decreasing)ξ by 30 percent increases(or decreases) always R_0 by 15 percent in the general female population. From the sensitivity index analysis for example $\Gamma_{\xi_a}^{R_0} = +0.5$ means that increasing (or de-

creasing) ξ_a by 10 percent increases(or decreases) always R_0 by 15 percent in both the adolescent and adult female population.

These information allow us to identify the robustness of the model predictions with respect to parameter values, the influence of each parameter in the basic reproduction number, and consequently in the disease evolution. Such analysis can provide critical information for decision makers and public health officials, who may deal with the reality of an infectious disease.

We trust that the research direction here initiated can be of great benefit to citizens affected by HPV infection, with an impact on a disease like cervical cancer, which causes a large disruption in the lives of sufferers and has enormous social and economic costs.

5.3 Recommendations

Further research work is recommended particularly to involve susceptible who are infected but not treated in the various population groups.

Vaccination programs should be intensify by the ministry of health of which the adolescent susceptible population should be given all three dose of HPV vaccine early enough before they become sexually active in order to fully bring the infection under control and to reduce cervical cancer cases in the future in Ghana.

Treatment options like Pap test screening should be intensify in in the country for all groups of female population to detect pre- cancerous cells in their early stage for easy treatment.

Again awareness programs should be put in place to educate women on the causes

and dangers of cervical cancer.

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.

Appendix A

```
[t h]=ode45(@Ddif,[20 40],[0.6 0.3 0.07 0.03])

plot(t,h(:,1),'r',t,h(:,2),'b',t,h(:,3),'g',t,h(:,4),'k')

xlabel('Age')

ylabel('S,I,R_t,R_p')

legend('Susceptible','Infectious','Temporal Recovery','Permanent Recovery')

function dh=Adif(t,h)

%Adolescence Age (12-20)

a1=0.4;a2=0.47;a3=1.6;u=5.33;b=2.07;N=704753;w=0.87;v=2;k=0.15;

dh=zeros(4,1);

dh(1)=u*N-(b*(1-(a1+a2))*h(1)*h(2))/N-((a1+a2)+u)*h(1);

dh(2)=(b*(1-(a1+a2))*h(1)*h(2))/N-(u+v)*h(2)+w*(1-a1)*h(3);

dh(3)=a2*h(1)+v*h(2)-(w*(1-a3)+ a3*k +u)*h(3);

dh(4)=a3*k+a1*h(1)-u*h(4);

function dh=dif(t,h)

a1=0.6;a2=2.87;a3=2.4;u=4.2;b=2.07;N=1021162;w=0.87;v=2;k=0.15;

dh=zeros(4,1);

dh(1)=u*N-(b*(1-(a1+a2))*h(1)*h(2))/N-((a1+a2)+u)*h(1);

dh(2)=(b*(1-(a1+a2))*h(1)*h(2))/N-(u+v)*h(2)+w*(1-a1)*h(3);

dh(3)=a2*h(1)+v*h(2)-(w*(1-a3)+ a3*k +u)*h(3);

dh(4)=a3*k+a1*h(1)-u*h(4);

function dh=Ddif(t,h)

a1=0.27;a2=0.6;a3=0.06;u=1.9;b=2.07;N=316409;w=0.87;v=0.4;k=0.15;
```

```
dh=zeros(4,1);

dh(1)=u*N-(b*(1-(a1+a2))*h(1)*h(2))/N-((a1+a2)+u)*h(1);
```

Appendix B

```
dh(2)=(b*(1-(a1+a2))*h(1)*h(2))/N-(u+v)*h(2)+w*(1-a1)*h(3);

dh(3)=a2*h(1)+v*h(2)-(w*(1-a3)+ a3*k +u)*h(3);

dh(4)=a3*k+a1*h(1)-u*h(4);

[t h]=ode45(@Adif,([10 22]),[0.3 0.4 0.2 0.1])

plot(t,h(:,1),'r',t,h(:,2),'b',t,h(:,3),'g',t,h(:,4),'k')

xlabel('Age')

ylabel('S,I,R_t,R_p')

legend('Susceptible','Infectious','Temporal Recovery','Permanent Recovery')

% Adolescent gragh Age(12-20)


[t h]=ode45(@Adif,([10 22]),[0.3 0.4 0.2 0.1])

plot(t,h(:,1),'r',t,h(:,2),'b',t,h(:,3),'g',t,h(:,4),'k')

xlabel('Age')

ylabel('S,I,R_t,R_p')

legend('Susceptible','Infectious','Temporal Recovery','Permanent Recovery')

% Adolescent gragh Age(12-20)

[t h]=ode45(@dif,([0 10])*0.15,[0.4 0.2 0.3 0.1])

plot(t,h(:,1),'r',t,h(:,2),'b',t,h(:,3),'g',t,h(:,4),'k')

xlabel('Time')

ylabel('S,I,R_t,R_p')

legend('Susceptible','Infectious','Temporal Recovery','Permanent Recovery')
```

```
[t h]=ode45(@dif,[0 10])*0.15,[0.4 0.2 0.3 0.1])

plot(t,h(:,1),'r',t,h(:,2),'b',t,h(:,3),'g',t,h(:,4),'k')

xlabel('Time')

ylabel('S,I,R_t,R_p')

legend('Susceptible','Infectious','Temporal Recovery','Permanent Recovery')
```